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ORIGINAL ARTICLE

Control of infectious mortality due to carbapenemase-producing *Klebsiella pneumoniae* in hematopoietic stem cell transplantation

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Carbapenemase-producing *Klebsiella pneumoniae* (KPC-Kp) infections are an emerging cause of death after hematopoietic stem cell transplantation (HSCT). In allogeneic transplants, mortality rate may rise up to 60%. We retrospectively evaluated 540 patients receiving a transplant from an auto- or an allogeneic source between January 2011 and October 2015. After an Institutional increase in the prevalence of KPC-Kp bloodstream infections (BSI) in June 2012, from July 2012, 366 consecutive patients received the following preventive measures: (i) weekly rectal swabs for surveillance; (ii) contact precautions in carriers (iii) early-targeted therapy in neutropenic febrile carriers. Molecular typing identified KPC-Kp clone ST512 as the main clone responsible for colonization, BSI and outbreaks. After the introduction of these preventive measures, the cumulative incidence of KPC-Kp BSI ($P = 0.01$) and septic shocks ($P = 0.01$) at 1 year after HSCT was significantly reduced. KPC-Kp infection-mortality dropped from 62.5% (pre-intervention) to 16.6% (post-intervention). Day 100 transplant-related mortality and KPC-Kp infection-related mortality after allogeneic HSCT were reduced from 22% to 10% ($P = 0.001$) and from 4% to 1% ($P = 0.04$), respectively. None of the pre-HSCT carriers was excluded from transplant. These results suggest that active surveillance, contact precautions and early-targeted therapies, may efficiently control KPC-Kp spread and related mortality even after allogeneic HSCT.

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INTRODUCTION

Carbapenemase-producing *Klebsiella pneumoniae* (KPC-Kp) bacteria have become emerging killers worldwide.[1–4] KPC-Kp bacteria are often resistant to multiple antibiotics.[5] The limited number of antimicrobial agents effective in KPC-Kp infections represents a tremendous challenge to clinicians, contributing to high morbidity and mortality rates, especially in intensive care[6] and solid-organ transplantation patients.[7–9] Recently, an increasing trend in KPC-Kp infections has been reported in hematological malignancies[10] and in hematopoietic stem cell transplantation (HSCT).[11] In allogeneic HSCT, KPC-Kp infections greatly contribute to an exceedingly high mortality rate (up to 60%). In patients with recent KPC-Kp infections before allogeneic HSCT—a condition with a high-risk of an early, life-threatening relapse after transplant—careful evaluation of the risk-benefit ratio of performing transplantation is necessary. Some authors, and particularly the Italian GITMO (Gruppo Italiano Trapianto Midollo Osseo), suggest that HSCT may be contraindicated or postponed in these patients.[12–14] To address this problem, we retrospectively collected data on epidemiology and outcomes of KPC-Kp carriers in 540 consecutive HSCT patients treated at our Institution from January 2011 to October 2015. Following an Institutional increase in the prevalence of KPC-Kp in June 2012, active surveillance was established in order to detect KPC-Kp carriers as early as possible and to monitor the local epidemiology. We reviewed our internal guidelines on the management of first-line antimicrobial therapy in febrile neutropenic patients with known colonization. Nurses, visitors and all staff members were carefully trained on infection control measures such as contact precautions and intensified hygienic measures. In case of a previous documented KPC-Kp isolation, patients were considered eligible to treatment of primary disease, without any delay.

