Biol Blood Marrow Transplant 24 (2018) 1721–1726

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

De-Escalation and Discontinuation of Empirical Antibiotic Treatment in a Cohort of Allogeneic Hematopoietic Stem Cell Transplantation Recipients during the Pre-Engraftment Period

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Article history:
Received 1 February 2018
Accepted 18 March 2018

Key Words:
De-escalation
Discontinuation
Neutropenia
Hematopoietic stem cell transplantation
Bloodstream infections
Fluoroquinolone prophylaxis

A B S T R A C T

To investigate rates and outcomes of antibiotic de-escalation during pre-engraftment neutropenia in allogeneic hematopoietic stem cell transplantation (HSCT) recipients. 110 consecutive HSCTs performed between January 2013 and March 2014 were analyzed. De-escalation was defined as narrowing the spectrum of antibiotic treatment either within (early) or after 96 hours (late) from starting antibiotics. Discontinuation, considered a form of de-escalation, was defined as stopping antibiotics before engraftment. De-escalation failure was defined as restarting/escalating antibiotics within 96 hours after de-escalation. Predictors of de-escalation were analyzed. Among 102 patients who started antibiotics and were included, 68 (67%) received monotherapy (mainly piperacillin-tazobactam, n = 58), whereas 34 (33%) received combination therapy (mainly meropenem plus glycopeptide, n = 24). Median duration of neutropenia was 17 days. Bloodstream infections (BSIs) were diagnosed in 28 patients (20%). Early de-escalation rate was 25.5% (n = 26) and mostly consisted of reducing the spectrum of β-lactams (n = 11, 42%). In comparison with theoretical scenario of continuing therapy until engraftment, the median savings in terms of antibiotic days were 10 for meropenem, 8 for piperacillin-tazobactam, and 7 for vancomycin. Failure rate of early de-escalation was 15% (4/26). Late de-escalation rate was 30.4% (n = 31) and failure rate 19% (6/31). The rate of de-escalation any time before engraftment was 55.9% (n = 57), including discontinuation in 33 patients (32%). Death at day 60 after HSCT occurred in 3 patients who never underwent de-escalation. Acute myeloid disease and BSIs were independent predictors of early de-escalation. De-escalation, including discontinuation, is feasible and safe in pre-engraftment neutropenia after allogeneic HSCT.

INTRODUCTION

The worldwide emergence of multidrug-resistant (MDR) bacteria is an alarming phenomenon burdened by increased mortality rates [1], with figures up to 46% and 42% among patients with hematologic malignancies in cases of carbapenem-resistant *Klebsiella pneumoniae* and MDR *Pseudomonas aeruginosa*, respectively [2]. Hematopoietic stem cell transplantation (HSCT) recipients, with their prolonged neutropenia and previous exposure to multiple antibiotic therapies, represent a population at high risk for adverse outcomes in case of MDR bacteria infections [3].

Counteracting the spread of MDR bacteria requires effective application of infection control protocols and the judicious prescription of antibiotics within dedicated stewardship programs [4]. Hence, several strategies have been developed, including the de-escalation approach proposed by the Fourth European Conference on Infection in Leukemia. This approach consists of prompt administration of a broad-spectrum treatment as soon as infection is suspected and subsequent streamlining within 96 hours [5]. A de-escalation strategy allows the best possible coverage of resistant pathogens immediately at the onset of signs and symptoms and subsequent reduction of selective pressure on bacteria through narrowing the spectrum if resistant bacteria are not isolated.

Financial disclosure: See Acknowledgments on page 1725.
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https://doi.org/10.1016/j.bbmt.2018.03.018
1083-8791/

Data regarding the rates and outcomes of de-escalation strategy are mostly provided by observational studies, and only 4 randomized clinical trials have been conducted to date [6-9]. Almost all studies have been performed in intensive care units (ICUs), and definitions and timing of de-escalation varied significantly [10]. In addition, only few studies and 1 recent randomized trial have focused on neutropenic cancer patients [9,11-14], but very limited data are currently available on the pre-engraftment period in HSCT. The safety of discontinuation of empirical treatment before the resolution of neutropenia has also been a source of debate [15,16]. The purpose of this study was to report the rates and outcomes of de-escalation (including discontinuation) during the pre-engraftment phase of allogeneic HSCT in patients with fever or infection and neutropenia.

