A retrospective review of infections and outcomes within 100 days of hematopoietic stem cell transplantation: insights from a new transplant program in the Philippines

Jia An G. Bello [a,1], Angela Beatriz Cruz [b], Ma. Patricia Virata [b], Alma Calavera [c], Cybele L. Abad [a,1,*]

[a] *Department of Medicine – Section of Infectious Diseases, The Medical City, Ortigas Avenue, Pasig City, Philippines*
[b] *Department of Medicine, The Medical City, Ortigas Avenue, Pasig City, Philippines*
[c] *Department of Medicine – Section of Hematology, The Medical City, Ortigas Avenue, Pasig City, Philippines*

A B S T R A C T

Background: Few hematopoietic stem cell transplantations (HSCT) are performed in lower-middle income countries. Only four institutions in the Philippines are able to perform transplants. This study describes the experience of a newly established program.

Methods: The charts of all adult patients who underwent HSCT at The Medical City from May 1, 2016 to December 31, 2019 were reviewed retrospectively.

Results: A total of 33 patients were included in the cohort, of whom 31 (93.9%) underwent autologous HSCT and only two (6.1%) underwent allogeneic HSCT. Most were female (21/33, 63%), and median age was 51 years (range 21–67 years). The primary indication for transplantation was multiple myeloma ($n = 21$), followed by diffuse B-cell lymphoma ($n = 6$). Fifteen of the 33 patients had a history of treated tuberculosis (TB) disease ($n = 4$) or latent TB infection ($n = 11$). The median time for neutrophil recovery was 7.4 days (range 4–13 days). Transplant complications included neutropenic fever ($n = 33$, 100%) and mucositis ($n = 14$, 42.4%). Bacterial infection was documented in 12 (36.4%) patients, with nine (24.2%) developing a bacterial blood stream infection of which seven were related to a central line. The overall mortality rate was at 6.1% (2/33) in the first 30 days post-transplant, with no additional mortality in the succeeding days until day 100.

Conclusions: This cohort with mostly autologous HSCT had favorable outcomes in the first 100 days. Rates of bacterial infection were high in the early post-transplant period. Latent TB infection was common, but no reactivation was observed. Longer-term follow-up of patients is needed to determine late post-transplant complications and outcomes.

1. Introduction

The number of hematopoietic stem cell transplantation (HSCT) procedures has continued to rise since the initial success of this treatment in 1957, but there is a huge geographic disparity in transplantation rates, ranging from as low as 0.1/10 million population in South East Asia and Africa to as high as 100/10 million in North America and Europe (Niederwieser et al., 2016). Limitations in terms of expertise, financial restrictions, lack of a national health insurance system and governmental support, and the inability to develop local transplant centers have contributed to the overall low numbers of procedures performed (Baylon et al., 2008).

In the Philippines, the first successful HSCT was performed in 1990 in a government hospital (Baylon et al., 2008). Three decades later, only three institutions are capable of performing HSCT, with only two actively performing transplants. In 2016, The Medical City (TMC) inaugurated its own HSCT program, the fourth in the country overall. Published data on the local experience remain scarce, and gaining a perspective on

the potential infectious complications that are endemic in settings outside of the USA and Europe is also important. This study was performed to provide insights into the authors' transplant experience, focusing on early complications and outcomes of patients undergoing HSCT.

2. Materials and methods

2.1. Study design and setting

All adult patients ≥18 years old admitted to TMC for either an autologous or allogeneic HSCT from May 1, 2016 to December 31, 2019 were included in this study. There were no non-myeloablative allogeneic stem cell transplants during this period. A retrospective chart review was performed and the following information was collected and recorded: baseline demographics (including age and sex), relevant medical history (co-morbidities), history of the underlying disease (including the stage at time of transplant, remission vs relapse, prior chemotherapy, etc.), and details of the transplant (including type of donor, transplant type (autologous/allogeneic), number of CD34 cells transplanted, condi-

tioning regimen, prophylaxis and medications, and in-hospital complications (including infections). Outcomes (death or survival) at 30 days and 100 days are described. The study was conducted in accordance with ethical guidelines and with the regulatory approval of the Institutional Review Board of TMC (TMC IRB # GCS MED 2018-105).

