Reduced Mortality From KPC-*K.Pneumoniae* Bloodstream Infection in High-Risk Patients With Hematological Malignancies Colonized by KPC-*K.Pneumoniae*

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Keywords: KPC-K.pneumoniae, hematological malignancy, carriers, bacteremia, mortality, initial active treatment

Posted Date: October 1st, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-74911/v1>

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Abstract

Background. KPC-*K.pneumoniae* bloodstream infection (KPC-KpBSI) mortality rate in patients with hematological malignancies is reported about 60%. The initial treatment active against KPC-*K.pneumoniae* is crucial for survival and KPC-*K.pneumoniae* rectal colonization usually precedes KPC-KpBSI. We evaluated the impact on KPC-KpBSI mortality of the preemptive use of antibiotics active against KPC-*K.pneumoniae*, as opposed to inactive or standard empiric antibiotics, for the empiric treatment of febrile neutropenia episodes in patients with hematological malignancy identified as KPC-*K.pneumoniae* intestinal carriers.

Methods. We compared the outcomes of KPC-KpBSIs occurring in high-risk patients with hematological malignancy known to be colonized with KPC-*K.pneumoniae*, during two time periods:

March 2012-December 2013 (Period 1, initial approach to KPC-*K.pneumoniae* spread) and January 2017-October 2018 (Period 2, full application of the preemptive strategy). The relative importance of the various prognostic factors that could influence death rates were assessed by forward stepwise logistic regression models.

Results. KPC-KpBSI-related mortality in patients with hematological malignancies identified as KPC-*K.pneumoniae* carriers dropped from 50% in Period 1 to 6% in Period 2 ($p<0.01$), from 58% to 9% in acute myeloid leukemia carriers ($p<0.01$). KPC-KpBSIs developed in patients identified as KPC-*K.pneumoniae* carriers were treated with initial active therapy in 56% and 100% of cases in Period 1 and Period 2, respectively ($p<0.01$), consisting in active antibiotic combinations in 39% and 94% of cases, respectively ($p<0.01$). In Period 1, the 61% of KPC-KpBSI were breakthrough (fatal in the 73% of cases) while no breakthrough KPC-KpBSI was observed in Period 2 ($p<0.01$). Overall, KPC-KpBSI-related mortality was 88% with no initial active treatment, 11.5% with at least one initial active antibiotic ($p<0.01$), 9% with initial active combination. Only the initial active treatment resulted independently associated with survival.

Conclusions. In high-risk patients with hematological malignancies colonized by KPC-*K.pneumoniae*, the empiric treatment of febrile neutropenia active against KPC-*K.pneumoniae* reduced KPC-KpBSI-related mortality to 6% and prevented fatal breakthrough KPC-KpBSI.

Introduction

The mortality rate associated with KPC-*K.pneumoniae* bloodstream infection (KPC-KpBSI) in neutropenic patients with hematological malignancies is reported up to 60% (1–10). The initial active antibiotic treatment is crucial for KPC-KpBSI survival (11–12), especially in high-risk vulnerable patients such as acute leukaemia patients undergoing intensive chemotherapy, and hematopoietic stem cell transplant (HSCT) recipients (7–10). A delay in KPC-KpBSI active antibiotic treatment is common in these patients since in most cases the recommended empiric antibiotic regimens for febrile neutropenia contain antibiotics without *in vitro* activity against carbapenem-resistant Enterobacteriaceae (CRE). Colonization

is a recognized predictive factor for KPC-KpBSI occurrence (10, 13–14), and the prevalence of colonized hematological patients hospitalized for chemotherapy treatments is increasing in Italy and many other countries with high KPC-*K.pneumoniae* nosocomial diffusion (15). On March 2012, KPC-*K.pneumoniae* spread at the Hematology Department of Sapienza University of Rome (Italy): we reported the 71% of KPC-KpBSI mortality rate, and a high rate of KPC-*K.pneumoniae* rectal carriers who developed KPC-KpBSI and died (8). Good-quality studies on CRE-BSI treatment in neutropenic patients were not available at that time, and recommendations were not sufficiently focused (16–17). We implemented the prompt identification of patients hospitalized who were KPC-*K.pneumoniae* carriers and we progressively increased the preemptive use of antibiotics active against KPC-*K.pneumoniae* for the empiric treatment of febrile neutropenia episodes in KPC-*K.pneumoniae* carriers. Options for CRE treatment are limited (19), and data on hematological patients scarce. Several issues pertain the clinical use of colistin, dosing, pharmacokinetics in critically ill patients, nephrotoxicity and uncertainties about susceptibility testing (12), moreover the emergence of resistance decreases the activity of colistin and other available antibiotics (20). Currently, evidences and recommendations support the use of active antibiotic combinations to treat serious CRE infections (12, 21–23). New combinations with β -lactamase inhibitors, including carbapenem/ β -lactamase inhibitor combinations, represent therapeutic alternatives (24–26) to limit colistin use and improve CRE treatment. Good response rates are reported with the use of the ceftazidime-avibactam for targeted or salvage treatment of KPC-KpBSI in immunocompetent patients (24–25), while data in the specific setting of patients with hematological malignancies are limited (27).

