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Oral decontamination with aminoglycosides is associated with lower risk of mortality and infections in high-risk patients colonized with colistin-resistant, KPC-producing *Klebsiella pneumoniae*

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Objectives: Invasive infections caused by KPC-producing *Klebsiella pneumoniae* (KPCKP) are associated with very high mortality. Because infection is usually preceded by rectal colonization, we investigated if decolonization therapy (DT) with aminoglycosides had a protective effect in selected patients.

Methods: Patients with rectal colonization by colistin-resistant KPCKP who were at high risk of developing infection (because of neutropenia, surgery, previous recurrent KPCKP infections or multiple comorbidities) were followed for 180 days. Cox regression analysis including a propensity score was used to investigate the impact of the use of two intestinal decolonization regimens with oral aminoglycosides (gentamicin and neomycin/streptomycin) on mortality, risk of KPCKP infections and microbiological success. The study was registered with ClinicalTrials.gov (NCT02604849).

Results: The study sample comprised 77 colonized patients, of which 44 (57.1%) received DT. At 180 days of follow-up, decolonization was associated with a lower risk of mortality in multivariate analyses (HR 0.18; 95% CI 0.06–0.55) and a lower risk of KPCKP infections (HR 0.14; 95% CI 0.02–0.83) and increased microbiological success (HR 4.06; 95% CI 1.06–15.6). Specifically, gentamicin oral therapy was associated with a lower risk of crude mortality (HR 0.15; 95% CI 0.04–0.54), a lower risk of KPCKP infections (HR 0.86; 95% CI 0.008–0.94) and increased microbiological response at 180 days of follow-up (HR 5.67; 95% CI 1.33–24.1). Neomycin/streptomycin therapy was only associated with a lower risk of crude mortality (HR 0.22; 95% CI 0.06–0.9).

Conclusions: Intestinal decolonization with aminoglycosides is associated with a reduction in crude mortality and KPCKP infections at 180 days after initiating treatment.

Introduction

Infections caused by KPC-producing *Klebsiella pneumoniae* (KPCKP) are an emergent problem worldwide; infections caused by these bacteria are associated with high mortality.[1–8]

The bowel is considered a key reservoir of KPCKP.[9,10] Decolonization therapy (DT) using oral non-absorbable antibiotics has been tested as a measure to control the transmission of these organisms. DT has been associated with eradication rates ranging from 42% to 68%.[11–14] However, doubts have been raised about the effectiveness of DT because patients are frequently recolonized and there is a risk of inducing drug resistance.[13,15]

Infections caused by carbapenemase-producing *K. pneumoniae* are supposed to be preceded by intestinal colonization in most of the cases. In fact, intestinal colonization is a key factor for developing infection especially in specific situations such as major surgery or neutropenia.[15–17] An association between colonization and crude mortality has recently been reported in critically ill patients.[18] Therefore, apart from preventing transmission, DT might be useful as a tool for preventing infections in high-risk situations. To test this concept, we analysed the impact of DT used in clinical practice on the mortality of the patients during an outbreak of KPCKP infection. Our hypothesis was that DT of patients colonized by KPCKP would be associated with decreased mortality.

Methods

Study design and patients

A retrospective cohort study of patients colonized by KPCKP was carried out in two hospitals from July 2012 to July 2015 in the context of simultaneous outbreaks caused by a colistin-resistant KPCKP strain belonging to ST512.

Rectal swab cultures were performed to detect patients colonized by KPCKP. All admitted patients detected as colonized were eligible; only patients admitted to ICU and neutropenic patients were screened weekly. To select patients at significant risk of developing infections due to KPCKP, the patients fulfilling at least one of the following criteria were included in the analysis: (a) neutropenia occurring within 2 weeks after the detection of colonization; (b) major surgery (including transplantation) performed within the following 2 weeks; (c) patients with multiple comorbidities, defined as patients with more than two chronic debilitating diseases including diabetes mellitus, chronic pulmonary disease, chronic liver disease, renal insufficiency, chronic cardiac insufficiency and immunodepression; and (d) prior severe and recurrent KPCKP infections. To avoid a survivor bias favouring decolonization, patients who were prescribed DT were only included if the therapy was administered during the first week from the date of culture. Patients with an active infection when colonization was detected were excluded from the study, as were patients who started DT during an active infection. The decision to use DT was based on the clinical judgement of the physician responsible for each patient. Patients who received DT were compared with those who did not.

