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FULL PAPER

Oral gentamicin therapy for Carbapenem-resistant *Klebsiella pneumoniae* gut colonization in hematologic patients: a single center experience

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SUMMARY

The mortality for carbapenem-resistant *Klebsiella pneumoniae* (KPC-Kp) infection ranges from 18 to 48% depending on the type of therapy. Mortality rates in hematologic patients are even higher, up to 85%. Gut decontamination with oral gentamicin might be an option to avoid a subsequent KPC-Kp infection in colonized patients.

We treated 14 hematologic patients with oral gentamicin, 80 mg four times daily, for 7 to 25 days in order to eradicate KPC-Kp from the gut, starting oral gentamicin therapy when possible after the discontinuation of systemic antibiotic therapy.

The overall decontamination rate in the entire study population was 71% (10/14). Out of the 4 patients who did not respond to oral gentamicin therapy, 1 KPC-Kp strain was gentamicin resistant and 4 patients received concomitant systemic antibiotic therapy (CSAT). One of these patients died from KPC-Kp sepsis. The decontamination rate was 90% (9/10) in patients receiving oral gentamicin only, versus 25% (1/4) in those also treated with CSAT. No new gentamicin-resistant KPC-Kp strain was isolated during oral gentamicin therapy

Oral gentamicin might be useful for gut decontamination and prevention of KPC-Kp infection. This option should be considered in patients colonized by a gentamicin-susceptible KPC-Kp strain and not receiving CSAT.

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INTRODUCTION

The worldwide spread of carbapenem-resistant *Klebsiella pneumoniae* (KPC-Kp) is a current health threat worldwide. The first Kpc-Kp was identified in 1993 (Naas and Nordmann, 1994). Since then, a large variety of carbapenemases have been identified in *Enterobacteriaceae*. KPC-*Kp* mortality infections range from 18 to 48% (Morrill *et al.*, 2015), up to 51-65% in bloodstream infections, depending on the type of therapy administered (mono vs combo), co-morbidities and risk-factors (Giacobbe *et al.*, 2015; Fraenkel-Wandel *et al.*, 2016). This result may be due to delayed time to active therapy, pharmacologic limitations of available treatment options, and the fact that patients with KPC-Kp infections tend to be critically ill (Morrill *et al.*, 2015). Patients with hematologic malignancies and hematopoietic stem cell transplant recipients are more vulnerable to carbapenemase-resistant *Enterobacteriaceae* (CRE) because of chemotherapy-induced gastrointestinal mucositis, prolonged hospitalizations and neutropenia, and frequent use of broad-spectrum antibacterial agents (Satlin *et al.*, 2014). The mortality of patients submitted to BMT and sepsis due to KPC-Kp might be as high as 85% (Girmenia *et al.*, 2015a). We decided to treat hematologic patients gut colonized by KPC-Kp using oral gentamicin regimen of 80 mg four times a day because of the higher gentamicin susceptibility rate reported in Italy than in other countries (Satlin *et al.*, 2014) and the few contraindications to using oral gentamicin for gut decolonization. In fact, this therapeutic regimen may be ideal for this use because of the rapid bactericidal activity *in vitro* against gentamicin-susceptible KPC-Kp strain, the virtual absence of systemic activity and systemic toxicity when administered orally, the low activity on the gastrointestinal flora, especially anaerobes (Qureshi *et al.*, 2012; Zuckerman *et al.*, 2010; Oren *et al.*, 2014; Saidel-Odes *et al.*, 2011; Tascini *et al.*, 2014).

The aim of our study was to test the efficacy of oral gentamicin in gut decontamination from KPC-Kp in hematologic patients, in view of immunosuppressive therapy, stem cell transplantation or to prevent sepsis after chemotherapy.

Key words:
Oral gentamicin, Hematologic patients, KPC-*Kp* colonization.

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MATERIALS AND METHODS

We performed a prospective study in a hematologic ward of an Italian second level hospital to quantify the efficacy of gentamicin gut decontamination from KPC-Kp in he-