2.2. The transplant unit

All patients are admitted to a dedicated transplant unit with eight single rooms, of which five are positive-pressure and three are negative-pressure. All patients are admitted to positive-pressure rooms unless there is an active airborne infection (e.g., tuberculosis (TB)). Fronting the unit is an ante-room for donning and doffing personal protective equipment (PPE). All providers and visitors wear disposable hair caps, gowns, and shoe covers. Each room is equipped with high-efficiency particulate air (HEPA) filters. Patients are eligible for discharge from the unit once they are clinically improved, afebrile >48 hours, engrafted (absolute neutrophil count (ANC) >500 cells/mm^3 for more than 2 days), and once they are no longer transfusion-requiring.

2.3. Pre-transplant screening, prophylaxis, and other protocols

Pre-transplant serological screening included testing for blood-borne pathogens (including HIV, hepatitis B virus, hepatitis C virus), cytomegalovirus (CMV), and herpes simplex virus 1 and 2 (HSV-1 and 2). Screening for latent TB infection (LTBI) was performed via interferon gamma release assay (IGRA), and the decision to treat was left to the discretion of the healthcare team. None of the patients were treated during the period of highest risk. All HSCT recipients were started on the following medications at the start of the conditioning regimen: ciprofloxacin 400 mg intravenous (IV)/oral (PO) every 12 hours as antibacterial prophylaxis, acyclovir at 400 mg IV/PO twice daily as antiviral prophylaxis, and fluconazole 400 mg by IV/PO once daily as antifungal prophylaxis. For allogeneic transplant recipients, an echinocandin was preferred until neutrophil engraftment, after which a shift to an oral azole was recommended and left to the discretion of the transplant team. Granulocyte-colony stimulating factor (G-CSF) was given on day 5 at 300 μg/day, until the ANC was >800 cells/mm^3.

All transplant recipients received peripheral blood stem cells. The conditioning regimen was melphalan for all myeloma patients, BeEAM (i.e., bendamustine or carmustine, etoposide, cytarabine, and melphalan) for all lymphoma patients, and busulfan, fludarabine, and cyclophosphamide for patients with acute myelogenous leukemia (AML).

2.4. Definition of terms

Febrile neutropenia was defined as a single oral temperature measurement of >38.3°C (101°F) or a temperature of >38°C (100.4°F) sustained over a 1-hour period, with an ANC of <500 cells/mm^3 or an ANC that is expected to decrease to <500 cells/mm^3 during the next 48 hours. Severe neutropenia was defined as an ANC <100 cells/mm^3 (Freifeld et al., 2011). Catheter-related bloodstream infection (CRBSI) was defined using the principle of differential time to positivity (DTP) (Raad et al., 2004). LTBI was defined as a state of persistent immune response as documented by a positive TB-specific IGRA and the absence of symptoms of active disease. Standard definitions were used for common infections such as urinary tract infection (UTI), cellulitis, and hospital-acquired pneumonia (HAP) (Gupta et al., 2011; Kalil et al., 2016).

2.5. Data analysis

Descriptive statistics were used, and the frequency distributions of demographic and clinical characteristics were determined for quantitative variables. The median was used as the measure of central tendency in this small patient population with small and large values.

3. Results

3.1. Baseline characteristics

Of the 33 patients included in the study, 21 (63.6%) were female and 12 (36.4%) were male. Median age was 51 years (range 21–67 years). An underlying lymphoid disorder was the primary reason for transplantation in an overwhelming majority (32/33, 97%). Thirty-one patients (93.9%) underwent autologous HSCT and only two (6.1%) underwent allogeneic HSCT. The median number of CD34 cells infused was 6×10^6 cells/kg body weight (range 4–23.3×10^6 cells/kg body weight). Multi-