MATERIALS/SUBJECTS AND METHODS

Patients and study design

A total of 540 consecutive patients transplanted at San Raffaele Scientific Institute from January 2011 to October 2015 were included in the study. Thirty percent of patients underwent autologous HSCT (162 out of 540) and 70% of patients underwent allogeneic HSCT (378 out of 540), of which 51% from a HLA-haploidentical donor, 28% from a HLA-matched-unrelated donor, 19% from a HLA-identical donor and 2% from a cord blood unit. Data were retrospectively collected. At the time of HSCT, 318 out of 540 (59%) patients had active disease, including stable, partial responses or refractory/progressive diseases. Patient characteristics are summarized in Table 1. Median follow-up among survivors was 616 days (range 30–1738). Preventive measures, starting from July 2012 onwards, included: (i) active surveillance through weekly rectal swabs performed from the time of hospital admission until discharge for the detection of KPC-Kp carriers; (ii)

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Table 1. Patient characteristics of the study population

	Pre-intervention Jan11 to Jun12 (174 pts)	*Post-intervention Jul12 to Oct15 (366 pts)*
Age, median (range)	55 (19–79)	53 (17–78)
Sex, M/F	106/65	223/143
Underlying disease		
AML	58 (33%)	138 (38%)
ALL	18 (11%)	17 (5%)
MDS	12 (7%)	23 (6%)
NHL/HL	30 (17%)/18 (10%)	69 (19%)/26 (7%)
MPD	9 (5%)	16 (5%)
MM	28 (16%)	64 (17%)
Others	1 (< 1%)	13 (3%)
Type of HSCT, cases		
Autologous	58 (33%)	104 (28%)
Allogeneic	116 (67%)	262 (72%)
Haplo	64 (56%)	128 (49%)
MUD	30 (26%)	77 (29%)
Sib	22 (18%)	51 (20%)
CBU	–	6 (2%)
Disease status at HSCT		
CR1	44 (25%)	106 (29%)
> CR2	26 (15%)	46 (13%)
Active	104 (60%)	214 (58%)
Previous KPC-Kp BSI	–	2 (<1%)

Abbreviations: BSI = bloodstream infection; CBU = cord blood unit allogeneic HSCT; Haplo = HLA-Haploidentical allogeneic HSCT; HL = Hodgkin lymphoma; MDS = myelodysplastic syndrome; MM = multiple myeloma; MPD = myeloproliferative diseases; MUD = matched-unrelated donor allogeneic HSCT; NHL = non-Hodgkin lymphoma; Sib = HLA-sibling allogeneic HSCT.

contact precautions in case of colonization; (iii) stopping antimicrobial prophylaxis (that is, levofloxacin) during neutropenic fever in carriers and starting a combined empirical broad-spectrum antimicrobial therapy, with at least two antibiotics among colistin, tigecycline, gentamycin, meropenem or ertapenem. After three consecutive negative rectal swabs contact precautions were relieved.[12]

Data from the pre-intervention period (from January 2011 to June 2012, 18 months, 174 patients) were compared with those from the post-intervention period (from July 2012 to October 2015, 39 months, 366 patients). Data collection started in January 2011, as no KPC-Kp isolates had been registered before 2011 at our HSCT ward. Transplant-related mortality (TRM) and KPC-Kp infection-related mortality by day 100 were evaluated before and after the implementation of specific management measures, and considered as study primary endpoints. KPC-Kp-related mortality at day 30 from the positivity of blood cultures was also evaluated.

Definitions. KPC-Kp colonization was defined as the isolation of the microorganism from any non-sterile body site (mainly rectal swabs, but also from the respiratory tract) in the absence of clinical signs or symptoms of disease. KPC-Kp bloodstream infections (BSI) were defined as the detection of the pathogen in the blood in presence of fever. Sepsis was defined as the presence of infection together with systemic manifestations of infection. Severe sepsis was defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion. Septic shock was defined as severe sepsis plus persistent hypotension despite adequate volume replacement.[15,16] A transmission chain was defined as two or more related KPC-Kp infection/colonization cases presenting the same clone and a link confirmed by classical epidemiological investigation. Contact precautions and hygienic measures in carriers included: isolation of patients in single rooms, hand hygiene with hydroalcoholic solution before and after entering the room, use of disposable gloves and gowns, dedicated single-patient-use of non-critical equipment, and, whenever possible, dedicated nurses. Intensified environmental decontamination (that is, daily cleansing of the room, at least 2–3 times per day cleansing of other patients' contact surfaces with chlorhexidine solution).

