Oral Gentamicin Gut Decontamination for Prevention of KPC-Producing Klebsiella pneumoniae Infections: Relevance of Concomitant Systemic Antibiotic Therapy

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Gut colonization represents the main source for KPC-producing Klebsiella pneumoniae (KPC-Kp) epidemic dissemination. Oral gentamicin, 80 mg four times daily, was administered to 50 consecutive patients with gut colonization by gentamicin-susceptible KPC-Kp in cases of planned surgery, major medical intervention, or need for patient transfer. The overall decontamination rate was 68% (34/50). The median duration of gentamicin treatment was 9 days (interquartile range, 7 to 15 days) in decontaminated patients compared to 24 days (interquartile range, 20 to 30 days) in those with persistent colonization (P < 0.001). In the six-month period of follow-up, KPC-Kp infections were documented in 5/34 (15%) successfully decontaminated patients compared to 12/16 (73%) persistent carriers (P < 0.001). The decontamination rate was 96% (22/23) in patients receiving oral gentamicin only, compared to 44% (12/27) of those treated with oral gentamicin and concomitant systemic antibiotic therapy (CSAT) (P < 0.001). The multivariate analysis confirmed CSAT and KPC-Kp infection as the variables associated with gut decontamination. In the follow-up period, KPC-Kp infections were documented in 2/23 (9%) of patients treated with oral gentamicin only and in 15/27 (56%) of those also receiving CSAT (P = 0.003). No difference in overall death rate between different groups was documented. Gentamicin-resistant KPC-Kp strains were isolated from stools of 4/16 persistent carriers. Peak gentamicin blood levels were below 1 mg/liter in 12/14 tested patients. Oral gentamicin was shown to be potentially useful for gut decontamination and prevention of infection due to KPC-Kp, especially in patients not receiving CSAT. The risk of emergence of gentamicin-resistant KPC-Kp should be considered.

Carbapenem-resistant Klebsiella pneumoniae strains producing KPC-type beta-lactamase (KPC-Kp) are multidrug-resistant (MDR) Gram-negative bacilli with limited therapeutic options and high associated mortality rates (>40%) (1–4). Gut colonization represents the main human reservoir for epidemic dissemination in hospitals and requires active surveillance for prompt carrier identification and infection control measures such as isolation or cohorting with dedicated staff (5, 6). Furthermore, gut colonization seems to be associated with a substantial risk (around 10%) of developing subsequent KPC-Kp infection (7, 8) and may be a contraindication for some surgical procedures, organ transplantation, and other major medical interventions. Gut colonization by KPC-Kp may last for months, even in the absence of hospital readmission (9). Therefore, gut decontamination for KPC-Kp colonization could be of interest as a complementary approach for removing patients from isolation, reducing transmission, and preventing subsequent infectious episodes in already-colonized patients.

In fact, various regimens for KPC-Kp gut decontamination have been investigated. Using an oral gentamicin regimen of 80 mg four times a day (QID), Zuckerman et al. reported decontamination of KPC-Kp from 10/15 (66%) hematology patients without selection of gentamicin-resistant strains (10). Oren et al., using oral gentamicin at 80 mg QID, reported decontamination of carbapenem-resistant K. pneumoniae from 11/26 (42%) patients (11). In a randomized double-blind, placebo-controlled trial in 40 patients with KPC-Kp-positive rectal swabs, Saidel-Odes et al. reported that administration of an oral gentamicin-polymyxin E combination cleared KPC-Kp colonization in 12/20 patients (60%) without selecting gentamicin- or colistin-resistant KPC-Kp strains (12). However, Brink et al. found that use of colistin for selective digestive tract decontamination was associated with the emergence of a colistin-resistant OXA-181-producing K. pneumoniae strain (13).

Oral gentamicin may be an ideal agent for gut decontamination from KPC-Kp for several reasons, including the following: (i) gentamicin is rapidly bactericidal in vitro against gentamicin-susceptible KPC-Kp strains; (ii) the oral formulation is virtually non-absorbable, without systemic activity and toxicity; (iii) the drug has a limited spectrum and no activity against anaerobes, being less disruptive to the gastrointestinal flora; and (iv) gentamicin is
not typically administered as part of combination regimens for serious KPC-Kp infections (1). The aim of our pilot study was to describe the microbiological and clinical responses to gut decontamination with oral gentamicin in 50 consecutive patients colonized by KPC-Kp who were receiving or not receiving concomitant systemic antibiotic therapy (CSAT).