METHODS

Patients

A retrospective observational study based on a prospective database was conducted at the Hematology Division of Ospedale Policlinico San Martino (Genoa, Italy). All patients receiving allogeneic HSCT between January 2013 and March 2014 were included.

Transplant Procedures

Donor choice, conditioning regimen, and graft-versus-host disease prophylaxis were performed according to local standard procedures [17,18]. Unmanipulated bone marrow was used as a stem cell source for related donors. In case of haploidentical donors, graft-versus-host disease prophylaxis consisted of cyclophosphamide 50 mg/kg on days +3 and +5, cyclosporine A until day +180, and mycophenolate mofetil from days +1 to +28 [19,20].

All patients received levofloxacin prophylaxis from the onset of conditioning until engraftment. Based on local epidemiology [21], first-line antibiotic treatment during neutropenia was piperacillin-tazobactam, whereas patients with severe clinical presentation or colonization and previous infection due to extended-spectrum β-lactamase–producing bacteria received meropenem. Methicillin-resistant *Staphylococcus aureus* (MRSA) coverage was added according to international guidelines [5,22].

Definitions

Neutropenia was defined as a granulocyte count < 500 cells/mm^3 and the engraftment date as the first of 3 consecutive days with neutrophils above 500 cell/mm^3 [3]. In case of nonengraftment, the follow-up was considered until day +60 after transplant or the day of second transplant, whichever occurred first.

Since 2012, a de-escalation strategy has been introduced in our center as a part of antimicrobial stewardship, with particular emphasis on preventing the selection of carbapenem-resistant strains [23]. De-escalation of empiric antibiotic treatment was defined as switching to a narrower spectrum β-lactam or stopping any antibiotic. Discontinuation, defined as stopping empirical therapy and resuming fluoroquinolone (FQ) prophylaxis at any time before the engraftment, was considered a form of de-escalation. Failure of de-escalation (including discontinuation) was defined as escalating/restarting antibiotic therapy, having a BSI, or fever recurrence within 96 hours from de-escalation/discontinuation.

Endpoints

The primary endpoint was the rate of early de-escalation, within 96 hours from the onset of the first antibiotic treatment, in agreement with recommendations [5]. Secondary endpoints were the rates of late de-escalation (after 96 hours of the antibiotic treatment), de-escalation occurring any time before engraftment, the number of days of antibiotic therapy saved by de-escalation, and outcomes (failure and survival at day +60).

Because traditionally empirical antibiotic therapy is stopped on the day of neutropenia resolution, the benefit in terms of saving days of antibiotic exposure through de-escalation was evaluated. Briefly, it was calculated by counting the number of days from the day of de-escalation to the day of the resolution of neutropenia, which in the theoretical scenario of continuing empirical therapy unmodified until engraftment would be the additional length of antibiotic administration. Factors associated with de-escalation were also investigated.

Statistical Analyses

The differences between the groups (de-escalation yes versus no) were assessed by means of the chi-square test or Fisher's exact test when appropriate for categorical variables and with Mann-Whitney test for continuous variables. Continuous variables were reported as median values with range. A backward multivariate logistic regression analysis included all variables associated in the univariate analysis with a $P < .2$. The analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY), and $P \leq .05$ was considered statistically significant.

RESULTS

Patients and Infections

Overall, 110 consecutive HSCT recipients received transplant during the study period, and their characteristics are reported in Table 1. Acute myeloid diseases (acute myelogenous leukemia or myelodysplastic syndrome) were the most frequent underlying disease (n = 52, 47%), whereas the most frequent donor was haploidentical (n = 76, 69%). The median length of neutropenia was 17 days in those who engrafted (range, 10 to 29); 6 patients did not reach engraftment (6%), and 3 of them received a second HSCT. The overall survival rate at day 60 post-HSCT was 97%.

Among 110 patients transplanted during the observation period, 8 patients (7%) did not receive antibiotic treatment and were not included in the study. The remaining 102 patients started antibiotic treatment because of fever (n = 100, 98%) or skin lesions suggesting bacterial infections (n = 2, 2%).