Table 1
Characteristics of the patients included in the study

Demographics	
Sex, n (%)	
Female	21 (63.6)
Male	12 (36.4)
Age (years), median (range)	51 (21–67)
Co-morbidities, n (%)	
Diabetes mellitus	6 (18.2)
Chronic kidney disease	3 (9.1)
Hypertension	11 (33.3)
None of the above	19 (57.6)
CMV recipient serostatus, n (%)	
R+	27 (81.8)
R−	4 (12.1)
Unknown	2 (6.1)
Hepatitis status, n (%)	
HBsAg-negative	31 (93.9)
HBsAg status unknown	2 (6.1)
Anti-HCV-negative	29 (87.9)
Anti-HCV status unknown	4 (12.1)
TB status, n (%)	
IGRA-positive	11 (33.3)
IGRA-negative	12 (36.4)
History of active TB	4 (12.1)
Unknown status	4 (12.1)
HIV status, n (%)	
Reactive	0
Non-reactive	32 (97)
Unknown	1 (3)
Primary reason for transplantation	
Myeloid (AML/MDS/CML), n (%)	1 (3)
Lymphoid (ALL, CLL, HL, MM, NHL, and other lymphomas), n (%)	32 (97)
Characteristics of transplant	
Type of graft, n (%)	
Peripheral blood	33 (100)
Conditioning regimen, n (%)	
Melphalan	21 (63.6)
BEAM	10 (30.3)
Other[a]	2 (6.1)
Transplant prophylaxis	
Antifungal, n (%)	33 (100)
Non-mold active azole (fluconazole)	31 (93.9)
Echinocandin (micafungin)	2 (6.1)
Antibacterial, n (%)	
Fluoroquinolone (ciprofloxacin)	32 (97)
Trimethoprim–sulfamethoxazole	31 (93.9)
Antiviral, n (%)	
Acyclovir	33 (100)
Other transplant data	
Transfusions, number of units of pRBC until day 100, median (range)	1 (0–15)
CD34 cells $\times 10^6$/kg body weight, median (range)	6 (4–23.3)
Duration of corticosteroids (days), median (range)	6 (0–14)
Laboratory data	
Any ANC <500 cells/mm^3, n (%)	33 (100)
Duration of neutropenia (days), median (range)	
ANC <500 cells/mm^3	7.4 (4–13)
ANC <100 cells/mm^3	5.7 (2–11)
Complications	
Mucositis, n (%)	14 (42.4)

Table 1 (*continued*)

Demographics	
Documented infection, any, *n* (%)	13 (39.4)
Viral	0
Fungal	1 (3)
Parasitic	0
Bacterial	12 (36.4)
Outcome	
Length of hospital stay, median (range)	28.4 (20–46)
Relapse, *n* (%)	1 (3)
Mortality within 30 days, *n* (%)	2 (6.1)
Mortality within 31–100 days, *n* (%)	0
Cause of death, *n* (%)	
Infectious	1 (3)
Non-infectious	1 (3)

ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; ANC, absolute neutrophil count; Anti-HCV, antibodies to hepatitis C virus; BEAM, carmustine (BicNU), etoposide, cytarabine (Ara-C), melphalan; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CMV, cytomegalovirus; CVAD, cyclophosphamide, vincristine, doxorubicin; HBsAg, hepatitis B surface antigen; HCT, hematopoietic cell transplant; HL, Hodgkin lymphoma; hyperCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin; IGRA, interferon gamma release assay; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; pRBC, packed red blood cells; TB, tuberculosis.

  [a] Busulfan + fludarabine + cyclophosphamide.

ple myeloma was the main indication for HSCT (*n* = 21). Hypertension was the most common comorbidity (*n* = 11, 33.3%), followed by diabetes mellitus (*n* = 6, 18.2%) and chronic kidney disease (*n* = 3, 9.1%) (Table 1).

Of the cohort, 27 (81.8%) recipients were CMV-positive, four (12.1%) were CMV-negative, and two (6.1%) had an unknown CMV serostatus. Of the two allogeneic transplant recipients, one was CMV donor- and recipient-negative (D−/R−) and the other was CMV donor-negative and recipient-positive (D−/R+). Four (12.1%) had history of prior treatment for pulmonary TB, 11 (33.3%) had a reactive IGRA, 12 (36.4%) were non-reactive, and the rest were not tested (Table 1). All patients with a reactive IGRA were monitored closely and not given prophylaxis for LTBI.

