Bone Marrow Transplantation (2018) 53:1131–1138
https://doi.org/10.1038/s41409-018-0141-5

ARTICLE

Protective environment for hematopoietic cell transplant (HSCT) recipients: The Infectious Diseases Working Party EBMT analysis of global recommendations on health-care facilities

Jan Styczynski[1] · Gloria Tridello[2] · J. Peter Donnelly[3] · Simona Iacobelli[4] · Jennifer Hoek[5] · Malgorzata Mikulska[6] · Mahmoud Aljurf[7] · Lidia Gil[8] · Simone Cesaro[2]

Received: 7 January 2018 / Revised: 28 January 2018 / Accepted: 29 January 2018 / Published online: 13 March 2018

Abstract

International guidelines on protective environment for HSCT recipients proposed a set of 10 global recommendations in 2009 on protective environment (GRPE) concerning hospital room design and ventilation. The EBMT Infectious Diseases Working Party undertook a survey on the status on protective environment for HSCT recipients with the aim of surveying current practices and their agreement with GRPE recommendations. The questionnaire consisted of 37 questions divided into 5 sections about filtration, air changes, maintenance, and the protective environment in rooms and the surrounding unit. Overall, 177 centres (response rate 33%) from 36 countries responded, indicating that 99.4% of patient rooms were equipped with HEPA filters, but only 48.6% of the centre's staff were aware of, and could confirm, regular replacement of filters based on manufacturers' recommendations. Well-sealed rooms were used in terms of windows (70.6%), ceilings (35%), and plumbing pipes (51.4%). The sensor monitors in the patient room used to determine when the HEPA filters require changing were installed only in 18.1% of centres. Only 1 centre fulfilled all 10 GRPE recommendations, while 62 centres fulfilled the 3 level "A" recommendations. In conclusion, HEPA-filtered rooms are available in almost all centres, while fewer centres fulfilled other requirements. Knowledge on the details and maintenance of protective environments in the HSCT setting was inadequate, reflecting a lack of communication between the health personnel involved, hospital infection control and the hospital maintenance services.

Introduction

The Centre for International Blood and Marrow Transplant Research (CIBMTR) coordinated the Guidelines for Preventing Infectious Complications among Hematopoietic Stem Cell Transplantation (HSCT) recipients [1]. International guidelines on protective environment for health-care facilities in which HSCT recipients are treated as announced in 2009 by CIBMTR, National Marrow Donor Program (NMDP), European Society for Blood and Marrow Transplantation (EBMT), American Society for Blood and Marrow Transplantation (ASBMT), Canadian Blood and Marrow Transplant Group (CBMTG), Infectious Diseases Society of America (IDSA), Society for Healthcare

Electronic supplementary material The online version of this article (https://doi.org/10.1038/s41409-018-0141-5) contains supplementary material, which is available to authorised users.

✉ Jan Styczynski
jstyczynski@cm.umk.pl

[1] Department of Pediatric Hematology and Oncology, Nicolaus Copernicus University Torun, Collegium Medicum, Bydgoszcz, Poland

[2] Department of Pediatric Hematology Oncology, Azienda Ospedaliera Universitaria Integrata, Policlinico G.B. Rossi, Verona, Italy

[3] Department of Haematology, Radboud UMC, Nijmegen, The Netherlands

[4] Department of Biology, University of Tor Vergata, Rome, Italy

[5] EBMT Data Office, Leiden, The Netherlands

[6] Division of Infectious Diseases, Department of Health Sciences, University of Genova, Ospedale Policlinico San Martino, Genova, Italy

[7] Oncology Centre, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia

[8] Department of Hematology, Medical University, Poznan, Poland

Epidemiology of America (SHEA), Association of Medical Microbiology and Infectious Disease (AMMI), and Centres for Disease Control (CDC), hereby referred as Global Recommendations on Protective Environment (GRPE).

A set of 10 recommendations, based on CDC criteria, were presented with respect to guidelines on hospital room design and ventilation for HSCT setting (Supplementary Tables 1 and 2) [1–3]. Specifically, HSCT recipients should ideally be accommodated in a protective environment that incorporates several features, including central or point-of-use HEPA (high-efficiency particulate air) filters with 99.97% efficiency for removing particles ≤0.3 μm in diameter, and ≥12 air exchanges per hour. As there were no well-executed randomised or controlled trials, very little evidence to hand from cohort case-controlled or multiple time-series studies and limited data from uncontrolled experiments, reliance had to be placed on descriptive studies, reports of expert committees or on the opinions of respected authorities. Hence, these recommendations could only be based on level III evidence.