We evaluated the impact of the preemptive strategy on KPC-KpBSI-related mortality in high-risk hematological KPC-*K.pneumoniae* carriers comparing the initial approach to KPC-*K.pneumoniae* spread and the routine application of the preemptive use of active therapy for the empiric treatment of febrile neutropenia.

Patients And Methods

We compared KPC-KpBSI developed in patients with hematological malignancies identified as KPC-*K.pneumoniae* carriers attending the Hematology Department of Sapienza University of Rome between March 2012- December 2013 (Period 1) and January 2017-October 2018 (Period 2).

Setting

The Hematology Department consists of 5 wards and 52 beds. The majority of patients are hospitalized for intensive chemotherapy treatments for acute leukemia and/or HSCT.

Screening for KPC-*K.pneumoniae* colonization

From March 2012, when KPC-*K.pneumoniae* spread at the Hematology Department, the screening for KPC-*K.pneumoniae* rectal colonization (13) was performed weekly in patients hospitalized in the ward where KPC-*K.pneumoniae* was first isolated. From September 2012, the screening was extended to all patients hospitalized in the Hematology Department, from October 2013, rectal swabs were collected also

prior to admission. From January 2018, hospitalized acute leukaemia patients were screened twice weekly. KPC-*K.pneumoniae* colonized patients underwent contact precautions.

Active empiric antibiotic treatments for febrile neutropenia in KPC-*K.pneumoniae* carriers.

Combination of colistin (9 million international units [IU] loading dose, then 4.5 million UI q12h) with tigecycline (100 mg loading dose, then 50 mg q12h) and/or gentamycin (3 mg/kg/die once-a-day), high-dose carbapenems (meropenem 2 g q8h), double carbapenem (meropenem plus ertapenem 1g once-a-day) and, from September 2017, ceftazidime-avibactam (2.5 g q8h) as monotherapy or combined with tigecycline and/or gentamycin.

Clinical data recorded

Data collected from Period 1 and Period 2: a) number of KPC-KpBSI occurred in KPC-*K.pneumoniae* carriers. b) number of hospitalized patients identified as KPC-*K.pneumoniae* carriers. c) type of hematological malignancy and chemotherapy treatment administered in the colonized patients with KPC-KpBSI. d) length of neutropenia (<1000 neutrophils/cmm) and profound neutropenia (<100 neutrophils/cmm) episodes. e) clinical presentation of KPC-KpBSI. f) antibiotic treatment. g) KPC-KpBSI outcome.

Microbiological studies

In Period 1, species identification and MIC determination of *K.pneumoniae* isolates were performed using the BD Phoenix automated microbiology system (Becton Dickinson Italia S.p.A Milano, Italy). MICs of imipenem, meropenem, ertapenem, gentamicin, colistin and tigecycline were also evaluated using Etest (BioMérieux Italia S.p.A., Firenze, Italy). In Period 2, species identification was performed using MALDI-TOF and susceptibility testing was determined using the automated VITEK2 system (bioMérieux, Marcy-l'Étoile, France). *K.pneumonia* blood isolates KPC genetic mechanism was determined with in vitro real-time PCR assay Xpert Carba-R assay (Cepheid, Sunnyvale, CA). For the 34 KPC-*K.pneumonia* blood isolates, MICs for imipenem, meropenem, ertapenem colistin, tigecycline, gentamicin and ceftazidime-avibactam were determined by broth microdilution (Sensititre Gram Negative MIC Plate, ThermoFischer Scientific, USA) and results were interpreted in accordance with the 2019 breakpoints proposed by the European Committee on Antimicrobial Susceptibility Testing (EUCAST 2019) (28).

Statistical analysis

Continuous variables were compared using the Kruskal-Wallis test. Categorical variables were compared with the Chi-Square test corrected for continuity or the Fisher's exact test when indicated; 95% confidence intervals (CIs) for the differences of means and proportions were calculated. Forward stepwise logistic regression models were used to assess the relative importance of the various prognostic factors that could influence the occurrence of death in patient populations reported in population (7-8): acute myeloid leukemia (AML), intensive chemotherapy, shock at onset, breakthrough KPC-KpBSI, active initial therapy.

The statistical calculations were carried out using the SPSS statistical package (SPSS for Windows, Release 15.0).

Results

Eighteen KPC-KpBSI developed among 27 patients identified as KPC-*K.pneumoniae* carriers in Period 1 and 16 KPC-KpBSI among 88 KPC-*K.pneumoniae* carriers in Period 2 were compared. The rate of KPC-*K.pneumoniae* colonized patients who developed KPC-KpBSI reduced from 67% (18/27) in Period 1 to 11% (16/88) in Period 2, $p < 0.01$ (Table 1).

