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Special Issues Related to Hematopoietic Stem Cell Transplantation in the Eastern Mediterranean Region and the First Regional Activity Report

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Abstract

Although several centers are now performing allogeneic HSCT in the Eastern Mediterranean (EM) region, the availability is still limited. Special issues including compatible donor availability and potential for alternate donor programs are discussed. In comparison to Europe & North America, differences in pattern of diseases and pre-HSCT general status particularly for patients with BM failure are described. Other differences including high seropositivity for CMV, Hepatitis B and C infection and specific observations about GVHD with its relation to genetically homogeneous community are also discussed.

We report that a total of 17 HSCT programs (performing 5 or more HSCTs annually) exist in 9 countries of the EM region. Only 6 programs are currently reporting to EBMT or IBMTR. A total of 7617 HSCTs have been performed by these programs including 5701 allogeneic HSCTs. Due to low HSCT team density (1.5583 teams/10 million inhabitants vs. 14.4333 in Europe) and very low HSCT team distribution (0.2729 teams/10,000 sq km area vs. <1 to 6 teams in Europe). GNI/capita had no clear association with low HSCT activity; however improvement in infrastructure & formation of EM regional HSCT registry are needed.

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Introduction

Hematopoietic Stem Cell Transplantation (HSCT) is a life-saving treatment for many diseases. However, because of the relatively high cost and the need for multi-disciplinary team and advanced laboratory support limited centers in the developing world are providing this modality of treatment.

High quality data about HSCT activity are widely available through the European Bone Marrow Transplantation Group (EBMT) and the Center for International Bone Marrow Transplantation Research (CIBMTR). However, both registries contain more data from centers located in Western Europe and North America.

Although the number of centers performing allogeneic HSCT in Eastern Mediterranean (EM) region as defined by the World Health Organization (WHO)[1] (Figure 1) has increased, there are no data as of today that exist about the transplant activities in this region or the issues related to HSCT in the listed countries.

During the last year, a collective effort has been carried out through program representatives in the EM region with the goal of simple identification of issues related to HSCT in the EM area and to conduct the first survey ever done for this region.

This is a part of an on-going collective effort by the programs in the region to ultimately establish an Eastern Mediterranean HSCT organization with the help of the EBMT, CIBMTR and in collaboration with the World Bone Marrow Transplantation Group (WBMT).

Methods

All programs in the WHO-designated Eastern Mediterranean region with consistent annual performance of equal or greater than five (5) cases per year for at least three consecutive years were identified and included.

Programs from each country were asked to submit a standardized report to include the following information:

1. Total population and Gross National Income (GNI)*
2. Geographic area of coverage for patient referral in each country**
3. Number of transplant centers and types of transplantation performed by each center
4. Approximate total number of transplantations performed per year
5. Predominant type of transplantation performed, including sibling donor availability vs. alternate donor
6. Distribution of disease entities and prevalent diseases being transplanted
7. Special observations regarding transplantation, such as the low prevalence of GVHD in genetically homogenous communities
8. Infectious disease issues related to transplantation in specific geographic areas
9. Approximate actual cost of transplantation, cost to the patient and type of coverage for HSCT
10. Obstacles in the performance of transplantation (e.g. prohibitive cost, donor availability)

11. Any additional unique observational issues related to transplantation in specific geographic areas
12. Participation in international registries
13. Areas of active research

As far as possible the European Bone Marrow Transplant (EBMT) Group Activity Survey was utilized as a template for analysis of the activity data and supplementary data was obtained from EBMT and CIBMTR as necessary.

* For uniformity the population and GNI per capita for the reported countries were obtained from WHO EMRO website (http://www.who.int/about/regions/emro/en/index.html) {last accessed on 12th September 2008} and divided according to the 'World Bank income categories', i.e., high income (11,116 $ or higher), upper middle income ($3,596 - $11,115), lower middle income ($906 - $3,595) and low income ($905 or less), as displayed at the website of the World Bank: (http://web.worldbank.org/WBSITE/EXTERNAL/DATASTATISTICS). Because GNI per capita values for five countries were not available on the WHO EMRO website, hence the quoted numbers in the table are based on GDP per capita (2007 estimates) from https://www.cia.gov/library/publications/the-world-factbook/index.html. As GNI comprises GDP plus net receipts of primary income (compensation of employees and property income) from non-resident sources, the GNI values are expected to be more than GDP.

** The areas of the reported countries were obtained from the website: https://www.cia.gov/library/publications/the-world-factbook/index.html.

HSCT "Team density" was calculated as the number of HSCT teams per 10 million inhabitants in each country. HSCT "Team Distribution" was calculated as the number of transplant teams per 10,000 sq km area in each country.

Results

The Eastern Mediterranean region has a total of 21 countries with a total population of more than 540 million. These 21 countries include one country with low income category, 5 with lower middle income category, 8 with upper middle income category and 7 with high income category countries according to WHO income groups based on GNI per capita. Only 9 of the 21 countries (encompassing 70.8% of the total EM region population) have at least one active HSCT programs available for their population (Table 1). The total numbers of the programs that exist as of present are 17. Unfortunately, only 6 out of this 17 do report data to EBMT and/or CIBMTR.