The first episode of suspected or documented infection was treated with monotherapy in 68 patients (67%), divided

Table 1
Population Characteristics of 102 Patients Included in the Analyses

Baseline variables	No. of Patients (%)
Gender	
Male	61 (59.8)
Female	41 (40.2)
Median age, yr (range)	48 (18-69)
Underlying disease	
Acute myeloid leukemia	52 (47)
Acute lymphoproliferative	25 (23)
Chronic lymphoproliferative	18 (16)
Chronic myeloproliferative	14 (13)
Aplastic anemia	1 (1)
Status of the underlying disease at transplant	
In remission	72 (65.5)
Active	38 (34.5)
Year of HSCT	
2013	91 (82.7)
2014	19 (17.3)
Donor type	
Matched related	21 (19)
MUD/MMR	13 (12)
Haploidentical*	76 (69)
Conditioning	
Myeloablative	59 (54)
Reduced intensity	51 (46)
Outcome variables	
Febrile episodes	
None	10 (9)
1	59 (54)
2	29 (26)
≥ 3	12 (11)
BSIs	
None	82 (74.5%)
1†	20 (18.2%)
≥ 2‡	8 (7.3%)

MUD indicates matched unrelated donor; MMR, mismatched related.

* In case of haploidentical donor, prophylaxis of graft-versus-host disease included of 2 doses of post-transplant cyclophosphamide.

† Causative pathogens: *E. coli* in 8, methicillin-resistant *Staphylococcus epidermidis* (MRSE) in 5, *S. aureus* and *Streptococcus mitis* in 2 each, *Pseudomonas* spp., and *Enterococcus faecium* and *Enterobacter cloacae* in 1 each.

‡ Causative pathogens: 2 episodes due to *E. coli;* 2 episodes due to *E. faecium*, *E. coli* and MRSE, *E. coli* and *E. faecium*, MRSE and *E. faecium*, *Pseudomonas aeruginosa and E. faecium*, *P. aeruginosa and S. viridans*, *E. coli* and MRSE, and *Candida.*

as follows: piperacillin-tazobactam (n = 58, 57%), meropenem (n = 5, 5%), ceftazidime (n = 2, 2%), and vancomycin for documented gram-positive infection (n = 3, 3%). Drug combinations were prescribed as first-line treatment in 34 patients (33%) and included meropenem plus MRSA coverage (n = 24, 23%), piperacillin-tazobactam plus MRSA coverage (n = 9, 9%), and meropenem plus daptomycin and amikacin (n = 1, 1%).

BSIs occurred in 28 patients (27%), and 8 patients (8%) had more than 1 episode. Among 37 isolated pathogens, the most frequent were *Escherichia coli* (n = 12, 32%), staphylococci (n = 11, 30%), and enterococci (n = 6, 16%).

Early De-Escalation

Early de-escalation rate was 25.5% (n = 26) and consisted of reducing the spectrum of gram-negative coverage in 11 patients (42%), discontinuing MRSA coverage in 6 patients (23%), both reducing the spectrum of gram-negative coverage and discontinuing MRSA coverage in 6 patients (23%), discontinuing piperacillin-tazobactam and resuming FQ prophylaxis in 2 patients (8%), and discontinuing aminoglycoside in 1 patient (4%). Later, 8 patients in the early de-escalation group discontinued the empirical therapy to FQ prophylaxis. The changes in antibiotic therapy and the main outcomes in different groups are outlined in Figure 1.

The failure of early de-escalation occurred in 4 patients (15.4%, 4/26), being in fever recurrence in 1, bartholinitis in 1, BSI due to a coagulase-negative staphylococcus in 1, and BSI due to extended-spectrum β-lactamase–producing *E. coli* in 1. These BSIs were not recurrences of previous infections. All failures were successfully treated with escalation of antibiotic therapy. No deaths were recorded in the early de-escalation group. Of note, the occurrence of a second episode of fever or infection any time before engraftment was similar (30.7% [8/26] versus 31.2% [23/76]) in those who did and did not undergo early de-escalation (the second group includes patients undergoing late de-escalation).

Compared with a theoretical scenario of continuing empirical therapy unmodified until engraftment, early de-escalation resulted in saving of a median of 10 days of meropenem (range, 1 to 28), 8 days of piperacillin-tazobactam (range, 2 to 17), and 7 days of vancomycin/anti-MRSA coverage (range, 1 to 21). Considering the group of 74 patients without BSI, failure of early de-escalation occurred in 5 of 11 patients (45.5%; all responded well to antibiotic escalation) versus second episode of fever occurring in 17 among 63 who did not perform early de-escalation (27%).