Phenotypic and genotypic characterization of KPC-Kp strains. Cultures for isolation of KPC-Kp were performed on MacConkey agar plates containing a 10 μg disk of carbapenem. After 24–48 h of incubation at 37 °C colonies growing close to the disk were collected and identified with MALDI-TOF mass spectrometry (Vitek MS bioMérieux, Florence, Italy). Antimicrobial sensitivity testing was performed by automated microdilution using the Vitek-2 AST-GN202 card and imipenem and meropenem minimum inhibitory concentrations were verified with the *E*-test. Resistance mechanisms were confirmed by phenotypic assays: the 'modified Hodge test' was used to detect carbapenemase activity, synergy between phenylboronic acid and carbapenems in combined disk tests was used to detect KPC-Kp, and synergy between EDTA and carbapenems in combined disk was used to detect metallo-β-lactamases. KPC-Kp strains were subjected to molecular typing by PFGE (pulsed-field gel electrophoresis), as previously described.[17] Outbreaks were identified by cluster analysis using the software InfoQuest FP version 5.1 (Bio-Rad, Hercules, CA, USA) and epidemiological investigation. To identify the circulating clones, selected strains representative of the different PFGE profiles underwent multilocus sequence typing following the procedure of the Pasteur Institute (http://bigsdb.web.pasteur.fr/klebsiella/klebsiella.html).

Statistical analysis

Categorical variables were evaluated by using the χ^2-test or Fisher's exact test, as appropriate. All *P*-values were two-tailed, and a *P*-value < 0.05 was considered statistically significant. Cumulative incidence functions were used to estimate TRM and KPC-Kp infection-related mortality.[18] TRM was defined as time from transplant to death without relapse/recurrence. Deaths from any cause without prior progression are events. Events related to the disease such as relapse/progression are competing events. Disease progression and GvHD were competing risks for KPC-Kp infection-related mortality. Univariate analysis was done using Gray's test for cumulative incidence (CI) function.[19] All tests were two-sided. The type-1 error rate was fixed at 0.05 for determination of factors associated with time to event outcomes. Statistics were performed with SPSS software version 22.0, GraphPad Prism version 5.0a and with R software version 3.0.2.

RESULTS

Contact precautions in carriers prevent KPC-Kp inter-patient spread

From January 2011 to June 2012 KPC-Kp was documented in nine patients, mostly isolated from blood cultures (8 out of 174, 4.6%). In one case (1 out of 174, 0.5%), the pathogen was isolated from respiratory material in the absence of fever and considered to be a colonizing agent. From July 2012 to October 2015, active surveillance allowed the identification of 31 out of 366 carriers (8.5%). Six of them (6 out of 366, 1.6%) also developed a KPC-Kp BSI, whereas 25 (25 out of 366, 6.8%) remained colonized without infections. Patients developing a BSI during the post-intervention period ($n = 6$) presented positivity to rectal swab: in four out of six (66.6%) rectal swabs anticipated the infection onset (range from −3 to −23 days), in two out of six (33.3%) rectal swabs became positive the same day of the infection or afterwards, demonstrating a strong association between colonization and BSI ($P < 0.0001$).