Table 2 lists the number of patients who received allogeneic or autologous HSCT in the 9 countries and some of the main issues related to HSCT in each country [2, 3, 4, 5, 6, 7, 8] which will be discussed in details below along with the economic/logistic indices related to the HSCT activity, team density and team distribution in this region. Overall it is easy to comprehend that, although the rate of transplantation has generally increased over the last five years, the ratio of transplantation to the total population of the individual country has remained low.

The specific issues related to allogeneic HSCT in Eastern Mediterranean region can be divided into donor availability, genetic issues, issues related to specific diseases, pattern of infections and logistics. Each is discussed below in detail:

I. **Donor availability.** The Eastern Mediterranean region consists of communities of large families with high population growth, which certainly increases the likelihood of finding a full matched sibling donor. For example, the reported likelihood of finding a full matched sibling donor in Saudi Arabia is 63.5%[9] while the number can be as high as 70% in some areas in Pakistan.[2] This is far higher than the likelihood of finding a donor for European and North American patients. Additionally, the overall outcome of class one antigen mismatch sibling allogeneic transplantation yields similar result to full matched sibling transplantation which is likely to reflect ethnically and genetically the homogenous make up of the population. This leaves a smaller percentage of patients requiring alternate donor source for their transplantation. A lower occurrence of acute and chronic graft versus host disease (GVHD) has also been observed. [10, 11, 12, 13] And this has also been supported by similar observations made in larger studies comparing the risk of graft versus host disease in different ethnic populations.[14] The lower occurrence of chronic graft versus host disease may have an obvious impact on diseases that are susceptible to graft versus leukemia (GVL) effects such as chronic myeloid leukemia (CML) and diseases with low proliferation rate. Cord blood transplantation remains the preferred alternate donor transplantation modality in the centers that offer alternate donor HSCT. This is due to relatively lower likelihood of finding a match through western registries and the logistic difficulties in timely performance of HSCT from matched unrelated donor typically available in Western Europe and North America.

II. **Polymorphism of genes.** Knowledge of the prevalence of polymorphism in certain genes such as cytokines genes related to the risk of development of GVHD as well as genes coding for enzymes responsible for drug metabolism is badly needed in certain communities with high likelihood of consanguinity and in the EM region at large. Inactivating mutations have been found in genes coding for enzymes belonging to the cytochrome P-450 system, and also in genes coding for other enzymes. A local pharmacogenomic study from Saudi Arabia has shown a unique profile of variations in metabolism genes in Arab population.[15] PCR analysis revealed that the frequencies of alleles and/or genotypes for CYP1A1 2A, GSTT1 null, GSTT1 and GSTM1 double null, and GSTP1 A1578G in Arabs were significantly higher than those reported in Caucasians.[15] Other alleles in Arabs, including CYP1A1 T3801C and GSTP1 A1578G were present in frequencies similar to Africans.[15] Several pharmacogenomic research projects are being pursued in the Eastern Mediterranean countries in relation to this matter.

III. **Disease specific issues.**

    i. **Severe Aplastic Anemia**. Higher proportion of patients with severe aplastic anemia in Eastern Mediterranean is heavily pre-transfused when referred for allogeneic HSCT. Accordingly, a strong lymphoablative component has to be included always in the conditioning chemotherapy to avoid graft rejection. Fludarabine is being increasingly utilized as a lymphoablative component, traditionally with Cytoxan for conditioning of aplastic anemia patients. The major reason for the emerging utilization of Fludarabine as the lymphoablative component is the prohibitive cost of antitymocytic globulin in addition to the lower likelihood of side effects with Fludarabine particularly in older patients. Large numbers of aplastic anemia patients are referred to the transplant centers with variety of infections including viral, bacterial and fungal infections. Recently, availability of new generation anti-fungal therapies has led to a dramatic improvement in the outcome of patients with fungal infections.

Sometimes, short term use of these combined drugs to treat proven fungal infection facilitates the timely performance of transplantation procedure. However, these new generation anti-fungal drugs are neither universally available nor affordable for all centers in the area. A small but a definite subset of patients presents with elevated liver enzymes on admission, some with positive hepatitis serology. However, a small but definite subset of patients has "sero-negative hepatitis aplasia syndrome" similar to what has been described in previous reports.[16, 17] These patients with negative hepatitis serology tend to respond to treatment with immunosuppression therapy only.