Table 1

Characteristics of patients with hematological malignancies KPC-*K.pneumoniae* carriers who developed KPC-*K.pneumoniae* BSI.

	Period 1 March 2012 - Dec 2013 N 18	Period 2 Jan 2017 - Oct 2018 N 16	p-value (absolute difference; 95% CI)
Male	7 (39%)	6 (37%)	0.2 (0.02; -0.31 to 0.34)
Mean age, years (range)	47.3 (28–68)	50.8 (3–68)	0.07 (-3.5; -13.2 to 6.24) ^a
Acute leukemia	16 (89%)	12 (75%)	0.2 (0.14; -0.11 to 0.39)
- Myeloid	12/16 (75%)	10/12 (83%)	0.4 (0.08; -0.38 to 0.21)
Other hematological diseases	2 (11%)	4 (25%)	0.2 (0.14; -0.39 to 0.11)
Intensive chemotherapy	15 (83%)	12 (75%)	0.4 (0.08; -0.19 to 0.35)
Allogeneic HSCT	1 (6%)	4 (25%)	0.1 (-0.19; -0.43 to 0.04)
Other treatment	2 (11%)	0 (0%)	0.2 (0.11; -0.03 to 0.25)
Length of neutropenia episode (mean days, range):	17.6 (5–35)	21.1 (11–40)	0.3 (-3.50; -9.2 to 2.2) ^a
- with <1000 neutrophils/cmm	8.4 (0–17)	12.5 (6–25)	0.07 (-4.1; -7.86 to -0.31) ^a
- with < 100 neutrophils/cmm			
N of KPC- <i>K.pneumonia</i> carriers identified during the period	27	88	
Carriers who developed <i>K.pneumonia</i> BSI	18 (67%)	16 (11%)	< 0.01 (0.48; 0.29 to 0.68)
^a Continuous variables were compared using Kruskal-Wallis test.			

As shown in Table 1, the characteristics of the KPC-*K.pneumoniae* carriers with KPC-KpBSI were similar in the two periods: the large majority of patients had acute leukaemia, mostly acute myeloid leukaemia (AML) undergoing intensive chemotherapy and they developed comparable neutropenia and profound neutropenia episodes. In both periods, KPC-KpBSI occurred during profound neutropenia in the majority of cases, and presented with shock in about half of the patients (Table 2). The 61% (11/18) of KPC-KpBSI

occurred in Period 1 were breakthrough, developing in patients who were already receiving inactive systemic antibiotics started (for 4.2 mean days, range 2–8 days) for the empiric treatment of a previous febrile neutropenia episode. None of KPC-KpBSI developed in Period 2 was breakthrough ($p < 0.01$).

Table 2
Clinical characteristic of KPC-*K.pneumoniae* BSI.

	Period 1 March 2012- Dec 2013 N 18	Period 2 Jan 2017- Oct 2018 N 16	p-value (absolute difference; 95% CI)
KPC- <i>K.pneumoniae</i> BSI onset:			
Shock	10 (56%)	7 (44%)	0.73 (0.12; -0.21 to 0.45)
Neutropenia:	18 (100%)	16 (100%)	-
< 1000 neutrophils/cmm	14 (78%)	15 (94%)	0.40 (-0.16; -0.38 to 0.06)
< 100 neutrophils/cmm			
Breakthrough KPC- <i>K.pneumoniae</i> BSI ^a	11 (61%)	0	< 0.01 (0.61; 0.38 to 0.83)
Initial active treatment	10 (56%)	16 (100%)	< 0.01 (-0.44; -0.67 to -0.21)
Combination	7 (39%)	15 (94%)	< 0.01 (-0.54; -0.80 to -0.29)
with colistin	7 (39%)		0.31 (0.13; -0.17 to 0.44)
with ceftazidime-avibactam	0	4 (25%)	< 0.01 (-0.68; -0.91 to -0.46)
Monotherapy	3 (17%)	11 (69%)	0.34 (0.11; -0.10 to 0.31)
tigecyclin ^b	3 (17%)	1 (6%)	0.13 (0.17; -0.005 to 0.33)
ceftazidime/avibactam	0	0	0.47;(-0.06; -0.18 to 0.05)
		1 (6%)	
Fatal KPC- <i>K.pneumoniae</i> BSI	9 (50%)	1(6%)	< 0.01 (0.44; 0.17 to 0.69)
death within 96 hours	4 (22%)	0	0.06 (0.22; 0.03 to 0.41)
shock	7 (39%)	0	< 0.01 (0.39; 0.16 to 0.61)
breakthrough BSI	8 (44%)	0	< 0.01 (0.44; 0.21 to 0.67)
inactive initial treatment	7 (39%)	0	< 0.01 (0.39; 0.16 to 0.61)
acute myeloid leukemia	7 (39%)	1(6%)	< 0.01 (0.33; 0.07 to 0.58)
^a Developed in KPC- <i>K.pneumoniae</i> carriers receiving standard empiric antibiotic treatment			
^b Associated with piperacillin/tazobactam as empiric treatment of febrile neutropenia			

As shown in Table 2, the 56% of KPC-KpBSI occurred in Period 1 and 100% of those occurred in Period 2 were treated with active therapy from the very onset, at least one active antibiotic, preemptively administered as empiric treatment of febrile neutropenia ($p < 0.01$). An active combination was used in 39% and 94% of cases in Period 1 and Period 2, respectively ($p < 0.01$) (Table 2). In Period 2, 4 of 16 (25%) KPC-KpBSI patients, negative at previous KPC-*K.pneumoniae* rectal screenings performed during the hospitalization, resulted as new carriers on the same day of febrile neutropenia onset and therefore received active antibiotics as empiric treatment.