matologic patients with and without concomitant infection. We considered eligible all patients with rectal swab cultures positive for KPC-Kp with hematologic disease. Our first end-point was the proved gut decontamination.
Rectal swab cultures were performed at the time of hospital admission and every 3 days thereafter. The direct rectal swab cultures on chromogen medium for all carbapenemase-producing Enterobacteriacae (chromID CARBA SMART, bioMerieux, Marcy-l'Etoile, France) was used to identify patients with KPC-Kp gut colonization, then confirmed by the validated direct screening method using boronic acid (Giani *et al.*, 2011). KPC-Kp stool isolates were identified by matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry (Vitek MS, bioMérieux). Antimicrobial susceptibility testing was performed using an automated system (VITEK2, bioMerieux) and susceptibility was also determined using a disk diffusion method according to EUCAST version 3.1 guidelines, and MICs of gentamicin were confirmed with E-test, according to the manufacturer's instructions (AB Biodisk, Solna, Sweden). Interpretation of susceptibility data was according to EUCAST breakpoints (version 3.1) (EUCAST site). If there was a discrepancy between the automated system and E-test, the E-test values were chosen (Arena *et al.*, 2014).
Patients who met the inclusion criteria were administered oral gentamicin (80 mg 4 times daily) for 7 to 25 days, having stopped the therapy 3 days after the proved decontamination. Decontamination was defined as 2 rectal swabs, taken at least 48 hours apart, negative for KPC-Kp. The follow-up period was 3 months. All patients provided written informed consent to participate to the study.

RESULTS

Fourteen patients with a hematologic disease and concomitant *KPC-Kp* positive rectal swab cultures were enrolled in the study. The patients were 5 females and 9 males, with a mean age of 68.5 years (range 39-80 years). Their underlying diseases were: acute myeloid leukemia (4 pts), non-Hodgkin's lymphoma (3 pts), multiple myeloma (2 pts), Hodgkin's lymphoma (1 pt), chronic lymphocytic leukemia (1 pt), myeloproliferative disorders (1 pt), myelodysplastic syndrome (1 pt) and Waldenstrom's macroglobulinemia (1 pt). Out of 14 KPC-Kp isolated, only 1 was resistant to gentamicin (MIC >16 mg/L), but we treated him because of the high gentamicin concentration reached in the gut and the importance of decolonization in this case. Two other strains had MIC of 4 mg/L at automated system but it was 2 mg/L when tested with E-test, therefore fully susceptible. All strains were resistant to carbapenems; 2/14 were resistant to colistin; 6/14 were resistant to fosfomycin; 2/14 resistant to tigecycline. Concomitant systemic associated therapy (CSAT) was administered to 4/14 patients (2 with carbapenem) due to infected surgical wound (2/4), urinary tract infection (1/4) and pneumonia (1/4). Only 2/14 patients were treated with meropenem before KPC-Kp gut colonization, for other infections.
The enrolled patients were treated with oral gentamicin for 7 to 25 days and the overall decontamination rate in the entire study population administered oral gentamicin was 71% (10/14). Four patients were not decolonized by gentamicin oral therapy: 1 of these was the patient harbouring gentamicin-resistant strain and 3 patients had CSAT (2/3 with carbapenem). One out of these 4 patients died from KPC-Kp sepsis. At 3 months of follow-up from the proved decolonization, no KPC-Kp re-colonization was documented. The decontamination rate was 90% (9/10) in patients receiving oral gentamicin only, versus 25% (1/4) in those also treated with CSAT. No new gentamicin-resistant KPC-Kp strain was isolated during oral gentamicin therapy (*Table 1*).

DISCUSSION

KPC-Kp infections are associated with high mortality and morbidity, especially in Intensive Care Units and hematologic patients (Girmenia *et al.*, 2015b). Patients with

Table 1

Pt	*Age*	*Previous Antibiotic therapy (30 days before)*	*Kp-KPC Gentamicin MIC (mg/L)*	*Gentamicin duration therapy*	*CSAT*	*Decolonization*	*Death due to Kp-KPC sepsis*
1	74	ciprifloxacin, daptomycin	0.75	14	fosfomycin	no	no
2	65	daptomycin, rifampicin,	1	7	daptomycin	yes	no
3	71	piperacillin/tazobactam, teicoplanin	2	14	none	yes	no
4	39	levofloxacin	>16	14	none	no	no
5	62	piperacillin/tazobactam, teicoplanin, meropenem	2	13	meropenem	no	no
6	63	piperacillin/tazobactam, teicoplanin, meropenem	2	11	meropenem	no	yes
7	72	none	1	8	none	yes	no
8	72	piperacillin/tazobactam	1	8	none	yes	no
9	79	ceftriaxone	0.75	7	none	yes	no
10	74	cotrimoxazole	1.5	7	none	yes	no
11	72	none	S	11	none	yes	no
12	77	none	S	12	none	yes	no
13	59	cotrimoxazole	S	10	none	yes	no
14	80	doxiciline	S	25	none	yes	no