3.2. Complications and outcomes

The median time for neutrophil recovery was 7 days (range 4–13 days) and the median length of hospital stay was 26 days (range 20–46 days). The duration of severe neutropenia was short, lasting a median of 5.7 days (range 2–11 days).

Transplant complications included neutropenic fever (*n* = 33, 100%) and mucositis (*n* = 14, 42.4%). Bacterial infection was documented in 12 (36.4%) patients, with nine (24.2%) developing a blood stream infection (BSI): eight bacterial and one (3%) fungal (*Candida* sp) BSI. Seven fulfilled the criteria for CRBSI using DTP, but four of seven had concomitant mucositis and could have had mucosal barrier injury (MBI) BSI. Of these infections, *Klebsiella pneumoniae* was the most common organism, followed by coagulase-negative staphylococci (Table 2). No patients developed CMV viremia or reactivation of TB within the first 100 days.

The overall mortality rate was at 6.1% (2/33) in the first 30 days post-transplant, with no additional mortality until day 100. The patient who underwent allogeneic HSCT for acute lymphocytic leukemia developed a cerebrovascular hemorrhage secondary to disseminated intravascular coagulation (DIC) on day 25. The other mortality was in a patient with natural killer (NK) T-cell lymphoma who developed septic shock secondary to severe *Clostridioides difficile* enteritis on day 8.

4. Discussion

The Medical City is now only one of four tertiary hospitals in the Philippines to offer HSCT. This study describes the authors' early experience with HSCT and highlights the following unique observations: autologous HSCT was associated with good outcomes; rates of early bacterial infection from CRBSI were high; and many recipients had evidence of LTBI.

Published data from the Philippines regarding transplants are scant, but an original article (Baylon et al., 2008) showed that of the first 21 transplants performed in two Philippine medical centers, 19 were allogeneic, reflecting the need for urgent transplantation in these patients. This is unusual, since it is usually recommended to start with autologous transplantations first, for several reasons: allogeneic HSCTs are very specialized, financially costly, and resource-intense, often requiring human leukocyte antigen (HLA) laboratory equipment and expertise; allogeneic transplantations also have greater morbidity due to many factors, especially graft-versus-host disease (GvHD). In contrast, autologous transplants are less complex in nature, less financially draining, and associated with much better outcomes (Chaudhri et al., 2017). In the earlier series, there were three early transplant-related mortalities (3/21, 14.3%) from *Candida* sepsis, severe sinusoidal obstruction syndrome, and multiorgan failure, respectively (Baylon et al., 2008). In the present cohort, there were only two mortalities. The short-term outcomes in this study were excellent, likely because the majority of transplants were autologous HSCT. As more transplant programs are initiated in the country, it is highly recommended to begin with autologous transplants first in order to gain experience in a subspecialty that requires particular expertise and intense resources. Autologous transplantation is indicated and offered as a best chance of cure depending on the underlying disease (e.g. multiple myeloma, diffuse large B-cell lymphoma, Hodgkin lymphoma) and disease status (remission, relapse). As such, the decision to choose it over allogeneic transplantation may not always be in the hands of the provider. Regardless, the decision to transplant is difficult and best made after careful consideration of the alternatives, risks, and benefits of the procedure (Majhail et al., 2015). It is also difficult to directly compare the efficacy of autologous and allogeneic transplants because the populations are different, but in general the former is associated with higher survival rates and better outcomes.

In the present study , the median time for neutrophil recovery was 7 days (range 4–13 days), which is shorter than in other studies, which have reported a range of 9–21 days for neutrophil engraftment in autologous recipients (Ergene et al., 2007; Gonçalves et al., 2009; Mushtaq et al., 2018; Pavlu et al., 2017), and between 16 -23 days among allogeneic recipients (Gonçalves et al., 2009). Early engraftment plays a crucial role in the success of HSCT, especially since delayed recovery is associated with higher morbidity and mortality. It is hypothesized that the shorter time to engraftment was influenced by the type of disease (mostly multiple myeloma), by giving standard doses of G-CSF per protocol (on day 5 until ANC was >800 cells/mm^3), and by the higher median number of CD34+ cells infused (6×10^6 cells/kg body weight).