Since the issue is clearly of practical importance to the global transplant community, the Infectious Diseases Working Party (IDWP) of the EBMT created a survey in order to determine the current status on protective environment for HSCT recipients with the aim of reporting current practices in hospital transplant room design and ventilation and their agreement with GRPE recommendations.

Methods

The questionnaire

A total number of 543 registered EBMT centres were invited to complete the questionnaire and return it to the EBMT Data Centre to establish what is actually done in Europe to fulfil the norms proposed. The questionnaire was designed to capture sufficient information to assess how many centres were able to meet the criteria proposed in the guidelines and also to gain an accurate impression of what was done to provide a protective environment. The questionnaire consisted of 37 questions in all (Supplementary Table 3) and was divided into 5 sections, which included the contact information and details of the protective isolation facility, including air filtration, air changes, maintenance, combination of isolation, protective environment room/unit and floor. Centres were asked to complete the form on a single computer and responses could be updated while the survey was open online from April to December 2012. The information obtained was handled to guarantee the anonymity of each centre. Only those questions that corresponded directly to the GRPE recommendations were used to assess whether centres were able to comply (Supplementary Table 1).

Definitions

HEPA filter was defined as a high-efficiency particulate air filter with a 99.97% efficiency for removing particles ≥0.3 μm in diameter.

A laminar air-flow room was one that contains HEPA-filtered air that moves in a parallel, unidirectional flow, i.e., the air enters the room from one wall and exits the room from the other wall.

Combined room was a room designed to accommodate patients for isolation to protect against air-borne infection and provide protective environment by means of laminar air flow and positive air pressure.

Statistical analysis

Descriptive statistics were computed for each variable with absolute and percentage frequencies being reported. Percentage of known and missing information were also reported. A statistical comparison was performed in order to detect differences in the proportion of information known according to the function of person completing the survey. Comparisons were performed using X^2 test or Fisher's exact test, as appropriate. A p value < 0.05 was considered statistically significant. All the analyses were performed using SAS v. 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Contact information

Overall, 238 (38.3%) of 543 centres from 37 countries responded and returned the questionnaire. However, reliable information was provided by 177 (32.6%) centres from 36 countries once duplicate responses had been eliminated, with an average response rate of 33% per country. Physicians completed 62%, nurses 19% and support staff 19% of the survey questionnaire. A total number of 71% of answers were provided to all questions. The total number of answered questions was higher among physicians than among other staff: 84% (range, 6–100%) vs. 63% (range, 3–97%), $p < 0.001$.

Responses were given from European countries ($n = 25$), Africa ($n = 3$), Asia ($n = 3$), South America ($n = 2$), Canada ($n = 1$), Australia ($n = 1$) and New Zealand ($n = 1$). The responding centres cared for adults ($n = 93$; 52.5%), children ($n = 32$; 18.1%), adults and children ($n = 41$; 23.2%), while 11 (6.2%) centres did not specify the age of patients.

Table 1 Overall positive results of the survey with respect to Global Recommendations GRPE