Two different decolonization regimens were used: (i) hard gelatin capsules containing 40 mg of neomycin sulphate and 80 mg of streptomycin sulphate (administered every 8 h orally for 2 weeks); and (ii) gentamicin solution (8 mg/mL) administered orally (as 80 mg of gentamicin every 6 h for 2 weeks). In patients with tracheal intubation or tracheostomy, an orabase paste of gentamicin (1.6 mg/g) was also applied to oral mucosa, gums, palate and tracheal stoma (0.5 g every 6 h for 2 weeks). The strain was susceptible to the antibiotic regimen used.

Day 0 was the day when DT was initiated (in decolonized patients) or the day colonization was detected for the first time (in non-decolonized patients). All patients were followed for 6 months or until death if this occurred before. When necessary, patients or their family members were contacted by telephone to determine their status.

Ethics

The study was approved by the Spanish Agency for Medicines and Healthcare Products (AEMPS, code FIC-CAR-2015-01) and by the ethics committees of the participating hospitals (code 2849), which exempted the need for informed consent. All the data collected were anonymized. The study was registered with ClinicalTrials.gov (NCT02604849). The analysis was performed following the STROBE recommendations[19] (Table S1, available as Supplementary data at *JAC* Online).

Variables

The main outcome variable was all-cause mortality at 180 days. Secondary outcome variables included rate of KPCKP infection during the follow-up and microbiological success of DT in the same period (see below). Gentamicin resistance rates were also analysed in strains isolated after DT. At least one surveillance culture was performed in all patients before the end of the follow-up period.

The following explanatory variables were collected from each patient: sex, age, place of residence, hospitalization in the previous 3 months, chronic underlying diseases, chronic disease severity according to the Charlson comorbidity index,[20] prior KPCKP infection, strain susceptibility to gentamicin, neutropenia, surgical procedures before and after KPCKP colonization, use of concomitant systemic antibiotic therapy while receiving DT, duration of invasive procedures during follow-up (central or peripheral venous catheter, urinary catheter or mechanical ventilation), development of KPCKP infection, source of infection, and severity of systemic inflammatory response at the presentation of the infection.

Definitions

The definitions were established prior to the collection of data and the statistical analysis. Intestinal colonization was defined as the isolation of

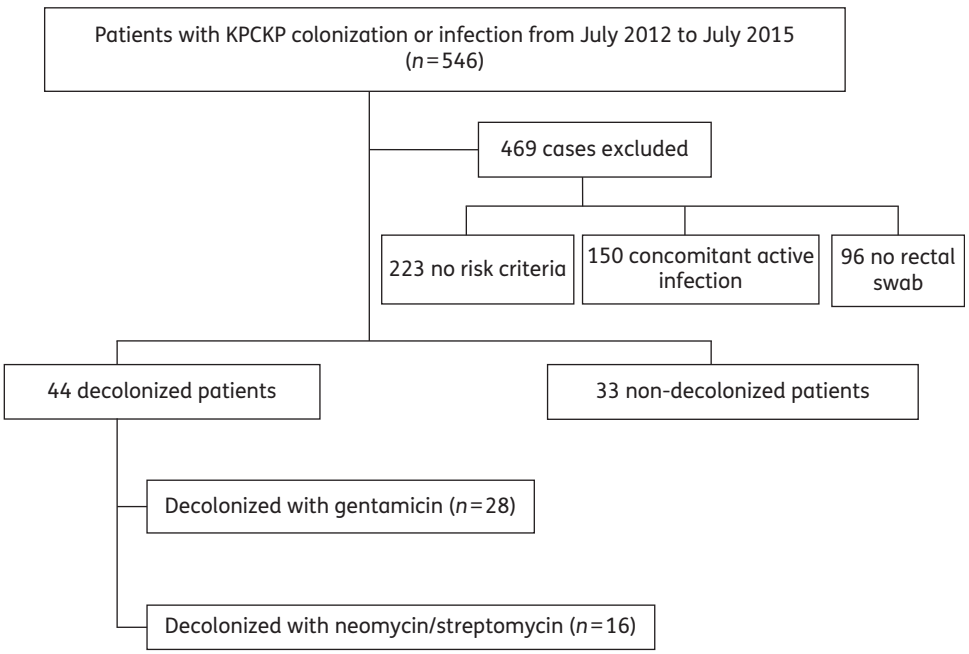

Figure 1. Study flow diagram.

a KPCKP phenotypically compatible with the epidemic clone in a rectal swab. Microbiological success of DT was defined as the absence of KPCKP in at least two rectal swabs performed at least 48 h apart after DT completion; patients who died before microbiological assessment were considered as microbiological failures. Infections were defined according to the CDC criteria.[21] The day the culture was performed to diagnose the infection was considered the day of onset of infection. Neutropenia was defined as a neutrophil count of <500 neutrophils/mm^3 for more than 72 h. Sepsis, severe sepsis and septic shock were defined according to previously established criteria.[22] The Cockroft–Gault formula was used to calculate creatinine clearance (CL_{CR}). Renal failure was defined as CL_{CR} <60 mL/min.