Although in the pre-intervention period the majority of patients, five out of nine (55.6%), were involved in nosocomial transmissions, in the post-intervention period only 14 out of 31 (45.1%) patients were part of a transmission chain. In this analysis all KPC-Kp isolates were considered. This result suggests a potential role of contact precautions and intensified hygienic measures in controlling inter-patient pathogen spread. Although this association did not reach statistical significance, it is clear that the number of patient harboring KPC-Kp in the pre-intervention group was potentially underestimated in the absence of active surveillance. After 3 months of stringent application of contact precautions, nosocomial transmission was reduced as follows: from July to September 2012 (three months), 9 out of 14 patients were involved in transmission (64.3%—three patients/month), from October 2012 to October 2015 (36 months), only 5 out

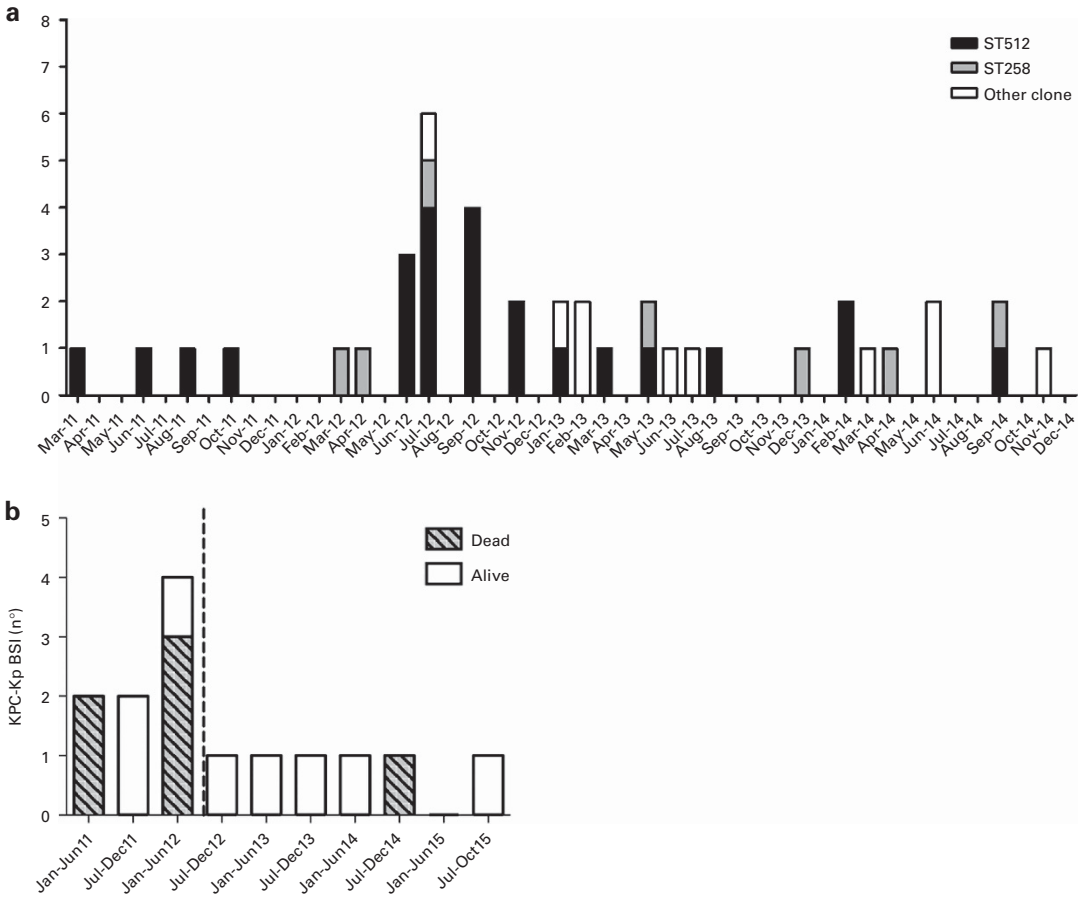

Figure 1. Frequencies of the main clones responsible for colonizations and BSI according to observation time (**a**). Distribution of KPC-Kp BSI and relative deaths (gray) before and after preventive measures (**b**).

of 14 patients were involved in transmission (35.7%—0.13 patient/month).