ii. Congenital Bone Marrow Failure Syndromes and Hemoglobinopathies. Marital consanguinity is highly prevalent in the Eastern Mediterranean countries and consequently, there is high prevalence of hemoglobinopathies including thalassemia and sickle cell anemia.[4, 6, 7] Patients with hemoglobinopathies and bone marrow failure syndromes are typically heavily pre-transfused before they are transferred to the transplant centers and consequently, these patients are iron overloaded and frequently with a positive serology for hepatitis B and/or C virus. Collectively, all these factors are a set-up for organ dysfunction and transplantation complications, most notably hepatic veno-occlusive disease (VOD). Despite all of the limitations, non-neoplastic indications for allogeneic HSCT remain one of the main reasons for HSCT in certain Eastern Mediterranean transplantation centers. This is particularly common in countries where there is significant case attrition for acute leukemias because of the sub-optimal set-up conditions for chemotherapy induction in the referring centers.[2, 3]

iii. **Chronic Myeloid Leukemia.** With the availability of the Tyrosine Kinase Inhibitor (TKI) therapy, allogeneic HSCT is no longer offered as a first-line treatment option for chronic myeloid leukemia patients in first chronic phase as it applies to other centers worldwide.[18] This is true for centers where TKI is available. However, in countries where TKI therapy is not available because of its prohibitive costs, or in situations where the physician is unable to count on the continuation of the medication supply, the physician faces the dilemma of choosing the best management strategy "available to the patient" and not the best treatment strategy in absolute terms. Accordingly, allogeneic HSCT for CML in first chronic phase remains more cost effective as once in life time procedure and one of the main indications for transplantation in some centers. This is also related to the fact that CML patients do not need an urgent transplantation and are frequently in an optimal physical shape to undergo such a procedure. This is in contrast to acute leukemias where timely transplantation is needed and where the patient is in less optimal shape to survive the procedure. In few countries, generics of TKI at a very affordable cost are widely available. However, for majority of the countries, the medication has to be purchased at the standard price with no significant price adjustment based on the per capita income of each country. The issue of lower incidence of chronic GVHD is an issue of great relevance in relation to the risk of relapse in CML. Accordingly, many centers are practicing early reduction and discontinuation of post-HSCT immunosuppression for patients with no history of acute GVHD in attempt to induce a limited de novo chronic GVHD to promote the development of GVL.

iv. **Acute Myeloid Leukemia.** An important requirement for offering allogeneic HSCT for patients with acute leukemias is the capability, both financially and logistically, of achieving complete remission through induction chemotherapies. At some centers in the EM region this becomes one of the competing factors for the limited slots of allogeneic HSCT and eventually benign conditions, such as aplastic anemia and thalassemia (not requiring daunting cost and support for induction chemotherapy), disproportionately become leading indication for allogeneic HSCT.[2, 3] Another interesting regional observation is the relatively poor outcome of acute myeloid leukemia (AML) with t(8;21) which is generally considered favorable. Unpublished data from King Faisal Specialist Hospital and Research Centre in Riyadh suggested the event-free survival of this leukemia with standard induction and high dose cytarabine chemotherapy consolidation is 16%. The relatively more aggressive behavior of AML with t(8;21) has been reported in South East Asia.[19] The observed lower outcome of management of this leukemia in non-whites in North American data also suggested that the behavior of this disease is not consistently favorable, possibly related to different breakpoints or expression of other biologic and/or molecular markers that are known to be associated with poor prognosis. [20, 21]

v. **Lymphoid Malignancies.** It is well established that the incidence of indolent lymphoid malignancies decreases as one moves east across the globe. A relatively higher percentage of intermediate and high grade lymphoma is observed in EM and accordingly, a relatively high proportion of eligible patients of the latter two entities are being transplanted compared to Western Europe and North America.[22]

IV. Issues related to Infections

i. **Cytomegalovirus (CMV) Infection**. High sero-positivity for CMV was reported in many countries in the EM region reflecting high rate of previous exposure to this virus. The reported sero-positivity was 100% among the recipients and 96% among donors in Saudi Arabia[23] and 100% in donors and recipients in Pakistan.[2] These data are also consistent with reports from India.[24] There are several strategies for the prevention of CMV disease in high sero-prevalence set-up that apply to the EMRO region. On one hand, adequate pre-emptive therapy is to be applied with early detection of CMV infection and on the other hand, the pre-emptive therapy is not to be continued for extended period beyond establishment of CMV antigen negativity to prevent interference with development of CMV specific immune reconstitution.[23, 25]

ii. **Hepatitis B Virus Infection**. The endemicity of hepatitis B virus (HBV) in the EM region is well established.[26, 27, 28] According to a report [28] in the EM region, Bahrain, Iran and Kuwait are areas of low endemicity; Iraq and the United Arab Emirates have intermediate endemicity; and Egypt, Jordan, Oman, Palestine, Yemen and Saudi Arabia have high endemicity.[28]

Viral replication is expected to take place during chemotherapy and immunosuppression with the risk of fulminant hepatitis at the time of tapering of the immunosuppressive therapy. In a retrospective analysis performed in Saudi Arabia[29] with the aim of identifying risk factors and clinical characteristics associated with HBV reactivation and clinical flare

after allogeneic HSCT among 128 patients with evaluable data, 42% had evidence of prior infection and recovery from HBV before transplant (hepatitis B core antibody positive, B surface antigen negative). Six (14%) reactivated with clinical flare as documented by sero-conversion and/or positive HBV DNA in the serum with biochemical hepatitis at 5.5, 18, 18, 19, 21 and 23 months post-transplant. Five of fifteen patients with chronic graft-versus-host disease (cGVHD) reactivated with clinical flare in contrast to 1/27 without cGVHD (RR: 9.0, *P<0.02).* HBV reactivation with clinical flare occurred during immunosuppressive therapy tapering or withdrawal in all patients.[29]