Microbiological variables and antibiotic susceptibility studies

Rectal swabs were cultured in chromogenic media for detection of ESBL or carbapenemase-producing Gram-negative bacilli. The chromogenic media used were Colorex™ ESBL and Colorex™ KPC plates (RPD Microbiology,

Table 1. Baseline characteristics of patients colonized by KPCKP, according to whether they were treated or not treated with DT

	Patients treated with DT (n=44)	Patients not treated with DT (n=33)	P^a
Age (years), mean (SD)	66.3 (2.84)	74.24 (2.36)	0.06
Male, *n* (%)	24 (54.5)	20 (60.5)	0.59
Long-term care facility resident, *n* (%)	5 (11.4)	2 (6.1)	0.42
Prior major surgery (2 weeks), *n* (%)	6 (13.6)	2 (6.1)	0.28
Prior hospitalization (3 months), *n* (%)	30 (68.1)	23 (69.7)	0.89
Comorbidities, *n* (%)			
diabetes mellitus	12 (27.3)	13 (39.4)	0.26
arterial hypertension	19 (43.2)	18 (54.5)	0.32
chronic kidney disease	13 (29.5)	6 (18.2)	0.25
haemodialysis	3 (6.8)	1 (3)	0.63
solid organ transplantation	5 (11.4)	1 (3)	0.23
haematopoietic precursor transplantation	4 (9.1)	1 (3)	0.39
Invasive procedures after colonization (duration in days), mean (SD)			
mechanical ventilation	0.5 (0.3)	0.7 (0.4)	0.26
central venous catheter	5.9 (1.01)	8.9 (1.9)	0.98
urinary catheterization	6.1 (1.9)	7.4 (2.06)	0.07
Charlson score, mean (SD)	2.8 (0.3)	3.1 (0.4)	0.91
Unit admission in the diagnosis of colonization, *n* (%)			
medical	31 (70.5)	17 (51.5)	0.09
surgical	12 (27.3)	11 (33.3)	0.57
ICU	1 (2.3)	5 (15.2)	0.06
Risk factor that indicated decolonization, *n* (%)			
neutropenia	18 (40.9)	7 (21.2)	0.07
major surgery (2 weeks later)	5 (11.4)	5 (15.2)	0.63
recurrent, severe KPCKP infections	15 (34.1)	15 (45.5)	0.31
multi-comorbid patients	6 (13.6)	6 (18.2)	0.59
Concomitant systemic antibiotics, *n* (%)			
none	18 (40.9)	21 (63.6)	0.05
carbapenems	10 (22.7)	4 (12.1)	0.1
β-lactam/β-lactamase inhibitor combinations	7 (15.9)	3 (9.1)	0.18
fluoroquinolones	6 (13.6)	4 (12.1)	0.43
others[b]	3 (6.8)	1 (3)	0.28
Mortality at 180 days of follow-up, *n* (%)	11 (25)	18 (54.5)	0.008
KPCKP infections during follow-up, *n* (%)	2 (4.5)	13 (39.4)	<0.001
Microbiological efficacy at 180 days of follow-up, *n* (%)	26 (59.1)	3 (9.1)	<0.001

CPE, carbapenemase-producing Enterobacteriaceae.
[a]*P* values comparing CPE-colonized and non-CPE-colonized patients were calculated using the Student's *t*-test for normally distributed continuous data, the Mann–Whitney *U*-test for non-normally distributed continuous data, Pearson's χ^2 test with Yates' continuity correction for categorical data and Fisher's exact test for categorical data in the case of expected counts <5.
[b]Others: aminoglycosides, oxazolidinones.