Clone ST512 is the main clone responsible for colonization, infections and outbreaks

No multiple strains were detected in the same patient at the same time. Molecular analysis identified sequence type (ST) 512 as the most frequent clone in HSCT patients, accounting for 57.5% (23 out of 40) of the strains. Clone ST258 accounted only for 17.5% (7 out of 40) of the strains, whereas the remaining strains (10 out of 40, 25%), were unrelated to one another and belonged to minor clones. For three cases molecular characterization was not available. We documented 19 cases of KPC-Kp nosocomial transmission: clone ST512 was responsible for 84.2% (16 out of 19) of transmissions, whereas ST258 accounted for the remaining 15.8% (3 out of 19). Frequencies of clones according to time are shown in Figure 1a.

Contact precautions in carriers allow a reduction in the incidence of KPC-Kp infections

Fourteen patients experienced a KPC-Kp BSI during the entire study period (five sepsis, one severe sepsis and eight septic shocks), and relative deaths are shown in Figure 1b. Twelve out of 14 BSI occurred after allogeneic HSCT, one before allogeneic HSCT and one before autologous HSCT. The two patients experiencing KPC-Kp BSI before HSCT later underwent the procedure without major complications or infection recurrence. The median time from hospital admission to the development of BSI was 20 days (range 1–46) and the median time from HSCT to the onset of BSI was 12 days (range 5–144). All patients developing KPC-Kp BSI had grade IV neutropenia. Five out 6 (83%) patients died of KPC-Kp induced multi-organ failure in presence of active/relapsing disease. Clinical and microbiological data of patients experiencing KPC-Kp BSI are summarized in Table 2.

Following the implementation of contact precautions and intensified hygienic measures in carriers, we observed a significant drop in the estimated CI of KPC-Kp BSI at 1 year after HSCT as shown in Figure 2a, in the post-intervention group the incidence was 1% (±1%), whereas in the pre-intervention group, CI was 4% (±2%) ($P = 0.01$). Sixteen patients received transplantation regardless of a previous colonization or KPC-Kp infection. In this group, only one fatality due to the pathogen occurred after HSCT, showing that KPC-Kp isolation before transplant does not substantially increase the likelihood of KPC-Kp-related mortality ($P = 0.043$). Moreover, we did not register any KPC-Kp-related death in non-colonized patients.

Prompt initiation of multiple targeted antimicrobial therapies reduces incidence of septic shocks and KPC-Kp-related mortality

According to Institutional guidelines and in absence of any information on colonization status, 8 out of 174 patients belonging to the pre-intervention group and developing neutropenic fever received inadequate first-line empirical treatment. Six of them developed septic shock and five out of six died of multi-organ failure within a median of 3 days (range 1–22). A KPC-

Table 2. Characteristics of patients developing a KPC-Kp bloodstream infection

Pt	*Age*	*Disease*	*HSCT*	*Disease status*	*Time from admission to KPC-Kp BSI*	*Septic shock*	*Time from septic shock to death (day)*	*ANC < 1 × 10^9/L before BSI (day)*	*ANC × 10^9/L at BSI onset*	*I line therapy*	*30 days status*	*Clone*	*outbreak*
Pre-intervention group													
1	65	AML	Haplo	Active	14	Yes	2	8	0	Pip/Tz, Metro	Dead	ST512	Yes
2	62	MFI	Haplo	Active	21	Yes	1	18	0.3	Ceftaz, CIP	Dead	ST512	No
3	37	ALL	Haplo	CR	15	Yes	–	13	0	Ceftaz, AMK, Vanco	Alive	ST258	Yes
4	67	MDS	Haplo	CR	10	No	–	11	0	Pip/Tz, Metro, Vanco	Alive	ST512	Yes
5	62	CMML	Sib	Active	35	Yes	22	17	0.7	Pip/Tz, Levo	Dead	ST258	No
6	40	ALL	CBU	Active	9	Yes	5	26	0	MER, Ceftriax, AMK	Dead	ST512	No
7	43	ALL	MUD	CR	46	No	–	0	0	MER, Ceftriax	Alive	ST512	No
8	70	AML	Sib	CR	30	Yes	3	27	0	Pip/Tz, TMP-SMX.	Dead	ST512	Yes
9	65	AML	Haplo	Active	14	Yes	2	8	0	Pip/Tz, Metro	Dead	ST512	Yes
Post-intervention group													
1	37	NHL	Haplo	Active	27	Yes	29	12	0	MER, ERTA, Gent	Dead	ST258	No
2	49	AML	MUD	CR	12	No	–	5	0	MER, AMK, Coli	Alive	ST307	No
3	57	NHL	Auto	Active	30	No	–	10	0	MER, Colistin, Tige	Alive	ST512	No
4	55	MFI	MUD	Active	17	Yes	–	10	0	Pip/Tz, Gent, Coli, Vanco	Alive	ST512	Yes
5	52	MM	MUD	Active	20	No	–	11	0	MER, Coli, Tige	Alive	ST512	Yes
6	67	MPD	MUD	CR	1	No	–	8	0.2	MER, Gent, Tige	Alive	ST307	No