HBV reactivation may also be an additional risk factor in causation of VOD and other related complications. Another problem is encountered when the only matched donor is hepatitis B surface antigen positive and HSCT needs to be carried out for an urgent indication. Of important note is that the availability of Lamivudine and other effective therapies for hepatitis B virus, had remarkably improved the outcome of allogeneic HSCT with HBV positive recipient and/or donor during the last decade.

iii. **Hepatitis C Virus Infection.** Hepatitis C virus (HCV) remains a major disease burden in the EM region. Prevalence rates across the world have changed with increased awareness about transfusion-related hepatitis C and more and more evidence supporting intravenous drug use as the leading risk factor for the spread of virus.[30] A high prevalence rate of HCV has been reported in Egypt in the recent past (up to 28% in some groups).[31] Lower rates have been reported among blood donors from various regions of Saudi Arabia (0.4-4.3%)[32,33] and in Yemeni patients (2.1%).[34]

HCV has six genotypes with numerous subtypes. Depending on the HCV genotype, length of treatment can differ. Genotype 1b is less responsive to alpha-interferon therapy compared to genotypes 2 and 3. Genotype 4 is the most common genotype in the EM region[30, 33, 35, 36, 37, 38] which unfortunately is least likely to respond to the standard interferon therapy, though recent studies using pegylated interferon demonstrated better results. A recent multi-center national study from Saudi Arabia, on patients with HCV showed that 59.6% had genotype 4, 25.1% had genotype 1, 8.3% had genotype 2 and 6.4% had genotype 3.[38] However, distribution of HCV genotypes is not uniform in the EM region, e.g., Iran has a major prevalence of HCV genotype 1 (55.8% cases).[39]

Traditionally, HCV is known to have less contribution to early post transplant morbidity and mortality, but obviously is likely to cause complications later in life such as liver cirrhosis. Difficult situations sometimes exist where the only matched donor is hepatitis C antibody positive and allogeneic HSCT is urgently needed such as in cases of acute leukemia or aplastic anemia.

iv. **Mycobacterium Tuberculosis.** Although mycobacterium tuberculosis is relatively an endemic disease in certain areas of EM, the likelihood of reactivation after HSCT is less frequent than what would be expected in an endemic area. Additionally, the likelihood of reactivation after HSCT is less than the reported rate of activation after transplantation for solid organs in the same set-up.[40] As a significant proportion of the population, especially older individuals, has a positive PPD status either from previous

exposure or BCG vaccination in childhood, the appropriateness of the universal routine prophylaxis with Isoniazid (isonicotinyl hydrazine or INH) for PPD positive HSCT recipient who has a low likelihood of re-activation will be questioned. Accordingly, many centers in EM believe that prophylaxis with INH in PPD positive patients should not be given routinely for patients who are completely asymptomatic with negative chest x-ray, which otherwise would expose the majority of patients to potential hepatotoxic medication that has many potential drug interactions with other medications used during HSCT. This practice may not be in line with the published Centers for Disease Control and Prevention (CDC) guidelines[41] regarding infection prophylaxis in HSCT, but is substantiated with our observations in the EM region. [2]

v. **Other Infections.** High prevalence of schistosomiasis in Egypt[42] and endemicity of malaria in certain areas of Pakistan[43] is well documented. Relevantly, poor malaria screening of asymptomatic blood donors led to some incidences of transfusion transmitted malaria in HSCT recipients during early transplant period in Pakistan.[2] In Egypt the relative risk to develop VOD after Allo-HSCT was calculated to be 16.8-fold higher in patients with previous history of schistosomiasis.[42]

V. **Logistic Issues Important to EM Region** Reports from the European Blood and Marrow Transplantation (EBMT) and the Centre for International Blood and Marrow Transplant Registry (CIBMTR) have illustrated earlier that number of transplants differ significantly between different countries.[44] This is true for all regions, but no detailed information is available about the EM region.

By tradition, some EBMT reports include data from few non-European countries that fall in the EM region (Iran, Saudi Arabia, and Tunisia) and report their HSCT activity to EBMT registry. Their data are in part included in some of the analyses. Hence, data published by the EBMT group may also be informative for patient counseling and decisions making by health care professionals and planners/ administrators in the EM region. However, more detailed information specific to this region is desirable.[45]

The EBMT has analyzed factors associated with differences in HSCT activity between the participating teams from more than 240 countries over a time span of 15 years. Results have revealed that gross national income (GNI) per capita, numbers of transplant teams per 10 million inhabitants or per 10,000 kilometers, team size and team experience all had impact on transplant activity.[46] Moreover, it was realized that some other factors might have been involved in the decisions to perform or not to perform HSCT.