KPC-KpBSI-related mortality reduced from 50% in Period 1 (9/18) to 6% in Period 2 (1/16), $p < 0.01$. Notably, KPC-KpBSI mortality rate in AML carriers decreased from 44% (7/16) in Period 1 to 8% (1/12) in Period 2, $p < 0.01$ (Table 1). The rate of patients who died for KPC-KpBSI among those identified as KPC-*K.pneumoniae* carriers reduced from 33% (9/27) in Period 1 to 1.1% (1/88) in Period 2, $p < 0.01$.

In Period 1, fatal KPC-KpBSI presented with shock in 7 (78%) of cases and death occurred within 1 week in 6 patients (66%), within 96 hours in 4 of them. Fatal KPC-KpBSI were breakthrough in the 89% (8/9) of cases (the breakthrough KPC-KpBSI mortality rate was 73%) and in the 78% (7/9) of cases were initially treated with inactive antibiotics. In Period 2, one AML patient with severe allogeneic-HSCT-related complications, died 10 days after KPC-KpBSI onset.

Overall, KPC-KpBSI observed in Period 1 and Period 2 were fatal in 29% (10/34) of cases: KPC-KpBSI mortality rate was 88% in patients not receiving initial active antibiotics, 11.5% in patients initially treated with at least one active antibiotic ($p < 0.01$). Notably, KPC-KpBSI mortality rate was 25% in patients treated with a single active antibiotic and 9% in those treated with active combinations. At univariate analysis, initial inactive treatment, breakthrough KPC-KpBSI and KPC-KpBSI occurrence in Period 1, resulted risk factors for mortality (Table 3). In the forward stepwise logistic regression analysis (Table 4), if the initial active therapy was not considered (Model 1), breakthrough KPC-KpBSI mortality rate resulted independently associated with death, but when the initial active therapy was added (Model 2), it resulted the only factor independently associated with survival. In both models, AML as underlying diseases, shock and intensive chemotherapy were not predictors of mortality.

Table 3
Univariate Analysis of Risk Factors for Mortality

	Survivors N 24	Non-survivors N 10	p-value (absolute difference; 95% CI)
Male	8 (33%)	5 (50%)	0.4 (-0.17; -0.52 to 0.19)
Mean age, years (range)	47.7(3–68)	52 (35–68)	0.6 (-4.30; -14.9 to 6.32) ^a
Acute leukemia	19 (79%)	9 (90%)	0.41 (-0.11; -0.35 to 6.32)
- myeloid	14 (58%)	8 (80%)	0.21 (-0.22; -0.53 to 0.10)
Other hematological disease	5 (21%)	1 (10%)	0.41 (-0.21; -0.53 to 0.10)
Intensive chemotherapy	20 (83%)	8 (80%)	0.58 (0.03; -0.25 to 0.32)
Other chemotherapy	1 (4%)	-	0.70 (0.04;-0.03 to 0.12)
Allogeneic stem cell transplant	3 (12%)	2 (20%)	0.46 (-0.08; -0.35 to 0.20)
Length of neutropenia episode (mean days, range)	19.4 (5–40)	18.9 (8–35)	0.70 (0.50; -5.90 to 6.90) ^a
with <1000 neutrophils/mmc	11.2 (5–25)	8.3(0–17)	0.29 (2.90; -3.29 to 9.09) ^a
with < 100 neutrophils/mmc			
Onset of KPC- <i>K.pneumoniae</i> BSI:	10 (42%)	7 (70%)	0.12(-0.28; -0.62 to 0.06)
Shock	21 (87%)	8 (80%)	0.61 (0.07; -0.20 to 0.35)
< 100 neutrophils/mmc			
Breakthrough KPC- <i>K.pneumoniae</i> BSI ^b	3 (12.5%)	8 (80%)	< 0.01 (-0.67; -0.95 to -0.39)

^aContinuous variables were compared using Kruskal-Wallis test.