Protective environment recommendation	Grading[a]	Survey question (Q)	Positive response	Total (%)
1. Ventilation: ≥12 air changes per hour.	AIII	Does the room have at least 12 air changes per hour? (Q9)	Yes	126 (71.2%)
2. Central or point-of-use HEPA filters with 99.97%efficiency for removing particles ≤0.3 µm in diameter.	AIII	Are your patient rooms equipped with HEPA filters? (Q6)	Yes	176 (99.4%)
		If yes, please specify (Q7)	Central	81 (45.8%)
			Local	85 (48.0%)
		Do you have HEPA filters with 99.97% efficiency for removing particles ≤0.3 µm in diameter? (Q12)	Yes	124 (70.1%)
3. Filters should be replaced regularly based on manufacturers' recommendations, and, when there is ongoing construction, filtration efficiency should be monitored frequently to best determine appropriate time for replacement.	AIII	How often are the filters changed? (Q14)	Regularly	52 (48.6%)[b]
		Do you have a written procedure for filter maintenance and removal? (Q15)	Yes	95 (53.7%)
4. Directed airflow so that air intake occurs at one side of the room and air exhaust occurs at the opposite side.	BIII	Is the airflow directed so that air intake occurs at one side of the room while the air exhaust occurs at the opposite side? (Q18)	Yes	105 (59.3%)
5. Consistent positive air pressure differential between the patient's room and the hallway ≥2.5 Pa (i.e., 0.01 inches by water gauge).	BIII	Is there a permanently installed device / mechanism to constantly monitor the differential air pressure between the room and the corridor? (Q20)	Yes	68 (38.4%)
		What is the pressure in the anteroom? (Q23)	Positive	34 (19.2%)
		Is there an air pressure monitoring device / mechanism in the anteroom in addition to the patient's room? (Q24)	Yes	31 (17.5%)
6. Well-sealed rooms (e.g., filling the gaps between walls and windows, outlets, floor, and ceiling) should always be used for HCT patients to prevent infiltration of air from outside the room that could allow entry of spores and hinder maintenance of proper pressure differential.	BIII	Are the room windows sealed to eliminate infiltration from outside? (Q27)	Yes	125 (70.6%)
		Do the protective environment rooms have monolithic ceilings? (Q28)	Yes	62 (35.0%)
		Are all plumbing pipes in the room sealed around wall penetrations? (Q29)	Yes	91 (51.4%)
7. Continuous pressure monitoring, especially while rooms are occupied.	BIII	Is there a monitoring system that will set off an alarm when the pressure differential between any protective environment room and adjacent hallway or anteroom falls to less than 2.5 Pa to alert staff to possible engineering failures? (Q34)	Yes	60 (33.9%)
8. Self-closing doors to maintain constant pressure differentials.	BIII	Are there self-closing doors to maintain constant pressure differentials? (Q33)	Yes	66 (37.3%)

Table 1 (continued)

Protective environment recommendation	Grading[a]	Survey question (Q)	Positive response	Total (%)
9. Consideration should be given to using monitoring systems that will set off an alarm when the pressure differential between any protective environment room and adjacent hallway or anteroom falls to less than 2.5 Pa, to alert staff to possible engineering failures.	CIII	Is a sensor monitor installed in the patient room used to determine when the HEPA filters require changing? (Q13)	Yes	32 (18.1%)
10. To enable the nursing staff to observe the HCT recipient even when the doors are closed, windows can be installed in either the door or the wall of the HCT recipient's room.	CIII	Are the nursing staff able to observe the patient even when the doors are closed? (Q35)	Yes	109 (61.6%)

[a]Grading according to [1, 3]

[b]Answers to Q14 were provided only when answer to Q13 was "no" ($n = 107$)

The rate of results fulfilling GRPE recommendations are shown in Table 1 with further details shown in Supplementary Tables 4A, B, C and D.

Air filtration and air changes

Among the participating centres, 99.4% of patient rooms were equipped with HEPA filters, with central or point-in-use room system being used in 45.8% and 48%, respectively (Supplementary Table 4A). The use of HEPA filters with 99.97% efficiency for removing particles ≤ 0.3 μm in diameter, and room ventilation with the rate of at least 12 air changes per hour were confirmed by 70.1% and 71.2% of centres, respectively. Only 48.6% of centre staff were aware of, and could confirm, regular replacement of filters based on manufacturers' recommendations, while 53.7% centres had a written procedure (Supplementary Table 4B) for regular filter maintenance and removal and to monitor filtration efficiency in order to best determine appropriate time for replacement, especially in case of ongoing construction. In 48% of centres, the transplant staff had access to air changes measurements, and in 18.1% a sensor monitor was available in the patient's room.

Maintenance

Half of the centres (50.3%) were using pre-filters (Supplementary Table 4B). In 59.3% centres, the airflow was directed so that air intake occurred at one side of the room while the air exhaust was placed at the opposite end, and 42.9% centres were equipped with a particle counter. A consistent positive air pressure differential between the patient's room and the hallway ≥ 2.5 Pa (i.e., 0.01 inches by water gauge) was reported by 38.4% centres that had a permanently installed device/mechanism to constantly monitor the differential air pressure between the room and the corridor. A policy for cleaning air duct grills was available for the transplant staff in 58.2% centres.