(Partial data related to this study have been presented at the 23rd ECCMID Meeting, April 2013 [ECCMID R2812].)

MATERIALS AND METHODS

We performed a pilot nonblinded, prospective study in three Italian hospitals to assess the feasibility of administering oral gentamicin for KPC-Kp gut decontamination. Because no published data were available regarding the possible treatment efficacy of oral decontamination therapy for KPC-Kp, we did not attempt to estimate a priori the required sample size for this pilot study. In an eight-month period, consecutive adult patients with a rectal swab culture positive for KPC-Kp within the previous 7 days were considered eligible for the study if they had (i) planned surgery, (ii) need for major medical intervention that could predispose to serious infection (e.g., cancer chemotherapy or immunosuppression), or (iii) need for transfer outside the hospital. All patients provided written informed consent to participate in the study. The study was approved by the Office of Responsible Research Practices Institutional Review Board of the Azienda Ospedaliera Pisana, Pisa, Italy. Patients who met the inclusion criteria were administered oral gentamicin (80 mg four times daily) for at least 8 days. The need for continued oral decontamination therapy beyond 8 days was determined by the physicians caring for the patient, who were not blinded to follow-up rectal swab culture results. Infection control procedures for patients with KPC-Kp gut colonization were similar at all participating institutions, consisting of patient isolation or cohorting with strict contact precautions and dedicated caregivers and equipment as described in CDC guidelines (14).

We used a validated direct screening method on rectal swab cultures to identify patients with KPC-Kp gut colonization (15). Rectal swab cultures were performed at the time of hospital admission and every 4 days thereafter. K. pneumoniae stool isolates were identified with the mini-API system (bioMérieux, Mercy L’Etoile, France) or by matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry (Vitek MS, bioMérieux). Detection of blakpc genes was confirmed by PCR as previously described (16). Antimicrobial susceptibility testing was performed using a disk diffusion method according to EUCAST version 3.1 guidelines (17), and MICs of gentamicin, colistin, and fosfomycin were determined with Etest, according to the manufacturer’s instruction (AB Biodisk, Solna, Sweden). Interpretation of susceptibility data was according to EUCAST breakpoints (version 3.1) (17). Pulsed-field gel electrophoresis (PFGE) of XbaI-digested genomic DNA of KPC-Kp to compare longitudinal isolates from patients who failed decontamination was performed and interpreted as described previously (18).

The gentamicin peak plasma concentration was determined with a fluorescence immunoassay method (Abbott, Abbott Park, IL) on day 3 of treatment on samples obtained 2 h after drug administration.

Study endpoints. The primary study outcome was decontamination of KPC-Kp gut colonization, defined by at least two consecutive negative rectal swab cultures. Patients with two or more consecutive positive rectal swabs were considered to have failed oral decontamination and were considered persistent carriers. We also evaluated clinical outcomes for patients administered oral gentamicin for KPC-Kp decontamination, including infectious episodes caused by KPC-Kp and death for any cause during a six-month period after oral gentamicin therapy, in decontaminated and persistent carrier groups. A separate analysis was performed with the 23 patients receiving oral gentamicin alone and with the 27 patients who received CSAT.

Statistical analysis. Data were expressed as mean ± standard deviation, median and interquartile range, or proportions, as appropriate. Comparisons were performed with the unpaired t test, Mann-Whitney test, or chi-square test with continuity correction, as appropriate. Gut decontamination events during oral gentamicin therapy were analyzed by the Kaplan-Meier method, with log rank test for curve comparison in patients treated or not with CSAT. To evaluate the influence of CSAT on gut decontamination, we performed a univariate logistic regression analysis adjusting for several potential confounders (KPC-Kp infection, intensive care unit [ICU] stay, days of gentamicin treatment, gender, and age). Predictors found to be statistically significant (P < 0.05) at the univariate logistic regression were then included in a multivariate logistic model. All computations were done with R statistical software (R, version 2.11.1, 2010; R Development Core Team 2006, R Foundation for Statistical Computing, Vienna, Austria). A P value of <0.05 was considered significant.