Abbreviations: AMK = amikacin; Auto = autologous HSCT; CBU = cord blood unit allogeneic HSCT; Ceftaz = ceftazidim; Ceftriax = ceftriaxone; CIP = ciprofloxacin; CMML = chronic myelomonocytic leukemia; ERTA = ertapenem; Gent = gentamycin; Haplo = HLA-Haploidentical allogeneic HSCT; MDS = myelodysplastic syndrome; MER = meropenem; Metro = metronidazole; MFI = idiopathic myelofibrosis; MM = multiple myeloma; MPD = myeloproliferative diseases; MUD = matched-unrelated donor allogeneic HSCT; NHL = non-Hodgkin lymphoma; Pip/Tz = piperacillin/tazobactam; Sib = HLA-sibling allogeneic HSCT; Tige = tigecycline; TMP-SMX = trimethoprim/sulfamethoxazole; Vanco = vancomycin.

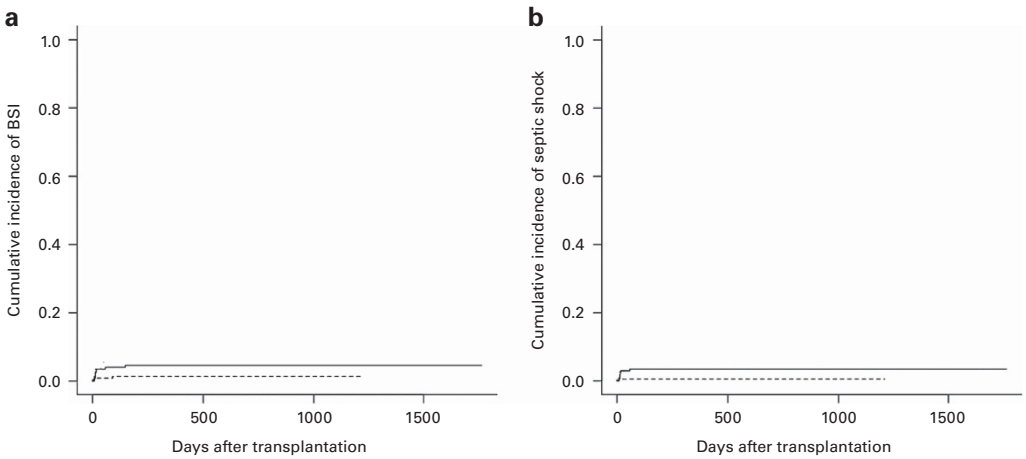

Figure 2. Estimated cumulative incidence of KPC-Kp BSI before (continuous line) and after (dashed lines) the implementation of preventive measures (**a**); the difference between the two groups was statistically significant according to Gray's test ($P = 0.01$). Estimated cumulative incidence of KPC-Kp septic shock before (continuous line) and after (dashed lines) the implementation of preventive measures (**b**); the difference between the two groups was statistically significant according to Gray's test ($P = 0.01$).