Combined air-borne infectious isolation and protective environment room

Combined rooms and anterooms were available in 52% and 45.8% of centres, respectively (Supplementary Table 4C), although most of the centres (85.9%) reported that they needed combination rooms. The pressure in the anteroom was reported to be positive in 19.2% centres, and negative in 19.8% centres, while an air pressure monitoring device/mechanism in the anteroom in addition to the patient room was present in 17.5% of centres. The ability to reverse the air flow in the patient's rooms was reported by 16.9% centres.

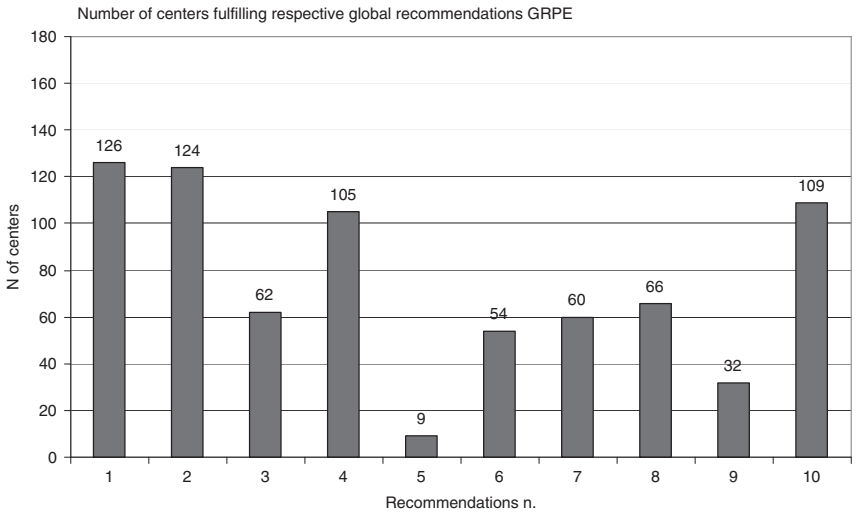

Fig. 1 Number of centres fulfilling respective Global Recommendations GRPE. Recommendations 1–3 are graded AIII, 4–8 graded BIII and 9–10 graded CIII

Well-sealed rooms were used in order to prevent infiltration of air from outside the room that could allow entry of spores and hinder maintenance of proper pressure differential, with respect to: windows (70.6%), monolithic ceilings (35%), and plumbing in the room (51.4%) of centres. Periodic air samples were cultured for fungi in 54.2% of centres.

Unit and floor

The heating ventilated air conditioning system and emergency power was present in 62.7% and 58.2% of centres, respectively (Supplementary Table 4D). In order to guarantee the continuous positive pressure, a monitoring system that would set off an alarm when the pressure differential falls to <2.5 Pa between the room and the adjacent hallway or anteroom to alert staff to possible engineering failures was installed in 33.9% of centres. Self-closing doors to maintain constant pressure differentials were present in 37.3% of centres. The sensor monitors in the patient room that is used to determine when the HEPA filters required changing was installed in 18.1% of centres. The nursing staff was able to observe the HSCT recipient through a window installed in the door or wall of the HSCT recipient's room or by a monitoring system was present in 61.6% of centres. In 38.4% of centres, protective isolation rooms were also available in Intensive Care Units (ICU) with signage being present in 70.6% cases to identify them clearly.

Overall ability of centres to fulfil the recommendations

Knowledge about the presence and maintenance of protective environment among the staff of HSCT units was limited, reflecting a lack of communication between health personnel working in the ward and hospital maintenance services. The rate of centres fulfilling respective survey questions corresponding to specific recommendations ranged between 17.5 and 99.4% (Table 1), while the rate of centres fulfilling complete requirements of respective recommendations ranged between 5 and 71% (Fig. 1). Only 1 centre was able to meet all 10 Global Recommendations GRPE [1] and few centres were able to meet all the relevant technical requirements (Fig. 2). Only 16 out of 53 (30.2%) JACIE accredited centres scored 3 out of 3 level "A" recommendations.

Discussion

This survey among EBMT centres was designed to determine the current status of technical aspects of protective environment and isolation facilities for recipients of HSCT and current practices in hospital transplant room design and ventilation and to assess their compliance with the 2009 GRPE recommendations [1]. Certain sections of the survey were dedicated to details of air filtration, air changes, maintenance, combined of air-borne infection isolation and protective environment room, ventilation systems for unit and floor in transplant centres. Direct anti-infective management of transplant patients was not the subject of this study.