^bDeveloped in KPC-*K.pneumoniae* carriers receiving standard empiric antibiotic treatment

^cAssociated with piperacillin/tazobactam as empiric treatment of febrile neutropenia (18)

	Survivors N 24	Non- survivors N 10	p-value (absolute difference; 95% CI)
Active initial treatment	23 (96%)	3 (30%)	< 0.01 (-0.76- -1.02 -0.50)
Combination	20 (83%)	2 (20%)	< 0.01 (0.63; 0.34 to 0.92)
with colistin	10	1	0.07 (0.32; 0.04 to 0.58)
with ceftazidime/avibactam	10	1	0.07 (0.32; 0.04 to 0.58)
Monotherapy	3 (12.5%)	1 (10%)	0.66 (0.02; -0.20 to 0.25)
tigecyclin ^c	2 (8.5%)	1 (10%)	0.66 (-0.16; -0.23 to 0.20)
ceftazidime/avibactam	1 (4.5%)	-	0.70 (0.4; -0.03 to 0.12)
Study Period	9 (37.5%)	9 (90%)	< 0.01 (-0.52; - 0.79 to -0.25)
Period 1 (March 2012-Dec 2013)	15 (62.5%)	1 (10%)	< 0.01 (0.52; 0.25 to 0.79)
Period 2 (Jan 2017- Oct 2018)			
^a Continuous variables were compared using Kruskal-Wallis test.			
^b Developed in KPC- <i>K.pneumoniae</i> carriers receiving standard empiric antibiotic treatment			
^c Associated with piperacillin/tazobactam as empiric treatment of febrile neutropenia (18)			

Table 4
Multivariate Models of risk factors for 30 days crude mortality in patients population
(Forward Stepwise logistic regression).

	OR (CI 95%)	p-value
MODEL 1		
Breakthrough KPC- <i>K.pneumoniae</i> BSI ^a	28 (3.9 to 199)	0.001
Acute myeloid leukemia	Not included in the Model	
Shock at onset	Not included in the Model	
Intensive chemotherapy	Not included in the model	
MODEL 2		
Initial active treatment	0.019 (0.002 to 0.20)	0.001
Breakthrough KPC- <i>K.pneumoniae</i> BSI ^a	Not included in the model	
Acute myeloid leukemia	Not included in the model	
Shock at onset	Not included in the model	
Intensive chemotherapy	Not included in the model	
^a Developed in KPC- <i>K.pneumoniae</i> carriers receiving standard empiric antibiotic treatment		

The susceptibilities to antibiotics of the 34 KPC-*K.pneumoniae* blood isolates are shown in Table 5. According to 2019 EUCAST breakpoints (38), colistin resistant strains were 33% and 22.5% in Period 1 and Period 2, respectively. A higher tigecyclin activity was observed in Period 2, all the isolates in Period 1 compared to 50% in Period 2 had tigecyclin MIC > 0.5 mg/L (p < 0.01). All isolates resulted susceptible to ceftazidime-avibactam.

Table 5

Susceptibility of *KPC-K.pneumoniae* blood isolates determined by broth microdilution according to 2019 EUCAST breakpoints (38).

	Period 1		Period 2	
N of blood isolates	18		16	
	MIC range (mg/L)	N(%) of susceptible isolates	MIC range (mg/L)	N (%) of susceptible isolates
colistin	0.25 -32	11 (67)	0.5–4	14 (87.5)
tigecycline	2–8	0	0.5–2	8 (50)
gentamicin	1.5 - >256	8 (44)	1 - >8	8 (50)
ceftazidime-avibactam	0.5/4– 8/4	18 (100)	0.5/4– 8/4	16 (100)
meropenem	> 32	0	> 32	0
imipenem	> 32	0	> 32	0
ertapenem	> 32	0	> 32	0

Discussion

Rectal colonization is a recognized predictive factor for CR-KpBSI occurrence (13–14). Patients with hematological malignancies colonized with CR-*K.pneumoniae*, mostly AML patients, are at high risk of developing BSI (4, 8, 10). In this population, the reported CR-KpBSI mortality rate is dramatic (1–10), mainly in acute leukaemia patients (7–8). AML, intensive chemotherapy and severe and/or prolonged neutropenia were associated with CR-KpBSI-related death (7–8), and septic shock and acute respiratory failure resulted predictors of mortality (7).

This study focuses on KPC-KpBSI-related mortality in high-risk patients with hematological malignancies. The prompt identification of KPC-*K.pneumoniae* carriers, and the preemptive antibiotic strategy applied to all the carriers -KPC-*K.pneumoniae* active therapy for the empiric treatment of febrile neutropenia- was associated with the drop of KPC-KpBSI-related mortality from 50%, observed between March 2012-December 2013, to 6% recorded 3 years later, between January 2017-October 2018. To our knowledge, this is the lowest rate reported so far.

KPC-*K.pneumoniae* colonized patients who developed BSI in the two periods had comparable high risk factors for KPC-KpBSI-related death: the majority had acute leukaemia, mainly AML, and had received intensive chemotherapy developing profound and prolonged neutropenia, KPC-KpBSI presented with shock in a similar proportion of patients, but KPC-KpBSI mortality rate was significantly higher in Period

1. Initial treatment with active antibiotics is crucial for survival to CR-KpBSI (7–8, 11–12), and the 78% of patients who died from KPC-KpBSI in Period 1 had received inactive initial antibiotic treatment.