Kp-targeted therapy was lately delivered to every patient based on the results of blood cultures with an average delay of 2 days (range 0–7), too late to prevent death. From July 2012 onwards, we actively looked for KPC-Kp carriers and modified our antimicrobial guidelines, starting a KPC-Kp-targeted combined antimicrobial therapy at the onset of fever in any KPC-Kp-colonized patient, with a policy of subsequent de-escalation at clinical improvement.

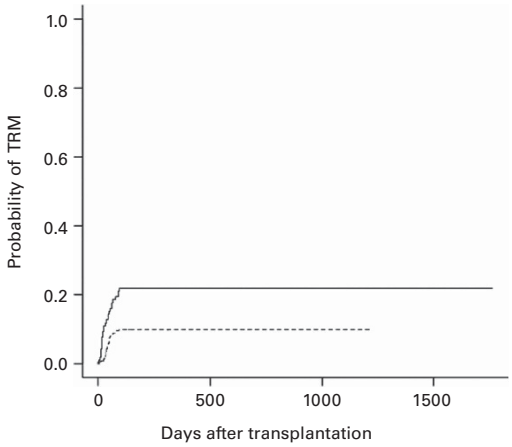

Figure 3. Estimated cumulative incidence curve of TRM after allogeneic HSCT before (continuous line) and after (dashed line) the implementation of preventive measures; the difference between the two groups was statistically significant according to Gray's test ($P = 0.001$). Relapses are considered as competitive events.

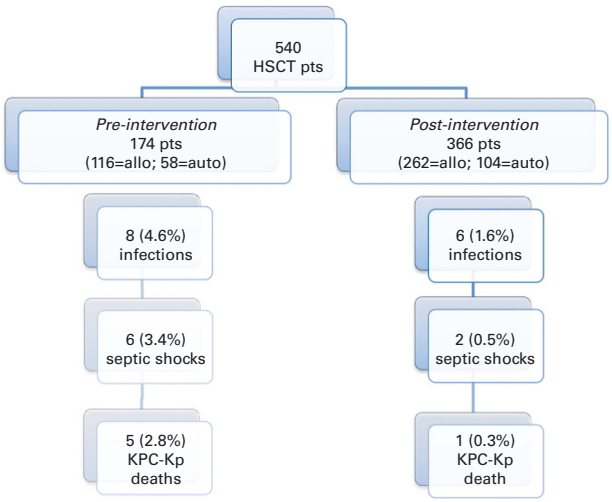

Figure 4. Flow-chart showing the numbers and relative percentages of KPC-Kp infections, septic shocks and deaths before (174 pts) and after the implementation of preventive measures (366 pts).

As a result, although in the pre-intervention group septic shock was documented in 6 out of 174 (3.4%) patients, in the post-intervention group this complication was documented only in 2 out of 366 (0.5%) patients. The estimated CI of septic shock at 1 year after HSCT was 3% (±1%) in the pre-intervention group and decreased to 1% (±1%) in the post-intervention group ($P = 0.01$) as shown in Figure 2b.

Moreover, the estimated CI of TRM at day 100 in allogeneic HSCT also was significantly reduced in the post-intervention group, being 10% (±2%) in comparison with 22% (±4%) of the pre-intervention group ($P = 0.001$), Figure 3. The estimated CI of 100- day TRM for autologous HSCT patients was 7% (±3%) and 3% (±2%) in the pre- and post-intervention period, respectively ($P = 0.24$). No KPC-Kp-related death was registered in autologous HSCT patients. Interestingly, 100-day KPC-Kp infection-related mortality was significantly reduced in the post-intervention group, being 1% (±2%) compared with 4% (±2%) ($P = 0.04$). The absolute numbers of BSI, septic shocks and KPC-Kp-related deaths are summarized in Figure 4. Because of the low number of deaths owing to KPC-Kp infection, multivariate analysis was not performed.