Table 2. Analysis of variables associated with mortality at 180 days of follow-up

Variable	Survivors, $n=48$	Deaths, $n=29$	Univariate analysis		Multivariate analysis (model 1)		Multivariate analysis (model 2)	
			HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (years), mean (SD)	70 (2.57)	69.2 (3.03)	1 (0.98–1.024)	0.79				
Sex, *n* (%)								
female	20 (41.7)	13 (44.8)	0.85 (0.41–1.77)	0.67				
male	28 (58.3)	16 (55.2)						
Neutropenia (<500 neutrophils/mm^3), *n* (%)								
no	39 (81.3)	13 (44.8)	2.29 (1.1–4.77)	0.03	4.07 (1.78–9.31)	0.001	4.07 (1.8–9.33)	0.001
yes	9 (18.8)	16 (55.2)						
Major surgery, *n* (%)								
no	41 (85.6)	26 (89.7)	0.78 (0.24–2.6)	0.69				
yes	7 (14.6)	3 (10.3)						
Recurrent, severe KPCKP infections, *n* (%)								
no	29 (60.4)	18 (62.1)	1.24 (0.58–2.65)	0.58				
yes	19 (39.3)	11 (37.9)						
Multi-comorbid patients, *n* (%)								
no	42 (87.5)	23 (79.3)	1.22 (0.49–3.01)	0.67				
yes	6 (12.5)	6 (20.6)						
Central or peripheral venous catheterization (days), mean (SD)	5.94 (1.45)	10.44 (1.82)	1.03 (0.99–1.06)	0.07	1.05 (1.001–1.09)	0.02	1.04 (1–1.09)	0.05
Urinary catheterization (days), mean (SD)	6.46 (1.88)	7 (2.05)	1.006 (0.98–1.03)	0.67				
Invasive mechanical ventilation (days), mean (SD)	0.46 (0.27)	0.86 (0.46)	1.06 (0.92–1.22)	0.41				
Concomitant systemic antibiotic therapy, *n* (%)								
no	24 (50)	15 (51.7)	1.2 (0.56–2.55)	0.63				
yes	24 (50)	14 (48.3)						
Charlson index, mean (SD)	2.75 (0.83)	3.23 (0.475)	1.12 (0.95–1.31)	0.18				
Unit admission in the diagnosis of colonization, *n* (%)								
medical	34 (70.8)	14 (48.3)	0.56 (0.27–1.18)	0.13				
surgical	11 (22.9)	12 (41.4)	1.63 (0.77–3.46)	0.2				
ICU	3 (6.3)	3 (10.3)	1.44 (0.43–4.79)	0.56				
DT, *n* (%)								
no	15 (31.3)	18 (62.1)	0.33 (0.15–0.73)	0.006	0.18 (0.06–0.55)	0.003	not considered	
yes	33 (68.8)	11 (37.9)						
DT used, *n* (%)								
not treated	15 (31.3)	18 (62.1)	reference		not considered		reference	
gentamicin	22 (45.8)	6 (20.7)	0.27 (0.1–0.71)	0.009			0.15 (0.04–0.54)	0.004
neomycin/streptomycin	11 (22.9)	5 (17.2)	0.46 (0.17–1.24)	0.12			0.22 (0.06–0.9)	0.04
Propensity score			0.37 (0.11–1.26)	0.11	0.95 (0.18–4.94)	0.95	0.94 (0.18–4.88)	0.94

Model 1: includes DT jointly. Likelihood ratio test: $\chi^2=23.84$; $P<0.001$; GL=4.
Model 2: includes DT separately according to regimen used. Likelihood ratio test: $\chi^2=24.15$; $P<0.001$; GL=5.

Barcelona, Spain). Susceptibility tests and identification were performed using a Gram-negative REV.2 WIDER panel (Siemens Healthcare Diagnostics, Camberley, UK) and Etest strips (Liofilmchem, Italy). The identification and susceptibility of the clinical isolates was assessed at each centre using standard microbiological procedures. The MICs were determined by the disc-plate diffusion method for neomycin (120 μg discs; IZASA) and by Etest strips for streptomycin according to CLSI guidelines. The epidemic *K. pneumoniae* isolates in these outbreaks were resistant to third-generation cephalosporins, aztreonam, carbapenems (meropenem MIC >32 mg/L), amikacin, tobramycin, fluoroquinolones and colistin, harboured bla_{SHV-11}, bla_{TEM-1} and bla_{KPC-3} genes, and belonged to ST512, as previously characterized in a reference laboratory.[23]