The recent EBMT report based on the activity survey 2006[47] shows that transplant rates predictably increased over time with nearly linear trends, in clear association with GNI per capita and distinctly by World Bank income category within a narrow window of variation for both autologous HSCT and allogeneic HSCT when breast cancer (autologous) and CML (allogeneic) were excluded.[47] Team density and team distribution were also associated with transplant rates.[47] Table 3 summarizes the various factors that affect HSCT activity in European countries as reported by the EBMT group.[47, 48] These included economic factors such as GNI per capita or health care expenditures per capita, team density, and team distribution. There were also clear differences in transplant rates for certain disease indications which might relate to a different prevalence of the disease, e.g. hemoglobinopathies. [47, 48] Our preliminary findings reported here are based on cumulative experience of 17 teams

in 9 countries of the EM region over the last two decades. Of the 17 teams, 16 (94 %) did both allogeneic and autologous HSCT and one (6%) restricted its activity to autologous HSCT only.

Team density in the EM region is very low (1.5583) as compared to 13.4333 in Europe)[48] and HSCT team distribution in the countries where significant HSCT exists is also very low (0.2729) in comparison to European countries where it ranges from <1 to 6 teams per 10,000 sq km area. [47, 49]

Figure 2 reflects total HSCT performed to date in the reported countries of the EM region is quite variable. HSCT teams in Saudi Arabia, Iran and Egypt have crossed the figure of 1000 transplants. Figure 3 exhibits GNI per capita based WHO income categories in the EM region. Most of the reported countries are in the upper middle income category, except Saudi Arabia and Oman being in the high income group and Pakistan being in the lower middle income category. Figure 4 reflects low HSCT team densities in most of the EM region, except one relatively small country (Lebanon) with a density of 4.932182. These numbers are very low compared with European data. Table 4 shows HSCT activity and the related economic/logistic indices in the EM region. It is evident that more than the GNI per capita (which is not easily changeable factor), team densities and team distribution need special attention of the health care planners. Patients must have access to a transplant team in order to receive a transplant. EBMT survey figures illustrate that probably one team per 1 – 2 million inhabitants and one team per 10,000 km^2 are reasonable targets. [47] Currently a good but uncertain number of patients from the EM region, especially from countries with WHO high income category, are referred to United States or Western Europe for HSCT. However authors have no estimates of such referrals. Such cases are mostly sponsored by the state, charity support or family resources.

For comparison, the EBMT data based on a 15-year observation period within the EBMT activity survey demonstrate that transplant rates in Europe are highly predictable, show a clear association with GNI per capita and are distinct in their evolution by World Bank income category.[47] These data indicate that although transplant teams do their best to meet the needs, they still fail to do so. They are limited by resources, as illustrated by the clear association of transplant rates with GNI per capita and World Bank income category.[47] EBMT data and our initial findings indicate that HSCT activity is also limited by the infrastructure, as documented by the association between transplant activity, team density and team distribution.[48]

The countries in EM region lacking significant HSCT activity suffer from limited economic resources and or lack of expertise and logistic support. In addition, more curable and more prevalent health problems may be competing for the limited resources in lower income category countries. A significant number of patients are referred from the EM region, especially from countries with WHO high income category, to United States or Western Europe for HSCT. However as noted above, the authors have no estimates of such referrals. Obviously, the programs offering HSCT facilities in the region are unable to meet the needs of the patients from their respective countries. Hence the desirable referral between countries of the EM region is not yet fully developed, although such a referral system may help those EM countries who particularly have no internal access to HSCT. Practically, it will be more prudent to help such countries in establishing their own HSCT centres through collaboration, training and outreach programs such as those offered by EBMT to develop medical and nursing work force.

This report is based on initial data from EM region which is obviously limited. Recent EBMT analysis on predictability of HSCT rates [47] also had some limitations. Firstly, there is no uniform database on the incidence or prevalence of the individual disease categories in the participating countries. Secondly, data were limited to Europe and it is difficult to extrapolate the conclusions in other continents. Nevertheless, it is likely that similar factors, such as GNI per capita and team density also affect transplant rates in the EM region. It is also likely that considerations on cost-effectiveness will affect decisions between HSCT and lifelong expensive therapies in countries of the EM region (CML being typical example).[50, 51]

Most of the EM region countries have health care systems, economically supported by the state as is the case in the Europe. If HSCT is performed in a private centre, the procedure cost is paid by the patient in full or in part and the remaining is paid by the charity resources. Most countries lack health care insurance systems covering the cost of HSCT procedure, making HSCT a financial ordeal for the patient and family.

It is clear that the need for HSCT will continue to increase in the near future. Improvement in supportive care and antimicrobial therapy, increasing donor pools worldwide, increasing availability of cord blood products and novel conditioning regimens should provide access to HSCT for patients previously not considered as candidates for these procedure.[1] Health care providers in the EM region will face this complex problem and they should initiate rigorous actions to put the infrastructure in place.

It is important to find the correct balance between a restricted number of HSCT teams (so that they have sufficient expertise and quality service) and an adequate number in order to guarantee access for all patients, independently of travel distances. Above all, there is no indication of an abundance of transplant beds. There is a need to provide infrastructure for more HSCT centers. The anxiety of health care agencies fearing abundance of HSCT centers (due to the example of CML) now seems unnecessary and they can be reassured that trends, with the advent of novel therapies which affect the demand for HSCT, are timely recognized. With up-to-date instruments, such as the EBMT activity survey, changes in therapy can easily be recognized at an early stage and appropriate measures can be taken to curtail the feared unnecessary growth of HSCT centers.

