

original research report

Hematopoietic stem cell transplantation practice variation among centers in the Eastern Mediterranean Region (EMRO): Eastern Mediterranean Bone Marrow Transplantation (EMBT) group survey

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INTRODUCTION: This practice survey is conducted to analyze clinical hematopoietic stem cell transplantation (HSCT) practice variability among centers in the WHO Eastern Mediterranean Region (EMRO), as represented by the Eastern Mediterranean Blood and Marrow Transplantation (EMBT) group.

METHOD: This internet based survey was completed by the medical program directors of the EMBMT centers; 17 centers participated. The survey collected data on various clinical aspects of HSCT practice.

RESULTS: Consistency in pre HSCT cardiac (100%), pulmonary (82%) and viral screen (100%) was observed. Obtaining informed consent was universal. Pre-HSCT psychological assessment is practiced in 50% of the centers. All centers used single-bedded rooms with HEPA filters. Visitor policy during neutropenic phase and the use of gowns, masks or gloves when examining patients varied among centers. MRSA/VRE screen and use of low bacterial diet were applied in 65% and 82%, respectively. Anti-bacterial prophylaxis is employed in 58% (Auto-SCT) and 60% (Allo-SCT) of the centers. Drug choice varied (cotrimoxazole, ciprofloxacin, levofloxacin, piperacillin–tazobactam); 60% of the centers used penicillin prophylaxis in GVHD patients. PCP prophylaxis is applied in 58% (Auto-SCT) and 87% (Allo-SCT) of the centers; cotrimoxazole is usually used. Anti-viral prophylaxis with acyclovir or, less commonly, valacyclovir is used in 70% (Auto-SCT) and 93% (Allo-SCT) of centers. Anti-fungal prophylaxis is applied in 70% (Auto-SCT), 93% (myeloablative Allo-SCT) and 87% (reduced intensity [RIC] Allo-SCT). Fluconazole is used in all Auto-SCT and majority of Allo-SCT recipients; few centers used other agents (itraconazole, voriconazole, amphotericin B) in Allo-SCT. Prophylactic G-CSF use varied among centers: Auto-SCT 77%, myeloablative Allo-SCT 33%, RIC Allo-SCT 27%. Use of ursodeoxycholic acid for venoocclusive disease (VOD) prophylaxis is variable: 60% (Allo-SCT) and 12% (Auto-SCT). Cyclosporine/methotrexate is the most commonly used GVHD prophylaxis in myeloablative Allo-SCT (93%); heterogeneity

was seen in RIC SCT. Treatment of steroid refractory acute GVHD varied (ATG 53%, higher steroid dose 40%). CMV monitoring varied between antigenemia (53%) and PCR (40%) techniques. Pre-emptive anti CMV therapy is used in 86% of the centers, while 7% used routine CMV prophylaxis; 7% had no specific CMV management policy.

CONCLUSION: Consistency was observed in areas of pre-SCT work up, use of single rooms, HEPA filters and GVHD prophylaxis. Heterogeneity is observed in other practice aspects including other isolation measures, anti-microbial prophylaxis, VOD prophylaxis, growth factor use and treatment of steroid refractory GVHD. Further studies are needed to probe the impact of such practice variations on post-transplant outcome and to ascertain the best clinical practice approach.

Hematopoietic stem cell transplantation (HSCT) is a therapeutic intervention provided by medical teams to patients who usually have serious medical disorders and it carries a potential for significant morbidity and mortality risks. Guidelines derived from randomized trials are available to guide practice approach in some aspects of HSCT, such as anti-microbial prophylaxis and growth factor use.¹⁻³ Conversely, other HSCT practice aspects such as isolation measures and therapy of steroid refractory acute graft versus host disease (GVHD) lack evidence-based guidance. Accordingly, practice variation is anticipated among HSCT centers. Indeed, variability of practice in the field of HSCT has been reported in the western literature, including variability among HSCT centers in prophylaxis strategies and management of post-transplant complications.⁴⁻⁷ Furthermore, individual physician practice variations have also been reported.^{8,9} A potential advantage of studying practice variability is identification of areas where dissemination of information and quality improvement systems may help improve patient care in HSCT centers.