hematology malignancies and hematopoietic stem cell transplant recipients may have a worse outcome in case of KPC-Kp infections, with a higher incidence of infection because of chemotherapy-induced gastrointestinal mucositis and neutropenia, prolonged hospitalizations and frequent use of broad-spectrum antibacterial agents. Therefore, infections caused by KPC-Kp are extremely worrisome and the mortality rates may be as high as 80% (Girmenia *et al.*, 2015a). An appropriate CRE-targeted antibiotic therapy (CTAT) was defined as a combination including at least two among colistin/polymyxin B, tigecycline and gentamicin, preferably with the addition of meropenem, and eventually fosfomycin (Averbuch *et al.*, 2013). The GITMO (Gruppo Italiano Trapianto Midollo Osseo) study confirmed the independent role of a first line CTAT on survival: in their study, half the patients who received a first line CTAT still died from the infection (Girmenia *et al*., 2015b).

Given the limited therapeutic options and the unsatisfactory efficacy of the available treatments, prevention of KPC-Kp infection is the first provision to implement, followed by screening for gut colonization and possibly gut decolonization, in order to reduce the risk of subsequent infections (Girmenia *et al.*, 2015a).

It is important to remember that gut colonization represents the main source for KPC-Kp epidemic dissemination, that, in our experience, 100% of patients with KPC-Kp infection were colonized earlier and that the rates of subsequent CRE infection in patients found to be colonized by screening culture are 9% overall (Schechner *et al.*, 2013), 27% among intensive care unit patients, 25.8% among autologous SCT patients and up to 39.2% among allogeneic SCT patients (Girmenia *et al.*, 2015b).

In our experience, considering the small number of patients analyzed, the decontamination rate in the entire population was 71%, and 90% considering the patients receiving oral gentamicin only.

Despite the small number of patients analyzed in this study, our results are similar to others. Using an oral gentamicin regimen of 80 mg four times daily, Zuckerman *et al*. reported decontamination of KPC-Kp in 66% hematology patients without selection of gentamacin-resistant strains (Zuckerman *et al.*, 2010). Tascini et al. reported a similar decontamination rate (68%) (Tascini *et al.*, 2014) with a significant difference in decontamination rate between the group of patients receiving oral gentamicin only (96%) and the patients receiving oral gentamicin during CSAT (44%). According to our experience, this evidence suggests that the selective pressure of CSAT on gut microbiota may favor the persistent carriage of KPC-Kp, thereby contributing to the higher failure rates observed versus monotherapy (Tascini *et al.*, 2014).

One patient was treated with gentamicin although the KPC-Kp strain was highly resistant to gentamicin. Considering that resistant breakpoints are settled for blood concentration of gentamicin, one might hypothesize that gentamicin concentration in the feces might be higher than clinical breakpoint for bloodstream infection. This single case demonstrates that it is not advisable to suggest gentamicin decontamination for gentamicin-resistant KPC-Kp strains.

Therefore, the selective oral decontamination therapy of KPC-Kp with oral gentamicin is safe and possibly effective and with this therapeutic option as a complementary approach for reducing the risk of severe infection with these notoriously difficult-to-treat MDR Enterobacteriaceae. The possible selection of gentamicin-resistant strains was negligible in our experience, because we stopped oral therapy when it was not effective and we tried to avoid oral gentamicin with CSAT, a strong inducer of KPC-Kp gut colonization, and a cause of persistent gut colonization by KPC-Kp.

We are aware that hematologic patients are usually treated with CSAT for febrile neutropenia or for prophylaxis during neutropenia. On the other hand, colonization and subsequent infections caused by KPC-Kp have an extremely high rate of mortality, therefore a strategy to avoid CSAT should be adopted.

So far only 2 studies in the literature evaluating patients with HM treated with oral gentamicin, for a total of 55 patients (Girmenia *et al.*, 2015a; Machuca *et al.*, 2016). Our experience adds another piece of information on the decontamination in these fragile patients. The concern over selecting gentamicin-resistant strains is probably overestimated and we might avoid selection of gentamicin resistance if we try to avoid CSAT and not prolong oral gentamicin therapy over 15 days if it is not effective. In our study we treated 2 patients for more than 15 days, without successive induction of gentamicin-resistant strains. The follow-up was only 90 days and in this kind of population and a longer period should be used in future experiences.

Avoiding colonization might be useful in hematological patients in order to shorten isolation procedures and leave available more beds in these units with limited resources. In fact, other authors have already demonstrated that some patients that are super-spreaders of KPC-Kp, reducing the gut burden of KPC-Kp might be useful from an epidemiological point of view (Lerner *et al.*, 2015).

Conflicts of interest

C.T. has received funds for speaking at symposia organized on behalf of Pfizer, Novartis, Merck, Angelini, Gilead and Astellas. All other authors: none to declare.

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