The response rate to this IDWP survey was 32.6%, which is relatively high compared to other EBMT surveys. Some questions only required knowledge of the accommodation such as monolithic ceilings, ability to observe the patient, whereas others required access to engineer's reports on filter maintenance and monitoring systems. Establishing certain details such as the number of air exchanges or the efficiency and regular changes of the filters (GRPE 5 and GRPE 9) were found to be most difficult for personnel of

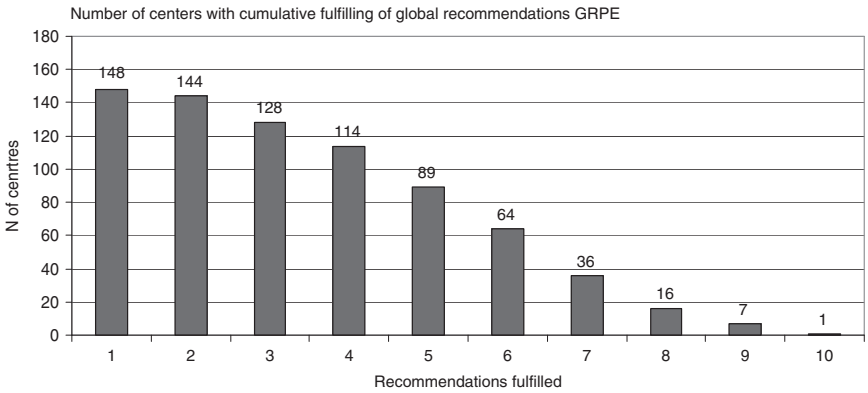

Fig. 2 Number of centres which fulfilled a specific number of GRPE recommendations

Table 2 Proposed recommendations for responsibilities of health-care and hospital personnel regarding supervision of protective environment facilities in transplant ward

Health-care Personnel	Responsibility of supervision of protective environment facilities	Estimated frequency	GRPE grading and respective number of recommendation
Transplant ward personnel			
Physician in charge	HEPA filters	Yearly	AIII (1–3)
Physicians	Directed airflow in the patient's rooms	Daily	BIII (4)
Nurse in charge	HEPA filtration efficiency	Yearly	AIII (1–3)
	Continuous pressure monitoring system	Daily	BIII (7)
	Monitoring system alarm	Daily	CIII (9)
Nurses	Continuous observation of patients (visual monitoring system)	Daily	CIII (10)
Cleaning staff	Function of self-closing door	Daily	BIII (8)
	Quality of sealing (floors, ceilings, plumbing pipes)	Before new patient admission	BIII (6)
Hospital technical personnel			
Hospital environmental services	HEPA filters maintenance and exchange	Yearly	AIII (1–3)
	Air pressure in the patient's rooms	Yearly	BIII (5)
Transplant ward personnel + hospital technical personnel			
All members of transplant personnel and hospital technical personnel	Common analysis of all aspects of protective environment	Yearly	Recommendations GRPE 1–10

HSCT units, whilst almost everyone reported that patient rooms were equipped with HEPA filters (GRPE 1 and GRPE 2). Similarly, only a few could confirm whether the pressure in the anteroom was monitored or not and provide affirmative answers to questions about ceilings and monitoring.

An earlier survey of the EBMT conducted in 2008 reported that most recipients of an allogeneic HSCT were housed in HEPA-filtered rooms, however, it concluded that recommendations for accommodating patients who were colonised or infected with an opportunistic pathogen were either poorly understood or not properly implemented [4].

Most centres were unable to show that their centre had implemented the recommendations endorsed by the EBMT, even the most important ones. This may be due to two factors. Firstly, the lack of specific technical facilities in the transplant ward. Secondly, physicians and other health care personnel of transplant ward do not have ready access to the necessary information on technical matters in their own centre. This also makes it difficult for inspectors to determine whether the protective isolation provided in a given centre meets the required standards.

Protective isolation in various forms has been promoted for patients with neutropenia for nearly 50 years [5]. However, there has been no economic analysis to show that it is cost-effective. Indeed, the data showing that protective isolation prevents infection is sparse and arose from the experience of a few early pioneers [6]. Others have

questioned the practice altogether as they could not find any benefits in terms of reducing infection and suggested that accurate hygiene measures would prove just as effective, while improving the quality of care and patient satisfaction as well as being less expensive [7]. There are also adverse effects of protective isolation to consider, not least that patients can suffer from being isolated in every sense of the word [8–10].