The Eastern Mediterranean Blood and Marrow Transplantation (EMBT) group was established relatively recently and covers HSCT activity in WHO Eastern Mediterranean Region (EMRO). Local resources and socioeconomic factors may be different from Western countries, and therefore one may hypothesize variation in practice in comparison to the West. Indeed, a number of factors identified as special issues related to HSCT centers in EMBT region have been identified, including type of donor available, high prevalence of viral sero-positivity for CMV and viral hepatitis, and low HSCT team density in comparison to Western HSCT centers.¹⁰ There are no reports on HSCT clinical routine practice within the EMRO region. This EMBT practice survey is conducted with the aim of analyzing clinical

HSCT practice variability among centers in the EMBT EMRO region.

METHODS

This was an internet based survey. It was completed by the medical program directors involved in HSCT clinical practice at any of the EMBT centers. Each medical HSCT program director completed one survey questionnaire only. Practitioners involved in autologous SCT only may answer questions applicable to their field of practice and leave questions related specifically to allogeneic SCT practice blank.

The survey contained 16 items and took approximately 15–20 min to complete. The first 4 items collected information on transplant center and physician characteristics. Two items collected information about isolation practices and pre HSCT work up in SCT centers. Six items asked questions about the practice of anti-microbial prophylaxis and growth factor use in each SCT center. GVHD prophylaxis and treatment were assessed by 2 items. Two questions covered VOD prophylaxis and CMV management strategies. The concepts of this survey were discussed and approved by the EMBT members during the annual EMBT meeting in 2011. A copy of the survey may be obtained from the corresponding author.

RESULTS

HSCT center characteristics

Responses from 17 HSCT centers in 10 countries were received. These countries were Algeria, Egypt, Iran, Jordan, Lebanon, Morocco, Oman, Pakistan, Saudi Arabia and Tunisia. Sixty-five percent of these centers were academic institutions, while 35% were considered both academic and community

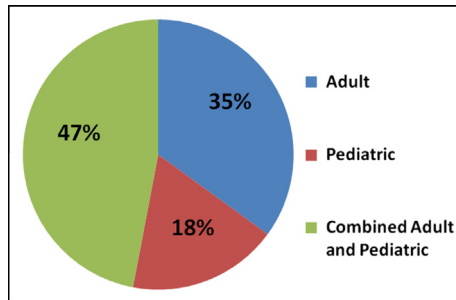


Figure 1. Practice specialty in EMBMT centers.

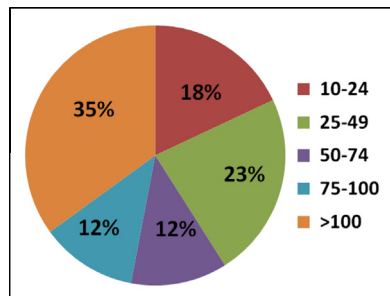


Figure 2. Number of SCT performed per year in EMBMT centers.

based. Practice specialty in these institutions varied: 35% performed adult transplants only, 18% pediatric only and 47% performed both adult and pediatric transplants (Figure 1). Faculty number within each transplant center varied widely: 59% had 3–5 faculties per center, 17% had 3 faculties, 12% 6–8 faculties and 12% had ≤ 2 faculties. The average number of transplants performed ranged between 10–24 per year, and >100 per year (Figure 2). Most institutions (88%) performed both allogeneic and autologous HSCT, while 12% performed autologous HSCT only.

Pre-SCT work up

Consistency in cardiac function assessment (100%) was seen, with all institutions reporting the implementation of formal left ventricular function assessment prior to HSCT. Majority of centers (82%) reported obtaining routine pulmonary function test as part of pre-transplant work up. Viral screen for hepatitis B and C and HIV was universal in all centers (100%). Similarly, obtaining informed consent was reported by all centers. Routine psychological assessment prior to SCT was practiced in only 50% of the centers (Figure 3). Centre specialty (adult vs. pediatric) was not clearly associated with any trend toward referring transplant recipients for psychological assessment pre-transplant. Similarly, no association was observed between psychological assessment and academic vs. academic/community based institutions.

Isolation practice

Variation in isolation practice strategies in EMBMT centers is summarized in Table 1. All centers used single bedded rooms with HEPA filters. Routine MRSA/VRE screen and use of low bacterial diet were applied in 65% and 82%, respectively. Use of gowns, masks or gloves when examining patients varied significantly between centers. Visitor policy during neutropenic phase varied among different centers: visiting was not allowed in 35% of the centers and restricted to 2 visitors at a time in 41% of the centers, while 24% of the centers reported other strategies.