DISCUSSION

KPC-Kp is rapidly spreading worldwide and is endemic in Italy, often causing outbreaks and becoming a major challenge in critically ill patients.[20–23] Although major advances have been made in supportive care, mortality owing to KPC-Kp infections in HSCT patients is still unacceptably high, being 16% for autologous and 64.4% for allogeneic transplants, according to a recent Italian GITMO survey.[11] The same authors state that a pre-transplant KPC-Kp infection and inadequate first-line treatment are independent risk factors associated with an increase in mortality in allogeneic HSCT patients.

In our experience in a heterogeneous population, in which high-risk patients were largely represented (that is, patients undergoing HLA-haploidentical HSCT for advanced diseases) clearly shows that previous KPC-Kp infection/colonization does not associates with an increased risk of infection-related mortality if appropriate preventive measures are used. This approach appears especially relevant because of the increasing number of patients with high-risk hematological malignancies for which HSCT is considered the only potentially curative option.[24]

After the initiation of active surveillance, we witnessed a significant reduction in the CI of KPC-Kp BSI at one year after HSCT (from 4% to 1%, $P = 0.01$). This can be attributed mainly to isolation of carriers into contact precautions, and to the careful implementation of the standard procedures, including strict asepsis during IV-lines management and intensified environmental hygiene. Nosocomial transmission was also reduced. We identified clone ST512 as the main clone responsible for inter-patient transmissions. From published data, this clone is characterized by a high transmission rate,[25] potentially favored, in this setting, by the severe immune incompetence of patients. Our results suggest a strong correlation between the presence of a KPC-Kp-positive rectal swab and the onset of BSI, underlying the importance of the active surveillance through rectal swabs as an instrument to detect patients at higher risk of developing subsequent BSI. In our study, a positive rectal swab anticipated the onset of sepsis in 66% of the cases, a proportion considerably higher than reported in the literature, albeit in other settings.[26] Nevertheless, the clinical usefulness of rectal swabs could be further improved by defining the optimal survey strategy (for example, increasing sample frequency) during the high-risk infection period before hematopoietic engraftment.

KPC-Kp BSI outcome was significantly different in the allogeneic versus the autologous group. No fatalities occurred in the autologous HSCT setting, probably because of the shorter period of aplasia and the absence of post-transplant immunosuppression. Although during the pre-intervention period, our KPC-Kp-related mortality was in line with that of published data, being 62.5%,[10,11,27] a significant mortality reduction was observed in the post-intervention group, being only 16.6%. In the allogeneic HSCT cohort of patients, day 100 TRM related to KPC-Kp BSI was reduced from 4% (pre-intervention) to 1% (post-intervention). We believe that the early initiation of KPC-Kp targeted therapy in neutropenic carriers at the onset of fever delays the progression to septic shock and reduces mortality. Tumbarello *et al*.[28] in a retrospective analysis of 125 bloodstream KPC-Kp infections, also demonstrated the advantage of a triple combination of colistin, tigecycline and meropenem on day 30 mortality versus monotherapy (69.7% survival versus 45.7%). These results strongly support the role of starting an early, KPC-Kp directed, antimicrobial polytherapy in carriers.

In conclusion, within the limitations of a single-center retrospective experience, our results suggest that in the setting of HSCT for advanced hematological diseases, the implementation of active surveillance through weekly rectal swabs, early contact precautions and intensified hygienic measures, specific staff training and the timely initiation of KPC-Kp-targeted combined

antimicrobial therapy at the very onset of fever in carriers, can reduce KPC-Kp-related mortality. In addition, KPC-Kp pre-transplant colonization does not appear to be a limiting factor in the selection of patients eligible for HSCT when appropriate measures are implemented.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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