Late De-Escalation

Late de-escalation rate was 30.4% (n = 31). It could be divided into reducing the spectrum of antibiotics (n = 9, 9%; stopping MRSA coverage in 7 and reducing the spectrum of gram-negative coverage in 2) and into direct discontinuation

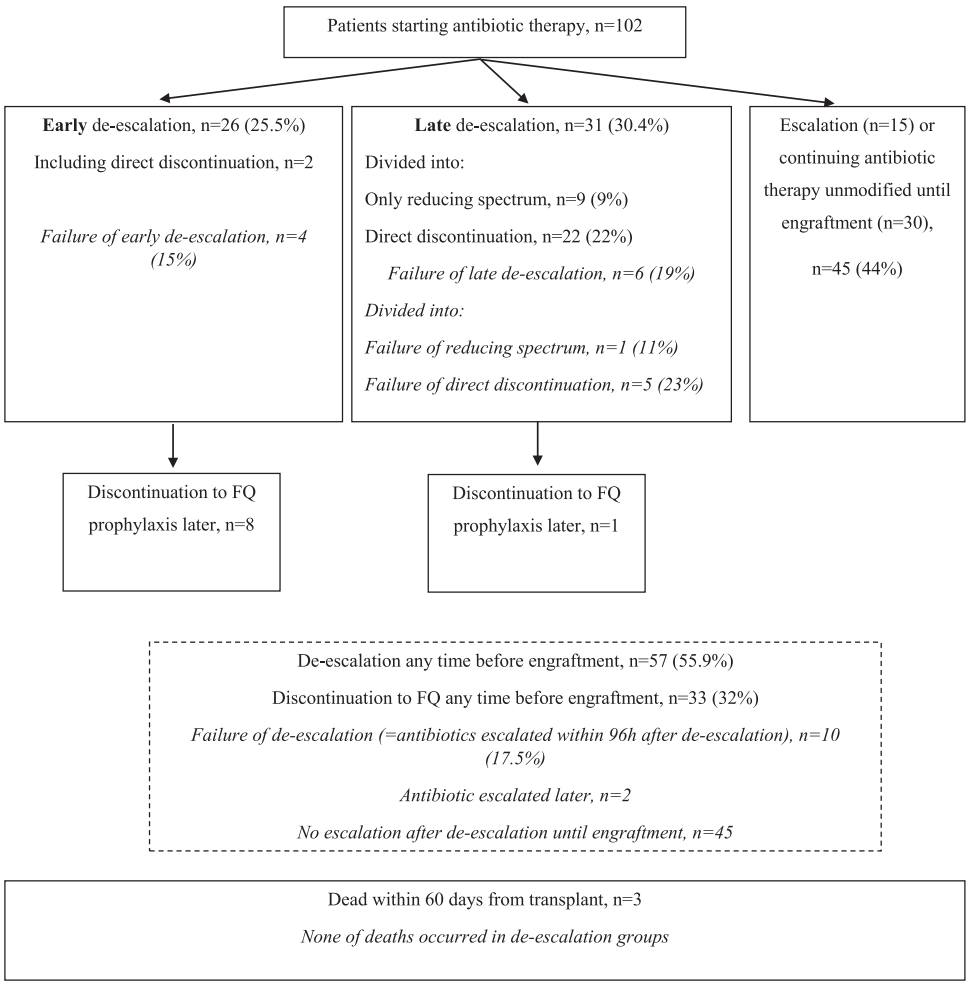

Figure 1. Summary of main results.

to FQ prophylaxis (n = 22, 22%) after a median of 10 days of antibiotic therapy (range, 4 to 22).

The failure of late de-escalation was registered in 6 of 31 patients (19%). It occurred after reducing the spectrum in 1 patient who developed subsequently a BSI due to *Pseudomonas putida* (11%, 1/9) and after direct discontinuation to FQs in 5 patients (23%, 5/22; fever recurrence n = 4, BSI due to *Enterococcus faecium,* n = 1). Additionally, 1 patient experienced a BSI due to coagulase-negative staphylococcus and restarted vancomycin 6 days after de-escalation while still on treatment with meropenem for *P. aeruginosa* sepsis, and another patient restarted meropenem and vancomycin 14 days after the discontinuation to FQs. Considering the group of 74 patients without BSI, failure of late de-escalation occurred in 2 of 27 patients (7%) versus subsequent episode of fever occurring in 10 among 36 who did not perform de-escalation (28%).