Not surprisingly, the most common complications encountered in this cohort were neutropenic fever (*n* = 33) and mucositis (*n* = 14). Neutropenic fever and mucositis are not unexpected, especially after transplant, and are commonly reported (Fanning et al., 2006; Wingard et al., 2010). In this cohort, it was possible to document the source of the febrile neutropenia infection in one third (36.4%) of transplanted patients, which is consistent with the existing literature (Freifeld et al., 2011). The majority of infections were bacterial in nature, which follows the timeline of infections post-transplant (Wingard et al., 2010).

The study findings also validate existing data that BSIs in the pre-engraftment period are frequent, ranging from 5% to 47.2% (Balletto and Mikulska, 2015; Gudiol et al., 2014; Lee et al., 2016). The ma-

Table 2
Summary of infections in the study cohort

Age (years)/ sex	Types of infection	Pathogen	Timing, from day 0	Outcome
67/M	CRBSI, HAP	*Staphylococcus epidermidis*	1	Recovered
33/M	UTI/ AGE	*Klebsiella pneumoniae*	3	
25/F	Secondary bacteremia	MDR *Klebsiella pneumoniae*	3	
22/M	CRBSI, AGE	*Staphylococcus haemolyticus*	3	
56/F	HAP, Cellulitis	*Acinetobacter baumannii, Klebsiella pneumoniae, Enterobacter cloacae*	7	
42/M	CRBSI	*Staphylococcus epidermidis*	9	
25/F	UTI, HAP	*Escherichia coli*	4	
48/F	UTI	*Klebsiella pneumoniae*	7	
42/F	Secondary bacteremia	*Klebsiella pneumoniae* ESBL-positive	8	
46/M	HAP, CRBSI	*Pseudomonas aeruginosa, Staphylococcus hominis*	92	
57/F	GIT	*Clostridioides difficile*	4	Mortality
63/F	CRBSI	*Klebsiella pneumoniae* ESBL-positive	7	Recovered
61/M	CRBSI	*Staphylococcus epidermidis*	6	
28/F	CRBSI	*Candida parapsilosis*	9	

AGE, acute gastroenteritis; CRBSI, catheter-related blood stream infection; ESBL, extended-spectrum beta-lactamase; F, female; GIT, gastrointestinal tract; HAP, hospital-acquired pneumonia; M, male; MDR, multidrug-resistant; UTI, urinary tract infection.

jority of BSIs (seven of nine, 77.8%) in this cohort were deemed related to a central line infection. The study institution, which is only able to survey for CRBSI rates in the ICU, has a median rate of 2.86/1000 patient-days (range 2.35–3.79/1000 patient-days), higher than reported rates in the region at 0.77 to 2.24/1000 catheter-days (Rosenthal et al., 2016). Although some BSIs (*n* = 4) may have been from MBI (Safdar et al., 2019) given the presence of mucositis in these patients, seven of nine CRBSIs met DTP criteria, which highlights the need for more stringent infection control measures in terms of line care, as all device-related BSIs are preventable. Fortunately for all patients, bacteremia resolved with antimicrobial therapy and removal of the infected catheter.

Many patients in the study cohort had either a history of treated TB disease (*n* = 4) or evidence of LTBI (*n* = 11), which was not surprising, since the Philippines is a TB endemic country with a prevalence of 434/100 000 population among those >15 years old with acid-fast bacillus (AFB) smear-positive TB (Lansang et al., 2021). The fact that no TB reactivation was observed in the study cohort was not unexpected, since TB reactivation in autologous HSCT is extremely rare, occurring in only 4% of published cases (Abad and Razonable, 2018). This supports the close monitoring of these patients over time rather than active treatment of LTBI, which has the potential for liver-related toxicity and drug–drug interactions.