Statistical analysis

Survival curves were plotted according to the Kaplan–Meier method and compared with the long-rank test. The Cox regression model was used to study the variables associated with mortality, occurrence of infection and microbiological success at 180 days. The Kleinbaum–Klein method was used to test for proportional hazards. Univariate analyses were performed separately for each of the variables to determine their crude HRs and 95% CIs. All biologically plausible variables with $P \leq 0.10$ in the univariate analysis were considered for inclusion in the Cox regression model for the multivariate analysis. Possible interactions between the variables were studied. A propensity score for receiving DT was calculated and used as an explanatory variable to control for prescription bias. The propensity score was calculated by performing a logistic regression model including the following variables: age, sex, chronic renal failure, neutropenia, major surgery (including transplantation) performed within two weeks after detection of colonization, prior severe and recurrent KPCKP infections, multi-comorbid patients, use of a central or peripheral venous catheter, urinary catheter or invasive mechanical ventilation, Charlson comorbidity index and unit admission in the diagnosis of colonization (medical, surgical or intensive care unit). The model obtained had an area under the receiver operating characteristic curve (AUROC) for receiving DT of 0.84.

Two multivariate models were built for the analysis of each outcome result. In the first one, the variable 'therapy' was dichotomic (non-DT versus DT); in the second model, the variable 'therapy' was categorized as non-DT, DT with gentamicin and DT with neomycin/streptomycin. A likelihood ratio test was performed to assess the goodness-of-fit of the model. The analyses were performed using SPSS 15.0 software.

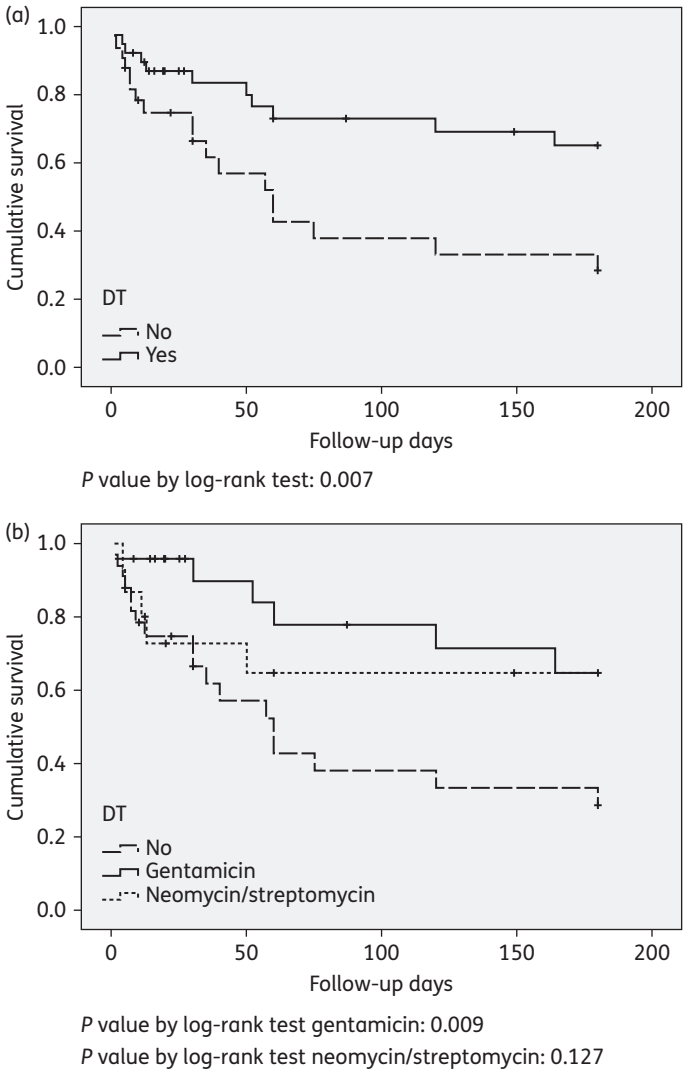

Figure 2. Kaplan–Meier curves according to DT or no DT (a), and DT with gentamicin and neomycin/streptomycin (b).

Results

During the study period, KPCKP was isolated from 546 patients in the two hospitals; 77 patients fulfilled the inclusion criteria, of which 44 received DT and 33 did not (Figure 1). The features of the patients are shown in Table 1; patients not treated with DT were less frequently neutropenic and were somehow older, admitted more frequently to ICU and had longer duration of venous catheterization. DT consisted of gentamicin in 28 patients (63.6% of those treated) and neomycin/streptomycin in 16 patients (36.4%).