This survey shows that knowledge about the maintenance of protective environments in the HSCT setting is inadequate, reflecting poor communication between health care personnel working in the ward, hospital infection control and hospital maintenance services. Only one centre was able to meet all 10 GPRE recommendations listed by Tomblyn et al. [1] and only few centres were able to meet all the relevant technical requirements. This may simply be a consequence of the fact that, in most cases, transplant wards were constructed many years ago and major reconstruction is either not possible or is prohibitively expensive. Hence, maintaining the current technical structure and facilities in the transplant ward is crucial to ensure protective environment for transplant patients.

The results of the survey show that, in general, health care personnel are interested in implementation of procedures shown to be protective (i.e., HEPA filters) but not in maintenance, which falls to other services to deal with. Although detailed knowledge about protective environments in the HSCT setting is not necessary for all health care staff, communication between them and hospital engineering services is mandatory for effective prevention of infectious complications.

We suggest that dedicated health care personnel should be selected to cooperate with the appropriate hospital maintenance services with regard to:

Review of type and incidence of selected infections either once yearly or after introduction of new equipment, and their association with protective environment systems and what has been changed;
Provide general information on protective environments to health care staff, patients and their relatives on notice boards of the ward/department;
Ensure detailed information on protective environments is easy to find;
Offer training in the field annually in order to inform and highlight the importance of the protective environment;
Undertake economic analysis to estimate cost effectiveness.

A protective environment plays a key role in ensuring the safety of patient after transplant so we propose a range of responsibilities for the transplant team in order to ensure they possess sufficient knowledge about what this entails (Table 2). It should be noted that daily check-up performed by physicians, nurses and cleaning staff is based on routine activity and does not require additional work, except when reporting failures in the system. A meeting of transplant ward personnel and hospital technical personnel responsible for environmental services is recommended once a year. In parallel, hospital infection control group should implement and run program of epidemiology, prophylaxis and management of infections in transplant unit.

In conclusion, GRPE recommendations on the technical aspects of protective isolation were based on expert opinion and very limited data and the results of this IDWP survey provide an overview of whether or not they are being fulfilled. It was clear that knowledge on the details and maintenance of protective environments in the HSCT setting was inadequate reflecting a lack of communication between the health personnel involved, hospital infection control and the hospital maintenance services.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15:1143–238.
2. Yokoe D, Casper C, Dubberke E, Lee G, Munoz P, Palmore T, et al. Infection prevention and control in health-care facilities in which hematopoietic cell transplant recipients are treated. Bone Marrow Transplant. 2009;44:495–507.
3. Centers for Disease Control and Prevention; Infectious Disease Society of America, American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep. 2000;49:1–125.
4. Hicheri Y, Einsele H, Martino R, Cesaro S, Ljungman P, Cordonnier C. Environmental prevention of infection in stem cell transplant recipients: a survey of the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Transpl Infect Dis. 2013;15:251–8.
5. Lynch J, Jameson B, Gamble DR, Kay HE. Five-year analysis of protective isolation. Lancet. 1971;1:1034–40.
6. Eckmanns T, Ruden H, Gastmeier P. The influence of high-efficiency particulate air filtration on mortality and fungal infection among highly immunosuppressed patients: a systematic review. J Infect Dis. 2006;193:1408–18.
7. Mank A, van der Lelie H. Is there still an indication for nursing patients with prolonged neutropenia in protective isolation? An evidence-based nursing and medical study of 4 years experience for nursing patients with neutropenia without isolation. Eur J Oncol Nurs. 2003;7:17–23.
8. Vottero B, Rittenmeyer L. The hospitalised patients' experience of being in protective/source isolation: A systematic review of qualitative evidence. JBI Libr Syst Rev. 2012;10:935–76.
9. Biagioli V, Piredda M, Alvaro R, de Marinis MG. The experiences of protective isolation in patients undergoing bone marrow

or haematopoietic stem cell transplantation: systematic review and metasynthesis. Eur J Cancer Care. 2017;26. https://doi.org/10.1111/ecc.12461. Epub 2016 Feb 19.

10. Biagioli V, Piredda M, Mauroni MR, Alvaro R, De Marinis MG. The lived experience of patients in protective isolation during their hospital stay for allogeneic haematopoietic stem cell transplantation. Eur J Oncol Nurs. 2016;24:79–86.