RESULTS

Fifty consecutive patients with KPC-Kp-positive rectal swab cultures were enrolled in the study over 8 months. All the KPC-Kp isolates from rectal swabs showed susceptibility to gentamicin (MIC<sub>90</sub> 1.5 mg/liter; MIC<sub>90</sub> 2 mg/liter; range, 0.125 to 2 mg/liter). All strains were resistant to carbapenems; 27/50 (54%) were resistant to colistin, 24/50 (48%) to tigecycline, and 7/50 (14%) to fosfomycin.

CSAT was administered to 27/50 of the study patients due to clinically documented pneumonia (n = 1) and 26 microbiologically and clinically documented infections: 18 KPC-Kp (bloodstream infection [BSI], n = 14; ventilator-associated pneumonia, n = 2; peritonitis, n = 1, urinary tract infection [UTI], n = 1), 2 Pseudomonas aeruginosa (BSI, n = 1; cellulitis, n = 1), 3 Escherichia coli (BSI, n = 2; UTI, n = 1), 2 Staphylococcus aureus (BSI, n = 1; cellulitis, n = 1), and 1 Staphylococcus epidermidis (BSI). The majority of patients (22/27) received combinations of two or more antibiotics, whereas five patients received monotherapy regimens. The prescribed antibiotics were tigecycline (n = 15 patients), meropenem (n = 12), colistin (n = 12), gentamicin (n = 8), fosfomycin (n = 4), imipenem (n = 4), co-trimoxazole (n = 3), piperacillin-tazobactam (n = 3), rifampin (n = 2), and teicoplanin (n = 1).

The enrolled patients were treated with oral gentamicin for a median of 16 days (interquartile range, 10 to 27 days), and the overall decontamination rate in the entire study population administered oral gentamicin was 68% (34/50). The median duration of gentamicin therapy was 9 days (interquartile range, 7 to 15 days) in decontaminated patients, versus 24 days (interquartile range, 20 to 30 days) in those with persistent colonization (P < 0.001). At 6 months of follow-up, KPC-Kp infections were documented in 5/34 (15%) patients who were successfully decontaminated, compared to 12/16 (73%) patients with persistent colonization (P < 0.001).

No difference in overall mortality was observed between decontaminated and persistently colonized patients. Patient characteristics and clinical outcomes for successfully decontaminated patients and persistent carriers are summarized in Table 1.

The probability of a persistent carriage status during oral gentamicin therapy was statistically lower in patients treated with gentamicin only than in those receiving CSAT (P = 0.007) (Fig. 1). The decontamination rate was 96% (22/23) in patients receiving oral gentamicin only, versus 44% (12/27) in those also treated with CSAT (P < 0.001). In the follow-up period, KPC-Kp infection was documented in 2/23 (9%) patients treated with oral gentamicin only and in 15/27 (56%) of those also receiving CSAT (P = 0.003). No difference in overall mortality rate between the
Two treatment groups was documented. Patient characteristics and microbiological and clinical outcomes for patients receiving gentamicin only and those also treated with CSAT are summarized in Table 2.

The univariate analysis identified CSAT, KPC-Kp infection, and ICU stay as significant variables (Table 3). The multivariate analysis confirmed CSAT and KPC-Kp infection as the variables associated with gut decontamination (Table 4).

Genotype analysis performed with PFGE on strains of 5/17 patients who failed gut decontamination with gentamicin showed that the KPC-Kp strains were genetically related (correlation index, >90%).

Gentamicin-resistant KPC-Kp strains were isolated during oral gentamicin therapy in 4/16 failed patients (25%).

The mean gentamicin peak blood concentrations, measured in 14/16 patients, were 0.7–1.1 mg/liter (range, 0 to 3.1 mg/liter). Only two patients showed a gentamicin blood level above 1 mg/liter. No drug treatment was interrupted for any reason, and no documented side effects attributable to gentamicin oral therapy were observed.