Crude mortality at 180 days was 25% (11/44) among patients who received DT and 54.5% (18/33) among those who did not (crude HR=0.18; 95% CI 0.06–0.55). The association was also observed in stratified analysis according to the type of DT (for gentamycin, crude HR=0.15; 95% CI 0.04–0.54; for neomycin/streptomycin, crude HR=0.22; 95% CI 0.06–0.9) (Table 2). Figure 2 shows the survival curves of patients according to DT. The variables associated with mortality are shown in Table 2. A propensity score for receiving DT was calculated as specified in the Methods section. Two multivariate models were constructed (Table 2). In the first one, DT was independently associated with lower HR of death; in the second, DT with gentamicin and neomycin/streptomycin were both associated with lower HR of death (likelihood ratio test for the models, $P<0.001$ and $P<0.001$, respectively).

The cumulative incidence of KPCKP infections was 4.5% (2/44) in the decolonized patients versus 39.4% (13/33) in the non-decolonized patients ($P<0.001$). The descriptive characteristics of the KPCKP infections during follow-up are shown in Table 3. There were no differences in the frequency of KPCKP infection between patients treated with gentamicin (1/28, 3.6%) and those treated with neomycin/streptomycin (1/16, 6.3%) ($P=0.6$).

The variables associated with the risk of developing a KPCKP infection during the follow-up are shown in Table S2. DT was also associated with a lower risk of KPCKP infections during the follow-up period (crude HR: 0.14; 95% CI 0.02–0.83). When patients who received treatment with gentamicin or neomycin/streptomycin were analysed separately, we found that patients treated with gentamicin had a lower KPCKP infection rate

Table 3. Descriptive characteristics of KPCKP infections during follow-up

	Decolonized patients ($n=2/44$)	Non-decolonized patients ($n=13/33$)	P
Age (years), mean (SD)	77.92 (2.01)	74 (1)	0.45
Male, *n* (%)	2 (100)	8 (61.5)	0.43
Prior KPCKP infection, *n* (%)	1 (50)	2 (15.4)	0.37
Causes of risk, *n* (%)			
neutropenia	1 (50)	2 (15.4)	0.37
major surgery (2 weeks later)	0	3 (23.1)	NA
recurrent, severe KPCKP infections	1 (50)	6 (46.2)	0.73
multi-comorbid patients	0	2 (15.4)	NA
Adequate treatment for prior KPCKP infection, *n* (%)	0	1 (7.7)	NA
Sepsis, *n* (%)	0	1 (7.7)	NA
Charlson index, mean (SD)	3 (0.7)	3 (1)	0.9
Length of hospitalization (days), median (IQR)	13 (32–2)	8 (16–4.5)	0.22
Concomitant systemic antibiotic therapy, *n* (%)	2 (100)	4 (30.8)	0.14
Source, *n* (%)			
surgical wound	0	3 (23.1)	NA
urinary	1 (50)	3 (23.1)	0.37
catheter	1 (50)	4 (30.8)	0.57
abdominal	0	3 (23.1)	NA
Mortality, *n* (%)	1 (50)	6 (46.2)	0.73

NA, not applicable.
P values comparing CPE-colonized and non-CPE-colonized patients were calculated using the Student's *t*-test for normally distributed continuous data, the Wilcoxon rank-sum test for non-normally distributed continuous data, Pearson's χ^2 test with Yates' continuity correction for categorical data and Fisher's exact test for categorical data in the case of expected counts <5.

than those who did not receive DT (crude HR=0.86; 95% CI 0.008–0.94); but the association was not significant for patients treated with neomycin/streptomycin (crude HR=0.59; 95% CI 0.03–2.24). The Kaplan–Meier curves for KPCKP infection according to DT are shown in Figure S1. Again, two multivariate models were built; in the first one, DT was independently associated with lower HR of KPCKP infection. In the second model, only DT with gentamicin was significantly associated with lower HR of KPCKP infection (likelihood ratio test, $P<0.001$ for both models). DT achieved microbiological success in 59.1% (26/44) in the decolonized patients and a 9.1% (3/33) in the non-decolonized patients ($P<0.001$). In the analysis of the variables associated with microbiological success, we did not get a multivariate model, as the DT was the only variable showing significant association (HR=4.06; 95% CI 1.06–15.6). When stratified by treatment regimen, DT with gentamicin was associated with higher microbiological success rate than no treatment (HR 5.67, 95% CI 1.33–24.1), and again the association was not significant for the neomycin/streptomycin regimen (Table S3).