KPC-KpBSI treatment based on culture results presents a high risk of delaying or never receiving appropriate therapy (1, 5). In hematological neutropenic KPC-*Kpneumoniae* carriers at high risk of KPC-KpBSI (8–10), the initial appropriate treatment can be ensured by the preemptive administration of active therapy at any febrile episode. This preemptive approach was fully applied in Period 2, and all the KPC-KpBSI patients received initial active therapy and KPC-KpBSI-related mortality dropped to 6%, as had already been observed applying the same strategy on a small population of HSCT carriers (9). The multivariate analysis confirmed that only the initial active antibiotic treatment was independently associated with survival and, differently from other reports (7–8), AML and shock were not predictors of mortality.

The role of initial active treatment in hematological patients with CR-KpBSI is critical. We previously reported the 90% of mortality in patients not receiving initial active treatment (8); another study observed inappropriate initial treatment in the 78% of non-survivors, associated with 21-day mortality and significant predictor of mortality (7). In the present study the overall KPC-KpBSI mortality rate in KPC-*Kpneumoniae* carriers not receiving initial active treatment was 88%, but reduced to 13% in those initially treated with at least one active antibiotic, and even to 9% with initial active combinations. The combination of active drugs had already been associated with a lower mortality rate (5) and independently associated with survival (7), and as a matter of fact in Period 2 all but one KPC-KpBSI patients received an active combination as initial treatment.

The 61% of KPC-KpBSI observed in Period 1 were breakthrough and the outcome was fatal in the 72% of cases. In Period 2, the preemptive administration of active antibiotics at the onset of febrile neutropenia could have prevented breakthrough KPC-KpBSI development, avoiding the overgrowth of the colonizing KPC-*K.pneumoniae* under inactive antibiotics and the subsequent blood-stream diffusion through the damaged mucosa, strongly contributing to the mortality reduction.

In high prevalence areas, active surveillance of the gastrointestinal tract is critical to avoid KPC-*K.pneumoniae* nosocomial diffusion (8–10, 14), particularly in hematological wards where several conditions favor KPC-*K.pneumoniae* spread (8). In our experience we focused on the search and prompt detection of KPC-*K.pneumoniae* carriers, with the purpose of identifying the patients at the highest risk to develop KPC-KpBSI who would mostly benefit from the preemptive active strategy, obtaining a targeted initial treatment for KPC-KpBSI. In patients with hematological malignancies we strongly recommend the careful screening for KPC-*K.pneumoniae* rectal colonization, that represented the cornerstone of the preemptive strategy we customarily applied in Period 2: all KPC-KpBSI analyzed in the two study Periods developed in patients known as KPC-*K.pneumoniae* carriers but, in Period 2 all KPC-KpBSI were initially treated with active therapy. It is to be noted that in 25% of KPC-KpBSI developed in Period 2, the increased frequency of rectal screening avoided the delay in the active initial treatment due to unrecognized new carriers.

Finally, the reduction in the probability of death from KPC-KpBSI led us to be less concerned about the occurrence of fatal KPC-KpBSI in prosecuting and scheduling intensive chemotherapeutic and/or HSCT programs in those patients identified as KPC-*K.pneumoniae* carriers.

Some considerations are needed. The preemptive strategy certainly increases the use of active drugs, and consequently a de-escalation of empirical active treatments should be carried out if KPC-*K.pneumoniae* infection is not confirmed. Nephrotoxicity, especially in hematological patients receiving many other toxic drugs -chemotherapeutics, immunosuppressants, antifungals- may represent a limitation in colistin use (19); furthermore the emergence of resistance (15, 19–20) observed in 26% of our KPC-*K.pneumoniae* blood isolates, makes colistin role uncertain. Ceftazidime-avibactam was widely used against KPC-*K.pneumoniae* infections with lower toxicity than colistin or aminoglycosides (19–24–25, 27); it proved active against all our KPC-*K.pneumoniae* blood isolates but resistance reported during (29) and independently (30) from previous ceftazidime-avibactam exposure, is troubling. New combinations with β -lactamase inhibitors, including carbapenem/ β -lactamase inhibitor combinations (26), could represent therapeutic alternatives also in the setting of hematological patients.

The monocentric design and the low number of patients included represent a limitation to the present report, and prospective larger studies are needed to confirm and generalize the results. Good-quality prospective randomized studies on CRE infections management are still needed, also in neutropenic haematological patients, and therefore our strategy -search of carriers and preemptive active treatment- obtained a noteworthy and promising reduction of KPC-KpBSI-related mortality in this population.

In conclusion, in high-risk haematological patients colonized with KPC-*K.pneumoniae*, the preemptive use of antibiotics active against KPC-*K.pneumoniae* as empiric treatment of febrile neutropenia resulted in a drop to 6% of KPC-KpBSI mortality rate, reduction of breakthrough KPC-KpBSI and probability of death for KPC-KpBSI, including AML patients.