De-Escalation Any Time before Engraftment and Outcome

Overall de-escalation rate (early and late) was 55.9% (n = 57) and was performed according to the results of a positive blood culture in 19 patients (33%) and without any isolated bacteria in 38 cases (67%). All BSIs occurring as failures were new episodes and not recurrences of previous infections. Failures of early or late de-escalation occurred in 10 patients (17.5%), with no cases of septic shock or death, and were successfully treated with antibiotics. Additionally, 2 patients modified antibiotic therapy more than 96 hours after late de-escalation (as reported above), whereas the remaining 45 patients (79%) did not have further infection episodes and did not modify the antibiotic therapy. Among those in whom discontinuation was performed, FQs prophylaxis was resumed for a median of 3 days (range, 1 to 17).

Nonengraftment occurred in 3 patients from the early de-escalation group and in 3 among those who never de-escalated. Death at 60 days after HSCT occurred only in 3 patients in whom de-escalation was never performed.

Predictors of De-Escalation

In univariate analyses early de-escalation was more frequent in patients with acute myeloid disease ($P = .006$), in those having ≥2 febrile episodes ($P = .01$), and in those having a BSI ($P = .001$), whereas de-escalation anytime was more frequent only in patients with acute myeloid disease ($P = .007$). The multivariate analyses confirmed that factors associated with early de-escalation were acute myeloid disease ($P = .019$) and presence of BSI ($P < .0001$), whereas acute myeloid disease was the only factor associated with de-escalation any time ($P = .019$) (Table 2).

DISCUSSION

This retrospective study showed that de-escalation and discontinuation of antibiotic treatment are feasible in the pre-engraftment phase of allogeneic HSCT, with failures responding well to restarting antibiotic therapy and similar rates of fever relapses or mortality compared with the non–de-escalation group. Early de-escalation was performed in one-fourth of patients. To the best of our knowledge, no data

Table 2
Factors Associated with De-Escalation at 96-Hour or De-Escalation at Any Time Before Engraftment in Univariate and Multivariate Analysis

	De-Escalation 96 Hours (n = 26/102 [25.5%])	*P*	De-Escalation Any Time Before Engraftment (n = 57/102 [55.9%])	*P*
Univariate analysis				
Age, yr (median 48 yr) (range)	49 (25-60)	.594	49 (21-69)	.492
Sex, n (%)		.799		.658
Male	15 (24.6)		33 (54.1)	
Female	11 (26.8)		24 (58.5)	
Diagnosis, n (%)		.006		.007
Acute myeloid disease	18 (38.3)		33 (70.2)	
Others	8 (14.5)		24 (43.6)	
Disease status at HSCT, n (%)		.12		.6
In remission	13 (20.3)		37 (57.8)	
Active	13 (34.2)		20 (52.6)	
Donor type, n (%)		.67		.59
Matched related	5 (27.8)		12 (66.7)	
MUD/MMR	2 (15.4)		7 (53.8)	
Haploidentical	19 (26.8)		38 (53.5)	
Conditioning, n (%)		.21		.39
Myeloablative	11 (20.4)		28 (51.8)	
Reduced intensity	15 (31.3)		29 (60.4)	
Neutropenia duration, days (median 17 days) (range)	17 (11-43)	.456	17 (11-43)	.096
Fever episodes, n (%)		.01		.39
≤1	10 (16.4)		32 (52.5)	
≥2	16 (39.0)		25 (61.0)	
BSIs, n (%)		.001		.134
Yes	15 (53.6)		19 (67.9)	
No	11 (14.9)		38 (46.3)	
	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*
Multivariate analysis				
Diagnosis				
Acute myeloid disease	1.00	.019	1.00	.008
Others	.291 (.105-.817)		.328 (.144-.747)	
BSIs				
No	1.00	<.0001		
Yes	6.291 (2.270-17.434)			

CI indicates confidence interval.

are available for comparison of such an early de-escalation, except for a study of septic cancer patients that showed a de-escalation rate of 58% within 5 days from ICU admission. However, only 21% of these patients were neutropenic on the first day of treatment, and, more importantly, the median number of antibiotics at ICU admission was 3, which made it easier to de-escalate some of them [11].

In the era of increasing antimicrobial resistance, the saving of days of antibiotic exposure is extremely important, not only from the global epidemiologic point of view but also from the perspective of the individual patients. In our study, in the 26 patients in whom early de-escalation was performed, a median 10 days of meropenem were saved, which constitutes an important carbapenem-saving approach. Additionally, savings in terms of exposure to glycopeptides and ureidopenicillin were also noted. It is unsurprising that early de-escalation in patients without BSIs might be followed by subsequent new fever episodes (45.5% in our cohort of patients with a median of 17 days of neutropenia), also because patients with BSIs continue at least 1 antibiotic for 10 days. However, all of them responded to antibiotic escalation, no BSI-related death occurred, and the possibility of reusing first-line antibiotic therapy was preserved.