These data clearly illustrate the need for more research to understand the mechanism of HSCT activity and into the mechanisms of technology dissemination in the EM region. If possible, such studies should be performed on a wider collaborative basis. This appears essential in order to enable health care agencies to provide adequate infrastructure for this high cost procedure especially in the EM region and other developing countries.

To improve the HSCT activity related performance standards acquisition of FACT and JACIE accreditation by the centres in EM region will obviously be helpful. However, potential logistic hurdles in accreditation related to transplant volumes, access to collection & processing facilities, and geographical factors might present challenges. Moreover, such requirements for accreditation may result in rationalization of health resources into centres capable of achieving accreditation where resources are limited. On the other hand, mandatory application of accreditation requirements, at least in the beginning, may challenge the efforts to establish new centres with already limited enthusiasm & resources.

Severe shortage of trained personnel in the field of HSCT at all levels mandates the need for an eastern Mediterranean HSCT League to promote recent technologies and improve experience related to HSCT in the region. Formation and identification of a regional HSCT training center for nurses, physicians, coordinators, researchers, data base instructors, etc will be highly instrumental in accomplishing this goal. This will be a source of exchanging experiences, providing training for new centers, and also serves as a reference for standardization of procedures. Other strategies may include initiating eastern Mediterranean 'Nursing Board' to manage the problems related to paramedical manpower, updating HSCT procedures and increasing awareness about HSCT among the staff and patients.

VI. **Other issues** Options for fertility preservation in the EM region are limited and are not optimally discussed with the patient and family due to other priorities competing for the resources and cultural issues related to scarcity of credible sperm banking facilities. Such facilities need to be built and strictly regulated as concept of surrogate sperm donor is socially not acceptable in most of the EM region.

Others areas that need improvement as mentioned earlier in the article include wider availability of alternate donor sources for the minority of patients who do not have matched sibling donors and the necessity of national and regional registries of donors to make larger pool of genetically similar donors available. Initiation of Regional Cord Blood Banks, which should offer a great potential for suitable alternative donors in an area where childbearing potential is high and many HLA antigens are expected to cluster, will minimize the incidence of not finding a matched donor.

Leading teams in the EM region are now working to establish their own national cord blood and unrelated donor programs.

Finally, a regional HSCT registry will be a step forward in promoting allogeneic HSCT in the EM region, identifying other regional problems, and may also be helpful in benchmarking HSCT outcomes. A study from United Kingdom and Ireland recently compared their data with the EBMT and demonstrated the potential for using national registries to benchmark transplant outcome using EBMT registry as reference. [52]

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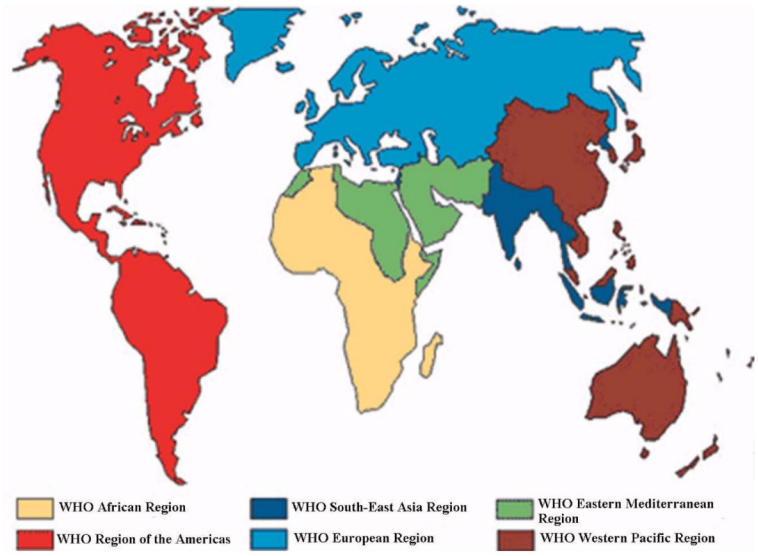

Figure 1. World Health Organization – Regions of the world. **
** **Taken from WHO website:** http://www.who.int/about/regions/en/index.html

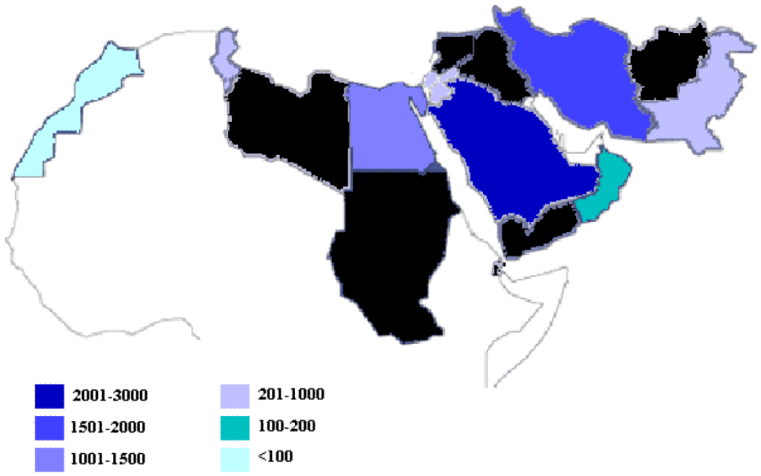

Figure 2. Total HSCT Performed in 9 Countries of the EM Region with significant HSCT programs