Anti-microbial and growth factor prophylaxis

Routine anti-bacterial prophylaxis is applied in 58% (autologous HSCT) and 60% (allogeneic HSCT) of the centers. Significant heterogeneity was observed among centers with anti-bacterial drug used (choices included cotrimoxazole, ciprofloxacin, levofloxacin

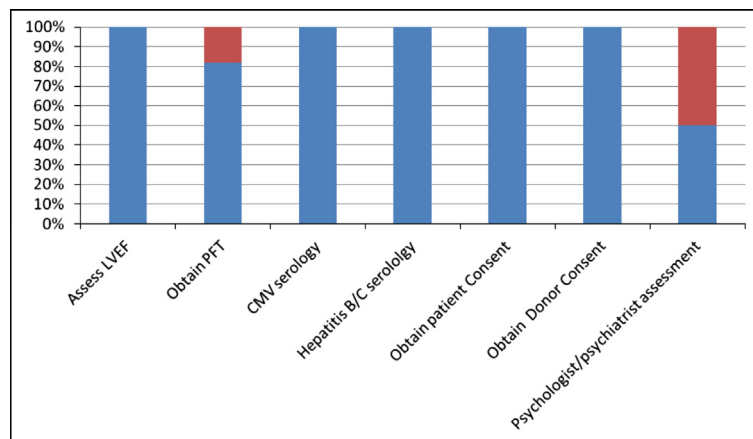


Figure 3. Pre-HSCT routine work up performed prior to HSCT in EMBMT centers. LVEF: left ventricular ejection fraction; PFT: pulmonary function test.

Table 1. Summary of variation in isolation practice strategies in EMBMT centers.

Isolation practice measure	Yes (%)	No (%)
Single bedded room	100	–
HEPA filter	100	–
Use of masks	81	19
Gloves when examining patients	53	47
Gowns when examining patients	70	30
Hand washing between patients	100	–
Routine MRSA/VRE screen	65	35
Use of low bacterial diet	82	18

and piperacillin–tazobactam). In patients with GVHD, routine penicillin prophylaxis is used in 60% of the centers.

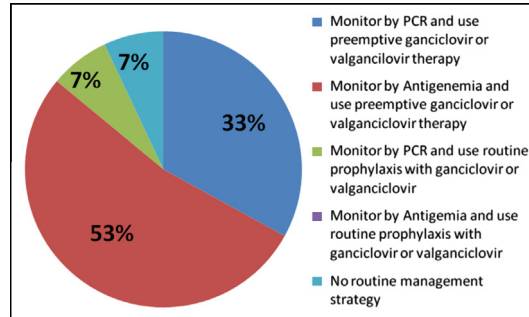
PCP prophylaxis is used in 58% (autologous SCT) and 87% (allogeneic SCT) of the centers. Among these centers, cotrimoxazole was universally used. Routine anti-viral prophylaxis is used in 70% (autologous SCT) and 93% (allogeneic SCT) of the centers, with acyclovir being the most commonly used agent and valganciclovir being used by few centers.

Anti-fungal prophylaxis in autologous SCT is applied in 70% of the centers, with fluconazole being universally used in these centers. In allogeneic SCT, anti-fungal prophylaxis is utilized in 93% (myeloablative SCT) and 87% (reduced intensity) of the centers; fluconazole was the most commonly used agent, while few centers reported using other antifungal agents (itraconazole, voriconazole and amphotericin B).

In autologous SCT patients G-CSF is routinely recommended (in the absence of febrile neutropenia or documented infection) in 77% of the centers. In allogeneic SCT recipients, prophylactic G-CSF is recommended in 33% (myeloablative SCT) and 27% (reduced intensity SCT) of the centers.

Veno-occlusive disease (VOD) prophylaxis

For autologous SCT, most centers (88%) reported not using ursodeoxycholic acid for VOD prophylaxis. In the allogeneic setting, routine use of ursodeoxycholic acid for VOD prophylaxis was reported in 60% of the centers (both in the myeloablative and reduced intensity SCT settings). There was no clear association between use of VOD prophylaxis and center specialty (adult vs. pediatric). Centers reported as purely academic were more likely to report using

**Figure 4.** CMV management strategies in allogeneic SCT in EMBMT centers.

ursodeoxycholic acid VOD prophylaxis than centers reported as being both academic/community-based.

GVHD prophylaxis and therapy

Cyclosporine/methotrexate was the most commonly reported GVHD prophylactic regimen in myeloablative allogeneic SCT setting (93%). Greater heterogeneity between centers was seen in reduced intensity allogeneic SCT: 39% reported using cyclosporine/methotrexate, 46% cyclosporine/mycophenolate and 15% other regimens. Treatment of steroid refractory acute GVHD varied between using ATG (53%) or higher steroid doses (40%). Among centers using ATG for this indication, Rabbit ATG was reported to be used in majority of cases.