Disease relapse and infections are the most common causes of death after autologous transplant (Bhatt et al., 2015), while infections, toxicity, and GvHD are the frequent causes of death after allogeneic transplant (Styczyński et al., 2020). In the study cohort, one patient died of a cerebrovascular hemorrhage from DIC and the other died as a result of a severe *C. difficile* infection (CDI). Both occurred within 30 days of transplantation. Hemorrhagic complications such as DIC are frequently seen in post allogeneic HSCT recipients, and patients who experience these complications have an increased mortality rate, up to 25% higher than in patients who do not bleed (Inoue et al., 2018; Labrador et al., 2015). Similarly, CDI is linked to significant morbidity and mortality especially after HSCT, due to changes in the gastrointestinal tract microbiota from nosocomial and antimicrobial exposure, prolonged neutropenia, chemotherapy, and immunosuppression (Alonso and Marr, 2013; Balletto and Mikulska, 2015; Trifilio et al., 2013; Weber et al., 2020). CDI is more frequently seen among allogeneic transplants, but is also reported among autologous HSCT with a peri-transplant prevalence of 7.3%, typically occurring between day −5 to day +5 (Weber et al., 2020) similar to the patient reported here who presented with diarrhea on day +3. Early recognition and treatment of CDI in autologous transplant recipients may diminish morbidity and mortality in auto-stem cell transplants.

In conclusion, this cohort with mostly autologous HSCT had favorable outcomes in the first 100 days. Bacterial infections remain a common cause of infectious complications. Despite a significant number of recipients with LTBI, reactivation was not observed. Longer-term follow-up of patients is needed to determine late post-transplant complications and outcomes, including the potential for reactivation of LTBI. Collaboration with other institutions and the development of a national Philippine transplant registry in the future would be ideal.

Acknowledgements

We would like to thank the Medical Records Department and the Institute of Personalized Molecular Medicine for their assistance during the course of this study.

Funding source

No funding was used for this study.

Ethical approval

The work described was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Informed consent was waived and the study was approved by the Institutional Review Board of The Medical City (TMC IRB # GCS MED 2018-105).

Conflict of interest

All authors have no conflict of interest to declare.

REFERENCES

Abad CLR, Razonable RR.. An update on Mycobacterium tuberculosis infection after hematopoietic stem cell transplantation in adults. Clinical transplantation 2018;32(12):e13430.

Alonso CD, Marr KA.. Clostridium difficile infection among hematopoietic stem cell transplant recipients: beyond colitis. Current opinion in infectious diseases 2013;26(4):326–31.

Balletto E, Mikulska M.. Bacterial Infections in Hematopoietic Stem Cell Transplant Recipients. Mediterranean journal of hematology and infectious diseases 2015;7(1).

Baylon H, del Rosario M, Tiangco B.. The status of blood and marrow transplantation in Philippines. Bone marrow transplantation 2008;42(Suppl 1):S118–Ss20.

Bhatt VR, Loberiza Jr. FR, Jing H, Bociek RG, Bierman PJ, Maness LJ, et al. Mortality patterns among recipients of autologous hematopoietic stem cell transplantation for lymphoma and myeloma in the past three decades. Clin Lymphoma Myeloma Leuk 2015;15(7):409–15 e1.

Chaudhri NA, Aljurf M, Almohareb FI, Alzahrani HA, Bashir Q, Savani B, et al. Establishing an autologous versus allogeneic hematopoietic cell transplant program in nations with emerging economies. Hematology/oncology and stem cell therapy 2017;10(4):173–7.

Ergene U, Cagirgan S, Pehlivan M, Yilmaz M, Tombuloglu M. Factors influencing engraftment in autologous peripheral hematopoetic stem cell transplantation (PBSCT). Transfusion and apheresis science: official journal of the World Apheresis Association: official journal of the European Society for Haemapheresis 2007;36(1):23–9.

Fanning SR, Rybicki L, Kalaycio M, Andresen S, Kuczkowski E, Pohlman B, et al. Severe mucositis is associated with reduced survival after autologous stem cell transplantation for lymphoid malignancies. British journal of haematology 2006;135(3):374–81.

Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 2011;52(4):e56–93.

Gonçalves TL, Benvegnú DM, Bonfanti G.. Specific factors influence the success of autologous and allogeneic hematopoietic stem cell transplantation. Oxidative medicine and cellular longevity 2009;2(2):82–7.