All patients included in the study were tested for sensitivity to gentamicin in follow-up cultures before the end of follow-up or prior to death. Gentamicin-resistant isolates were obtained in follow-up cultures in 6/44 (13.6%) patients who received DT, and in 1/33 (3%) patients who were not treated ($P=0.008$). Of the 18 DT patients with microbiological failures, gentamicin-resistant isolates were found in 6 (33.3%).

Discussion

The results of this study suggest that selected patients colonized by KPCKP may benefit from administration of DT with aminoglycosides (particularly gentamicin) in terms of a reduction in the risk of death and of infection due to KPCKP.

Eradication of the bacteria from the intestinal flora is the ultimate goal of DT when used with the purpose of controlling the transmission of these organisms; however, failures of this strategy are common, and this is therefore not a recommended routine infection control measure.[11–14] Additionally, if decolonization is to be used, it should not be administered as the only infection control measure but in tandem with other measures. However, we were interested in testing the concept that the main goal of decolonization might be to prevent infections and death in specific, high-risk colonized patients. This is based on the fact that colonization precedes infection in most cases; also, there is evidence that colonization by carbapenem-resistant Enterobacteriaceae is associated with increased mortality in critically ill patients.[18] Tascini *et al.*[12] analysed 50 patients treated with DT and found that patients who were effectively decolonized with gentamicin

had a lower risk of KPCKP infections (15% versus 73%) than those in whom the DT was not effective, but no differences in mortality were shown. To our knowledge, there are no previous studies evaluating the impact of DT on long-term mortality including a control group of untreated patients. Our results suggest that a decolonization regimen with aminoglycosides, in high-risk scenarios, is effective in reducing crude mortality, and therefore should be investigated in randomized clinical trials.

An important concern with the use of DT with gentamicin is the risk of inducing or selecting resistance to this antibiotic, which is a potentially useful antibiotic for the treatment of infections.[24] In this study, oral gentamicin was associated with isolation of gentamicin-resistant isolates in a substantial proportion of treated patients, similar to that found by Tascini *et al*.[12] Therefore, we warn against indiscriminate use of DT with aminoglycosides, which should be used only in selected patients at high risk of developing invasive infections.

The efficacy of DT for eradicating colonization in real life can be reasonably questioned.[25] Our results, which are similar to those described in the literature,[12,13,15] confirm that the rate of complete microbiological eradication is not high, as it was only 59.1% at 180 days. We hypothesized that the clinical benefit found with DT is related to a critical reduction in the KPCKP load in the bowel of the patients, enough to reduce the risk of infection during the highest-risk period. Although a previous study found lower microbiological efficacy of gentamicin in patients receiving concomitant antibiotic therapy,[12] we could not demonstrate such association.

This study is subject to the limitations of observational studies. Potential unmeasured confounders and insufficient control of confounding are obviously possible despite our efforts. Specifically, there was a larger number of older individuals, central venous catheter days and ICU admission, but fewer neutropenic patients in the group that was not administered DT; also, the concomitant use of antibiotics showed some differences. The limited sample size is a major drawback of this study. The strengths include strict definitions, a pre-registered design and analysis, a 'hard' primary outcome such as mortality, the use of time-dependent analyses and of advanced methods to control for confounders such as the propensity score.

In conclusion, our study suggests that the effectiveness of decolonization should be conceived of in terms of reducing the rate of KPCKP infection and mortality in selected high-risk patients, and not only in terms of prevention of transmission through microbiological eradication.

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Transparency declarations

J. R.-B. has served as a scientific advisor for AstraZeneca, Merck, Achaogen and Basilea, and has been a speaker for Astellas, Merck and AbbVie. All other authors: none to declare.

Supplementary data

Tables S1–S3 and Figure S1 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

References

1 Tzouvelekis LS, Markogiannakis A, Psichogiou M *et al*. Carbapenemases in *Klebsiella pneumoniae* and other Enterobacteriaceae: an evolving crisis of global dimensions. *Clin Microbiol Rev* 2012; **25**: 682–707.

2 Zarkotou O, Pournaras S, Tselioti P *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.

3 Tumbarello M, Viale P, Viscoli C *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.

4 Souli M, Galani I, Antoniadou A *et al*. An outbreak of infection due to β-lactamase *Klebsiella pneumoniae* Carbapenemase 2-producing *K. pneumoniae* in a Greek University Hospital: molecular characterization, epidemiology, and outcomes. *Clin Infect Dis* 2010; **50**: 364–73.