CMV management strategies in allogeneic HSCT

CMV monitoring varied among centers between the use of antigenemia (53%) and PCR (40%) techniques. Pre-emptive anti CMV therapy is applied in the majority (87%) of the centers, while 7% used routine CMV prophylaxis and 7% had no specific routine CMV management policy. Summary of CMV management strategy is illustrated in Figure 4.

DISCUSSION

The present study describes the current aspects of HSCT practice within the EMBMT group in the EMRO region. We found a high degree of consistency in aspects of pre-transplant cardiac and pulmonary function assessment as well as serology screen for viral hepatitis and HIV viruses. This likely reflects the beliefs of most transplant physicians of the importance of adequate organ function prior to HSCT. Indeed, organ function assessment is fundamental in recent HSCT comorbidity scores, reflecting important prognostic information and sometimes impacting on intensity of conditioning regimen used in selected patients.¹¹

An important pre-transplant assessment tool is mental evaluation and psychological support prior to HSCT. Only 50% of the centers indicated they would routinely arrange for patients to meet with a psychologist. Clearly, the support of a psychologist may alleviate distress and fears that many patients have prior to undergoing this major therapeutic intervention with potential morbidity and mortality. Furthermore, routine psychologist interview may identify salient depression or anxiety disorders that may require intervention in these patients. In fact, some reports suggest increased mortality post HSCT in patients with pre-transplant depressive features.^{12,13} The reason for the relatively low rate of formal mental assessment prior to HSCT is not clear, but may possibly be related to unavailability of specialized staff in these centers.

HEPA filters and single bedded rooms were universal in all centers, reflecting the standard accepted practice worldwide. In contrast, there was a significant heterogeneity in other isolation measures and visitor policy during neutropenic phase, which are areas that lack specific evidence-based guidelines.

Anti-microbial prophylaxis showed significant heterogeneity among centers. This is surprising given the availability of published evidence based guidelines in this regard.^{2,3} The implementation of anti-bacterial prophylaxis was relatively low. PCP prophylaxis was used more commonly, yet a small percentage indicated PCP prophylaxis is not routinely used in all patients. Similar results pertain to anti-fungal prophylaxis. In centers practicing PCP and anti-fungal prophylaxis, there was in general consistency of agents used, with cotrimoxazole and fluconazole, respectively being most commonly used.

Although prophylactic growth factor use is more common in autologous than allogeneic HSCT, the overall pattern is not consistent with published guidelines, which recommends its use in autologous, but not allogeneic HSCT.¹⁴ Of note, there was no correlation between pattern of G-CSF and center specialty (adult vs. pediatric). Only 60% of the centers performing allogeneic HSCT reported the use of urso-

deoxycholic acid as prophylaxis for VOD. This is a potentially lethal complication post HSCT, occurring mainly in myeloablative allogeneic HSCT recipients and a number of randomized clinical trials demonstrated that ursodeoxycholic acid is effective in its prevention.¹⁵⁻¹⁷

Reports on type of GVHD prophylaxis in myeloablative allogeneic HSCT were consistent with the currently most widely used regimen, namely cyclosporine/ methotrexate. Types of GVHD prophylaxis regimen reported to be used in reduced intensity setting were more heterogeneous as expected, which is similar to practice trends in Western transplant centers. CMV monitoring and management strategies were generally consistent with current practice guidelines and trends, which favor pre-emptive rather than routine prophylaxis approach.^{3,18}

An area of potential weakness in our study is limiting the survey to program directors in EMBMT centers. However, questionnaire types in this survey were predominantly designed to answer mainly practice policy in each HSCT based on each center's standard protocol; this was felt to be answered by the program director reflecting on corresponding center's HSCT protocols. Surveys with vignette type questions enquiring about specific clinical scenario management would be more suitable to be answered by each individual HSCT physician to reflect individual practice variability.

Results of this brief survey should encourage further studies of HSCT practice in the EMRO region. In future studies, we intend to analyze individual physician variability of practices within the EMBMT region, and reflect on potential factors that may affect practice variability in this region. Our results suggest an area of potential improvement toward more consistency in practice in fields where evidence based literature and consensus guidelines are available. In cases where such evidence is lacking, demonstration of practice variability among HSCT centers reinforces the need to conduct randomized trials and observational studies in order to ascertain the best clinical practice approach.

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