Gudiol C, Garcia-Vidal C, Arnan M, Sánchez-Ortega I, Patiño B, Duarte R, et al. Etiology, clinical features and outcomes of pre-engraftment and post-engraftment bloodstream infection in hematopoietic SCT recipients. Bone marrow transplantation 2014;49(6):824–30.

Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 2011;52(5):e103–20.

Inoue Y, Matsunawa M, Sano F, Miura I.. Efficacy of Recombinant Human Soluble Thrombomodulin in Treating Disseminated Intravascular Coagulation Complicating Allogeneic Hematopoietic Stem Cell Transplantation. Acta haematologica 2018;140(2):121–7.

Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 2016;63(5):e61–e111.

Labrador J, López-Corral L, Vazquez L, Sánchez-Guijo F, Guerrero C, Sánchez-Barba M, et al. Incidence and risk factors for life-threatening bleeding after allogeneic stem cell transplant. British journal of haematology 2015;169(5):719–25.

Lansang MAD, Alejandria MM, Law I, Juban NR, Amarillo MLE, Sison OT, et al. High TB burden and low notification rates in the Philippines: The 2016 national TB prevalence survey. PloS one 2021;16(6).

Lee LE, Barsoumian AE, Brown AW, Wiggins MA, Renshaw JS, Osswald MB, et al. Rates of Microbiologically Diagnosed Infection and Pathogen Detection in Hematopoietic Stem Cell Transplant Patients. Military medicine 2016;181(11):e1685 -e91.

Majhail NS, Farnia SH, Carpenter PA, Champlin RE, Crawford S, Marks DI, et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation 2015;21(11):1863–9.

Mushtaq F, Farooq U, Rashid K, Junaid A, Aziz T, Iqbal Y, et al. Trends and outcomes-first 100 bone marrow transplants at a Tertiary Care Center in Islamabad, Pakistan. Bone marrow transplantation 2018;53(9):1228–30.

Niederwieser D, Baldomero H, Szer J, Gratwohl M, Aljurf M, Atsuta Y, et al. Hematopoietic stem cell transplantation activity worldwide in 2012 and a SWOT analysis of the Worldwide Network for Blood and Marrow Transplantation Group including the global survey. Bone marrow transplantation 2016;51(6):778–85.

Pavlu J, Auner HW, Szydlo RM, Sevillano B, Palani R, O'Boyle F, et al. Analysis of hematopoietic recovery after autologous transplantation as method of quality control for long-term progenitor cell cryopreservation. Bone marrow transplantation 2017;52(12):1599–601.

Raad I, Hanna HA, Alakech B, Chatzinikolaou I, Johnson MM, Tarrand J.. Differential time to positivity: a useful method for diagnosing catheter-related bloodstream infections. Annals of internal medicine 2004;140(1):18–25.

Rosenthal VD, Al-Abdely HM, El-Kholy AA, AlKhawaja SAA, Leblebicioglu H, Mehta Y, et al. International Nosocomial Infection Control Consortium report, data summary of 50 countries for 2010-2015: Device-associated module. American journal of infection control 2016;44(12):1495–504.

Safdar N, Abad CL, Maki DG. Intravascular Catheter and Implantable Device Infections in Transplant Patients Intravascular Catheter and Implantable Device Infections in Transplant Patients. In: Safdar A, editor. Principles and Practice of Transplant Infectious Diseases. New York, NY: Springer; 2019.

Styczyński J, Tridello G, Koster L, Iacobelli S, van Biezen A, van der Werf S, et al. Death after hematopoietic stem cell transplantation: changes over calendar year time, infections and associated factors. Bone marrow transplantation 2020;55(1):126–36.

Trifilio SM, Pi J, Mehta J.. Changing epidemiology of Clostridium difficile-associated disease during stem cell transplantation. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation 2013;19(3):405–9.

Weber S, Scheich S, Magh A, Wolf S, Enßle JC, Brunnberg U, et al. Impact of Clostridioides difficile infection on the outcome of patients receiving a hematopoietic stem cell transplantation. International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases 2020;99:428–36.

Wingard JR, Hsu J, Hiemenz JW.. Hematopoietic stem cell transplantation: an overview of infection risks and epidemiology. Infectious disease clinics of North America 2010;24(2):257–72.