5 Qureshi ZA, Paterson DL, Potoski BA *et al*. Treatment outcome of bacteremia due to KPC-producing *Klebsiella pneumoniae*: superiority of combination antimicrobial regimens. *Antimicrob Agents Chemother* 2012; **56**: 2108–13.

6 Patel G, Huprikar S, Factor SH *et al*. Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. *Infect Control Hosp Epidemiol* 2008; **29**: 1099–106.

7 Neuner EA, Yeh JY, Hall GS *et al*. Treatment and outcomes in carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections. *Diagn Microbiol Infect Dis* 2011; **69**: 357–62.

8 Endimiani A, Depasquale JM, Forero S *et al*. Emergence of bla_{KPC}-containing *Klebsiella pneumoniae* in a long-term acute care hospital: a new challenge to our healthcare system. *J Antimicrob Chemother* 2009; **64**: 1102–10.

9 Munoz-Price LS, Quinn JP. Deconstructing the infection control bundles for the containment of carbapenem-resistant Enterobacteriaceae. *Curr Opin Infect Dis* 2013; **26**: 378–87.

10 Buehlmann M, Bruderer T, Frei R *et al*. Effectiveness of a new decolonisation regimen for eradication of extended-spectrum β-lactamase-producing Enterobacteriaceae. *J Hosp Infect* 2011; **77**: 113–7.

11 Zuckerman T, Benyamini N, Sprecher H *et al*. SCT in patients with carbapenem resistant *Klebsiella pneumoniae*: a single center experience with oral gentamicin for the eradication of carrier state. *Bone Marrow Transplant* 2011; **46**: 1226–30.

12 Tascini C, Sbrana F, Flammini S *et al*. Oral gentamicin gut decontamination for prevention of KPC-producing *Klebsiella pneumoniae* infections: relevance of concomitant systemic antibiotic therapy. *Antimicrob Agents Chemother* 2014; **58**: 1972–6.

13 Saidel-Odes L, Polachek H, Peled N *et al*. A randomized, double-blind, placebo-controlled trial of selective digestive decontamination using oral gentamicin and oral polymyxin E for eradication of carbapenem-resistant *Klebsiella pneumoniae* carriage. *Infect Control Hosp Epidemiol* 2012; **33**: 14–9.

14 Schechner V, Kotlovsky T, Kazma M *et al*. Asymptomatic rectal carriage of blaKPC producing carbapenem-resistant Enterobacteriaceae: who is prone to become clinically infected? *Clin Microbiol Infect* 2013; **19**: 451–6.

15 Oren I, Sprecher H, Finkelstein R *et al*. Eradication of carbapenem-resistant Enterobacteriaceae gastrointestinal colonization with

nonabsorbable oral antibiotic treatment: a prospective controlled trial. *Am J Infect Control* 2013; **41**: 1167–72.

16 Zimmerman FS, Assous MV, Bdolah-Abram T *et al*. Duration of carriage of carbapenem-resistant Enterobacteriaceae following hospital discharge. *Am J Infect Control* 2013; **41**: 190–4.

17 Gonzalez-Padilla M, Torre-Cisneros J, Rivera-Espinar F *et al*. Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*. *J Antimicrob Chemother* 2015; **70**: 905–13.

18 Dautzenberg MJ, Wekesa AN, Gniadkowski M *et al*. The association between colonization with carbapenemase-producing enterobacteriaceae and overall ICU mortality: an observational cohort study. *Crit Care Med* 2015; **43**: 1170–7.

19 von Elm E, Altman DG, Egger M *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453–7.

20 Charlson ME, Pompei P, Ales KL *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–83.

21 Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008; **36**: 309–332.

22 Levy MM, Fink MP, Marshall JC *et al*. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; **31**: 1250–6.

23 Lopez-Cerero L, Egea P, Gracia-Ahufinger I *et al*. Characterisation of the first ongoing outbreak due to KPC-3-producing *Klebsiella pneumoniae* (ST512) in Spain. *Int J Antimicrob Agents* 2014; **44**: 538–40.

24 Daneman N, Sarwar S, Fowler RA *et al*. Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. *Lancet Infect Dis* 2013; **13**: 328–41.

25 Wittekamp BH, Bonten MJ. Antibiotic prophylaxis in the era of multidrug-resistant bacteria. *Expert Opin Investig Drugs* 2012; **21**: 767–72.