List Of Abbreviations

KPC-KpBSI: KPC-*K.pneumoniae* bloodstream infection

CRE: carbapenem-resistant Enterobacteriaceae

HSCT: hematopoietic stem cell transplant

AML: acute myeloid leukaemia

Declarations

Ethics approval and consent to participate: The internal Ethical Committee of the Hematology, Sapienza University of Rome, approved this retrospective study.

Consent of publication: Not applicable

Availability of data and materials: data supporting the results reported in the article can be found in archived database and are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

AM: conception and design of the study, acquisition of data, analysis and interpretation of data, and a major contributor in writing the manuscript.

GG: interpretation of data and a major contributor in writing the manuscript.

SS: performing and interpreting microbiological examinations

CM: acquisition and analysis of clinical and hematological data

SC: acquisition and analysis of clinical and hematological data

MLM: acquisition and analysis of clinical and hematological data

WB: contribution in the analysis of the patient clinical data

CC: contribution in the analysis of the patient clinical data

SMT: acquisition and analysis of clinical and hematological data

AMT: acquisition and analysis of clinical and hematological data

API: contribution in the analysis of the patient clinical data

GB: performing statistical analysis and contribution in reviewing the manuscript.

RF: contribution in reviewing the manuscript.

Acknowledgments: We thank Dr. Maura Di Pietrantonio for her thoughtful suggestions in reviewing the paper in English.

References

1. Satlin MJ, Jenkins SG, Walsh TJ The global challenge of carbapenem-resistant Enterobacteriaceae in transplant recipients and patients with hematologic malignancies. Clin Infect Dis 2014; 58(9) : 1274–83

2. Pagano L, Caira M, Trecarichi EM, Spanu T, Di Blasi R, Sica S et al Carbapenemase-producing *Klebsiella pneumoniae* and hematologic malignancies. *Emerg Infect Dis* 2014; 20 : 1235–6.
3. Freire MP, Pierrotti LC, Filho HH, Ibrahim KY, Magri AS, Bonazzi PR C et al. Infections with *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae* in cancer patients. *Eur J Clin Microbiol Infect Dis* 2015 ; 34 : 277–86.
4. Girmenia C, Rossolini GM, Piciocchi A, Bertaina A Pisapia G Pastore D et al. for the Gruppo Italiano Trapianto Midollo Osseo (GITMO). Infections by carbapenem-resistant *Klebsiella pneumoniae* in SCT recipients: a nationwide retrospective survey from Italy. *Bone Marrow Transplant*, 2015 ; 50(2) : 282-8
5. Tofas P, Skiada A, Angelopoulou M, Sipsas N, Pavlopoulou I, Tsaousi S et al. Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections in neutropenic patients with haematological malignancies or aplastic anaemia: Analysis of 50 cases. *Int J Antimicrob Agents* 2016; 47(4) : 335–9.
6. Poucha SM, Satlin MJ. Carbapenem-resistant Enterobacteriaceae in special populations: solid organ transplant recipients, stem cell transplant recipients, and patients with hematologic malignancies. *Virulence* 2017; 8(4) : 391–402
7. Trecarichi EM, Pagano L, Martino B, Candoni A, Di Blasi R, Nadali G et al. for the Haematologic Malignancies Associated Bloodstream Infections Surveillance (HEMABIS) registry– Sorveglianza Epidemiologica Infezioni Fungine in Emopatie Maligne (SEIFEM) group. Bloodstream infections caused by *Klebsiella pneumoniae* in onco-hematological patients: clinical impact of carbapenem resistance in a multicentre prospective survey. *Am J Hematol* 2016; 91 : 1076-1081
8. Micozzi A, Gentile G, Minotti C. Cartoni C, Capria S, Ballarò D et al. Carbapenem-resistant *Klebsiella pneumoniae* in high-risk haematological patients: factors favouring spread, risk factors and outcome of carbapenem resistant *Klebsiella pneumoniae* bacteremias. *BMC Infect Dis* 2017 ; 17: 203
9. Forcina A, Baldan R, Marasco V, Cichero P, Bondanza A, Noviello M et al. Control of infectious mortality due to carbapenemase-producing *Klebsiella pneumoniae* in hematopoietic stem cell transplantation *Bone Marrow Transplant*, 2017; 52(1) : 114-119
10. Cattaneo C, Di Blasi R, Skert C, Candoni A, Martino B, Di Renzo N et al. Bloodstream infections in haematological cancer patients colonized by multidrug-resistant bacteria. *Ann Hematol.* 2018; 97(9) : 1717-1726
11. Zarkotou O, Pournaras S, Tselioti P, Dragoumanos V, Pitiriga V, Ranellou K et al. Predictors of mortality in patients with bloodstream infections caused by KPC-producing *Klebsiella pneumoniae* and impact of appropriate antimicrobial treatment. *Clin Microbiol Infect*, 2011; 17: 1798–803.
12. Bassetti M, Giacobbe DR, Giamarellou H, Viscoli C, Daikos GL, Dimopoulos G et al Critically Ill Patients Study Group of the European Society of Clinical Microbiology and Infectious Disease (ESCMID); Hellenic Society of Chemotherapy (HSC) and Società Italiana di Terapia Antinfettiva (SITA). Management of KPC-producing *Klebsiella pneumoniae* infections. *Clin Microbiol Infect.* 2018; 24(2) : 133-144.