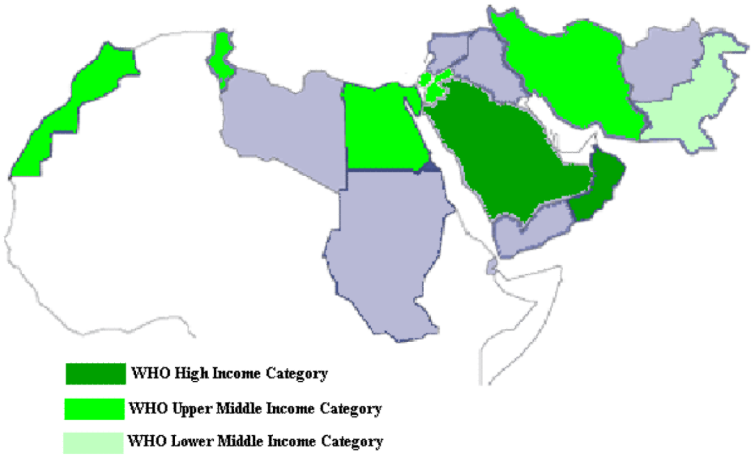

Figure 3. GNI Per Capita based WHO Income Categories of the 9 Countries of the EM Region with significant HSCT programs

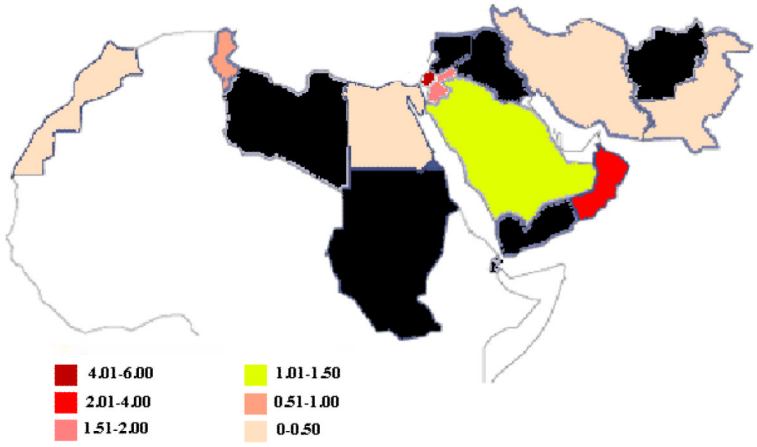

Figure 4. HSCT Team Densities in 9 Countries of the EM Region with significant HSCT programs

Table 1

Eastern Mediterranean Region Countries[1] – populations & status of HSCT programs

Country	Population[1]	Active HSCT Program Available*
Afghanistan	26,088,000	
Bahrain	739,000	
Djibouti	819,000	
Egypt	74,166,000	Yes
Iran	70,270,000	Yes
Iraq	28,506,000	
Jordan	5,729,000	Yes
Kuwait	2,779,000	
Lebanon	4,055,000	Yes
Libya	6,039,000	
Morocco	30,853,000	Yes
Oman	2,546,000	Yes
Pakistan	160,943,000	Yes
Qatar	821,000	
Saudi Arabia	24,175,000	Yes
Somalia	8,445,000	
Sudan	37,707,000	
Syria	19,408,000	
Tunisia	10,215,000	Yes
United Arab Emirates	4,248,000	
Yemen	21,732,000	

* Program with consistent annual accrual of ≥ 5 HSCT cases/year for at least 3 consecutive years

Table 2

List of the number of patients who received HSCT in various countries (data from major centers*) in the EM region and some of the main issues related to allogeneic HSCT in each country

Countries (HSCT data up to)	Allo-HSCT	Auto-HSCT	Total	Some of the Reported Special Issues
Saudi Arabia (up to Dec 2006)	2,135	654	2,789	Heavily pre-transfused aplastic anemia patients High CMV – Sero-positivity High prevalence of HBV & HCV. Poor tolerance to 4th dose (day 11) Methotrexate. Lack of national or regional registry for alternate donor program. Genetic tools for better risk profiling for GVHD needed.
Iran[5] (up to Oct 2007)	1,381	598	1,979	β-Thalassemia is common.
Egypt 4 (up to June 2007)	1,090	272 +	1,362	Low motivation of donors. Lack of matched unrelated donors. High prevalence of HBV & HCV. Schistosomiasis endemicity. High prevalence of β-thalassemia (carrier state 9-11%) and such patients are heavily pre-transfused and poorly chelated.
Pakistan[2] (up to Dec 2006)	350	50	400	Only 3 small centers for a population of 165 million. 100% CMV positive donors & patients. Patients with aplastic anemia & β-thalassemia are the most common recipients. Sub-optimal transfusion services. Endemicity of malaria, hepatitis B & C and tuberculosis. High rate of fungal infections.
Tunisia[3] (up to June 2007)	299	Data N/A	299 +	Majority of transplants are done for non-malignant disorders (mostly aplastic anemia) & Fanconi's anemia.
Jordan[6] (up to Mar. 2007)	237	83	320	Most common malignant indications are leukemia and MDS. 90% Thalassemia patients on waiting list with 3 years average waiting time. High rate of invasive fungal infection along with high cost of new antifungals.
Oman[7] (up to Aug 2006)	125	4	129	High rate of consanguinity (first cousins 24.1%). 42% transplant patients have inherited disorders including β-Thalassemia. Primary immunodeficiency increasingly being recognized as an important HSCT indication.
Lebanon[8] (up to Mar. 2007)	84	228	312	High number of thalassemia patients. High rate of consanguinity in mountainous regions.
Morocco[9] (up to May 2007)	0	27	27	Limited number of beds available for HSCT. High prevalence of sickle cell disease. Efforts to start allogeneic HSCT program are ongoing.
TOTAL	**5,701**	**1,916**	**7,617**	