The overall pre-engraftment de-escalation rate in our study was 55.9%, which represents the highest percentage so far demonstrated in a cohort of exclusively neutropenic patients. Among the studies with similar populations, the maximum de-escalation rate was 44%, reported by Mokart et al. [12] in septic neutropenic patients in ICU. However, the main differences, which limit the comparison with our cohort, are the limited number of patients (30%, n = 30) who were still neutropenic at the de-escalation of empirical treatment and the fact that the definition of de-escalation included also antifungal and antiviral drugs [12].

Despite a different setting, we demonstrated an overall de-escalation rate that is consistent with that known for non-neutropenic patients in 14 studies from ICUs (34% to 62%) [10]. Even though patients in the ICU might be more frequently hemodynamically unstable, neutropenic allogeneic HSCT recipients are at particularly high risk of rapid clinical deterioration and death in case of inadequate empirical treatment [24,25].

None of the aforementioned studies on de-escalation conducted in neutropenic patients was a randomized control trial (RCT); thus, these results, which report similar mortality with de-escalation approach, should be carefully interpreted as underlined by a recent meta-analysis [26]. On the other hand, it is extremely challenging to apply randomization criteria to de-escalation strategy, because clinician judgment is a key factor in selecting patients who might benefit from this approach, and no objective algorithm has been validated. This intrinsic bias of evaluating mortality stems from the fact that less severely ill patients are de-escalated more frequently, as outlined in some studies [11,12,27,28].

Feasibility and safety of antibiotic treatment discontinuation in neutropenic patients, which is mildly endorsed by 2010 Infectious Diseases Society of America guidelines [22] and recommended by Fourth European Conference on Infection in Leukemia [5], was an object of a recent RCT performed in neutropenic patients [9]. It provided an excellent demonstration that empirical antibiotic therapy discontinued after 72 hours of apyrexia and clinical recovery is safe and able to reduce unnecessary exposure to antimicrobials [9]. Although our approach did not standardize the time of discontinuation, it was performed in 32% of patients, and none of patients who failed discontinuation and needed to restart antibiotic therapy developed septic shock or died. On the contrary, Micol et al. [16] prematurely interrupted their study in neutropenic patients with acute myeloid leukemia and fever of unknown origin because 3 of 7 patients demonstrated fever relapse within 3 days from antibiotic discontinuation and 1 developed septic shock. However, these results are in contrast with a retrospective study in neutropenic patients and our experience, in which 19% and 17.5% of patients needed subsequent escalation of antibiotics but no case of severe infection (severe sepsis or shock) or death occurred [13]. More importantly, the recent RCT on discontinuation also found no differences in the number of days with fever, severe adverse event, or death noted between the 2 study arms [9].

In our cohort the most important predictor of early de-escalation was the diagnosis of BSI, which can be explained by the fact that the presence of an isolated pathogen gives a clinician a valid support to streamline the empirical treatment. The fact that patients with acute myeloid disease were more likely to undergo de-escalation might be explained by the fact that infectious complications in this population present frequently with clear clinical picture. In these patients more indolent viral or other opportunistic pathogens might be less frequent than in patients with long pretransplant history of chemotherapy and steroid treatment, as for example in lymphoma or myeloma.

The limitations of this study include its retrospective nature and limited number of patients. However, the data on antibiotic administration were collected from clinical charts reporting specifically any changes in antibiotic treatment, and this cohort included the largest number of neutropenic subjects included in a de-escalation study. In addition, an important aim of de-escalation strategy, which is the possibility of inducing less resistance in patients' microbiota and avoiding selection of resistant bacteria already present, could not be assessed, because this requires long-term observation periods. Finally, objective criteria in whom de-escalation could be confidently performed were not established; thus, they may depend on physician's expertise. In conclusion, in a setting of prolonged neutropenia and severe immunosuppression, de-escalation and discontinuation strategies offer the chance to reduce antibiotic exposure during pre-engraftment neutropenia.

ACKNOWLEDGMENTS

Preliminary results were presented as an abstract at the 26th European Congress of Clinical Microbiology and Infectious Diseases in Amsterdam, Netherlands, April 9-12, 2016.

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to report.

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