13. Giannella M, Trecarichi EM, De Rosa FG, Del Bono V, Bassetti M, Lewis RE et al. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection among rectal carriers: a prospective observational multicentre study. *Clin Microbiol Infect* 2014; 20 : 1357–62.
14. Amit S, Mishali H, Kotlovsky T, Schwaber MJ, Carmeli Y Bloodstream infections among carriers of carbapenem-resistant *Klebsiella pneumoniae*: etiology, incidence and predictors. *Clin Microbiol Infect*, 2015; 21 (1): 30–4
15. Conte V, Monaco M, Giani T, D'Ancona F, Moro ML, Arena F, et al. AR-ISS Study Group on Carbapenemase-Producing *K. pneumoniae*. Molecular epidemiology of KPC-producing *Klebsiella pneumoniae* from invasive infections in Italy: increasing diversity with predominance of the ST512 clade II sublineage. *J Antimicrob Chemother*. 2016; 71(12) : 3386-91
16. 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. *Clin Infect Dis*, 2011; 52 : 56–93.
17. Averbuch D, Orasch C, Cordonnier C, Livermore DM, Mikulska M, Viscoli C et al. on behalf of ECIL4, a joint venture of EBMT, EORTC, ICHS, ESGICH/ESCMID and ELN. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. *Haematologica*, 2013; 98 :1826–35.
18. Bucaneve G, Micozzi A, Picardi M, Ballanti S, Cascavilla N, Salutari P et al. Results of a multicenter, controlled, randomized clinical trial evaluating the combination of piperacillin/tazobactam and tigecycline in high-risk hematologic patients with cancer with febrile neutropenia. *J Clin Oncol*, 2014; 32 : 1463–71.
19. Perez F, Chakhtoura NG, Papp-Wallace K, Wilson BM, Bonomo RA. Treatment options for infections caused by carbapenem-resistant Enterobacteriaceae: can we apply “precision medicine” to antimicrobial chemotherapy? *Expert Opin Pharmacother* 2016; 17(6) : 761–781.
20. Capone A, Giannella M, Fortini D, Giordano A, Meledandri M, Ballardini M et al. for the SEERBIO-GRAB network. High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality. *Clin Microbiol Infect*, 2013; 19 : 23–30.
21. Tumbarello M, Viale P, Viscoli C, Trecarichi EM, Tumietto F, Marchese A et al. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: importance of combination therapy. *Clin Infect Dis* 2012; 55 : 943–50.
22. Hirsch EB, Guo B, Chang K, Cao H, Ledesma KR, Singh M et al. Assessment of antimicrobial combinations for *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*. *J Infect Dis*, 2013; 207 : 786-93
23. Daikos GL, Tsaousi S, Tzouveleakis LS, Anyfantis I, Psychogiou M, Argyropoulou A et al. Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. *Antimicrob Ag Chemother*, 2014; 58(4) : 2322–8.

24. van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F et al. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae Clin Infect Dis, 2018; 66: 163-171
25. Tumbarello M, Trecarichi EM, Corona A, De Rosa FG, Bassetti M, Mussini C et al. Efficacy of ceftazidime-avibactam salvage therapy in patients with infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*. Clin Infect Dis 2019; 68 : 355-364
26. Zhanel GG, Lawrence CK, Adam H, Schweizer F, Zelenitsky S, Zhanel GG et al. Imipenem-Relebactam and Meropenem-Vaborbactam: two novel Carbapenem- β -Lactamase inhibitor combinations. Drugs 2018; 78(1) : 65-98
27. Castón JJ, Lacort-Peralta I, Martín-Dávila P, Loeches B, Tabares S, Temkin L et al. Clinical efficacy of ceftazidime/avibactam versus other active agents for the treatment of bacteremia due to carbapenemase-producing Enterobacteriaceae in hematologic patients. Int J Infect Dis, 2017; 59 : 118–123
28. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0, 2019. http://www.eucast.org/clinical_breakpoints/.
29. Spellberg B, Bonomo RA. Ceftazidime-Avibactam and Carbapenem-Resistant Enterobacteriaceae: “We’re Gonna Need a Bigger Boat”. Clin Infect Dis, 2016; 63(12) : 1619-1621
30. Gaibani P, Re MC, Campoli C, Viale PL, Ambretti S. Bloodstream infections caused by KPC producing *Klebsiella pneumoniae* resistant to Ceftazidime/avibactam: epidemiology and genomic characterization. Clin Microbiol Infect. 2020; 26(4):516.e1-516