N/A: Not available.

*Programs with annual accrual of ≤ 5 HSCT cases per year for at least 3 consecutive years.

Table 3

Factors associated with differences in transplant rates between European countries[40, 41]

Economic factors
Gross National Income per capita
Health care expenditures/capita
Health care system
Logistic factors
Team density
Team distribution
Local factors
Disease prevalence
Infrastructure
Ongoing studies
Unknowns

Table 4

HSCT Activity and the Related Economic/Logistic Indices in the EM Region

Countries	Population in Millions[1]	Area x 10,000 sq km	GNI per capita US$ (WHO income Category)¶	Total HSCT Performed In Major Centers	Teams Performing HSCT*	HSCT Team Density	HSCT Team Distribution
Saudi Arabia	24.175	214.969	14,740 (High)	2,789	3	1.240951	0.013956
Iran[5]	70.270	164.8	8,050 (U. Middle)	1,979	2	0.284616	0.012136
Egypt[4]	74.166	100.145	4,440 (U. Middle)	1,362 +	3	0.404498	0.029957
Pakistan[2]	160.943	80.394	2,350 (L. Middle)	400	3	0.186401	0.037316
Tunisia[3]	10.215	16.361	7900 (U. Middle)	299 +	1	0.978953	0.061121
Jordan[6]	5.729	9.23	5,280 (U. Middle)	320	1	1.745505	0.108342
Oman[7]	2.546	21.246	14,680 (High)	129	1	3.927730	0.047068
Lebanon[8]	4.055	1.04	5,740 (U. Middle)	312	2	4.932182	1.923077
Morocco[9]	30.853	4.4655	4,360 (U. Middle)	27	1	0.324118	0.223939
Afghanistan	26.088	64.75	≥ 1,000** (L. Middle)	N/A	N/A	N/A	N/A
Bahrain	0.739	0.0665	15,110 (High)	N/A	N/A	N/A	N/A
Djibouti	0.819	2.3	2,540 (L. Middle)	N/A	N/A	N/A	N/A
Iraq	28.506	43.7072	≥ 3,600** (U. Middle)	N/A	N/A	N/A	N/A
Kuwait	2.779	1.782	23,080 (High)	N/A	N/A	N/A	N/A
Libya	6.039	175.9540	≥12,300** (High)	N/A	N/A	N/A	N/A

Countries	Population in Millions[1]	Area x 10,000 sq km	GNI per capita US$ (WHO income Category)¶	Total HSCT Performed In Major Centers	Teams Performing HSCT*	HSCT Team Density	HSCT Team Distribution
Qatar	0.821	1.1437	≥ 80,900** (High)	N/A	N/A	N/A	N/A
Somalia	8.445	63.7657	≥ 600** (Low)	N/A	N/A	N/A	N/A
Sudan	37.707	250.581	2,160 (L. Middle)	N/A	N/A	N/A	N/A
Syria	19.408	18.405	3,930 (U. Middle)	N/A	N/A	N/A	N/A
United Arab Emirates	4.248	8.36	22,630 (High)	N/A	N/A	N/A	N/A
Yemen	21.732	52.797	920 (L. Middle)	N/A	N/A	N/A	N/A
TOTAL / (Mean)	**540.283**	**1296.2626**	**11252.85** (U. Middle)	**7,617**++	**17**++	**(1.5583)**++	**(0.2729)**++

N/A: Not available, **U. Middle**: Upper Middle, **L. Middle**: Lower Middle,

*Programs with annual accrual of = 5 HSCT cases per year for at least 3 consecutive years.

++Total / (mean) values from the reported 9 countries having active HSCT programs

¶Most of EMRO countries have a health care system that is economically supported by the state and acceptance at HSCT centres, where available, is through referral system.

**The quoted numbers are based on GDP per capita (2007 estimates) from https://www.cia.gov/library/publications/the-world-factbook/index.html because GNI per capita values for these 5 countries are not available on WHO EMRO site. As GNI comprises GDP plus net receipts of primary income (compensation of employees and property income) from non-resident sources, the GNI values are expected to be more than GDP.

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