**DISCUSSION**

Gut colonization with KPC-Kp represents the main source for the epidemic dissemination of carbapenem-resistant *Enterobacteriaceae* and is associated with a substantial risk of developing subsequent infection (7, 8). Selective gut decontamination of KPC-Kp therefore could be an important complementary approach for reducing...
a colonized patient’s risk for spreading or developing severe infection with multidrug-resistant (MDR) Enterobacteriaceae (10, 11, 12).

In our population of 50 KPC-Kp-colonized patients treated with oral gentamicin, we observed a favorable microbiological outcome (overall gut decontamination rate, 34/50 [68%]). Our results are similar to those reported for a small group of hematology patients treated with the same regimen (10/15 [66%]) (10) and for a cohort of medical and surgical patients receiving oral gentamicin in combination with polymyxin E (12/20 [60%]) (12). Recently, Feldman et al. reported that spontaneous resolution of carriage may occur in the majority of patients with remote (>4 months) versus recent acquisition (19). However, Oren et al. reported a spontaneous eradication of carbapenem-resistant Enterobacteriaceae from stools in only 7/102 patients (7%) after a median follow-up period of 140 days (range, 20 to 737) (11); furthermore, some patients (such as those represented in our study) may benefit from more rapid clearance of KPC-Kp colonization due to planned major therapeutic interventions.

It is noteworthy that infectious episodes due to KPC-Kp documented in the six-month follow-up period were significantly lower in the group of successfully decontaminated patients (5/34 [15%]) than in the group of persistently colonized patients (12/16 [73%]). Interestingly, Zuckerman et al. reported that 5/15 patients who failed gentamicin decontamination subsequently died, with three of these deaths due to KPC-Kp BSI (10). Our experience seems to support the relevant role of gut decontamination in preventing subsequent infectious episodes due to KPC-Kp.

In our study, we observed a significant difference in decontamination rate between the group of patients receiving oral gentamicin only (22/23 [96%]) and the patients also receiving oral gentamicin during CSAT (12/27 [44%]). 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. This hypothesis is supported by the reports of Schwaber et al. (20), suggesting the role of antibiotic use as a predictor for KPC-Kp acquisition, and Ben-David et al. (21), identifying antibiotic exposure during the prior 3 months as one of the risk factor for persistent carriage. In our experience, 16/27 (59%) patients treated with CSAT received a carbapenem antibiotic. The specific role of carbapenems in favoring selective pressure and the acquisition of KPC-Kp has also been reported (22, 23). However, we cannot exclude the possibility that CSAT was a marker for more severely ill, debilitated patients, who are more likely to have a natural history of persistent KPC-Kp colonization.

The genotype analysis, although performed on a few strains isolated from 5/17 patients who failed gut decontamination with gentamicin, showed a high correlation rate and no acquisition of new clones.

It is noteworthy that patients treated with only gentamicin had fewer KPC-Kp infectious episodes (2/23 [9%]) than the group also receiving CSAT (15/27 [56%]). This significant difference suggests that gut decontamination for asymptomatic KPC-Kp carriers may be an effective strategy worthy of evaluation in prospective randomized trials, especially among patients who do not require immediate additional systemic antimicrobial therapy. Considering the small sample size, it was also not surprising that we were unable to detect an overall survival difference between successfully and unsuccessfully decontaminated patients who did not receive CSAT (22% versus 37%; P = 0.406). Detection of such a difference would likely require a prospective randomized trial with several hundred patients per treatment arm.

According to the multivariate analysis results, CSAT and KPC-Kp infections are the variables associated with gut decontamination; these variables might identify a subgroup of more critically ill patients who would be less responsive to gentamicin oral therapy.

Oral gut decontamination is associated with some risks. Gentamicin oral therapy may favor the emergence of resistant KPC-Kp, especially in patients who failed to respond to gut decontamination regimens. Gentamicin-resistant KPC-Kp strains were in fact isolated in our study from 4/16 (25%) persistent carriers. Although previous reports of experience with oral gentamicin did not mention the emergence of resistant strains (10, 12), this potential risk should be considered, and gut decontamination should be interrupted as soon as patients fail.

### Table 2: Patient characteristics and microbiological and clinical outcomes for patients treated with gentamicin only versus those receiving concomitant systemic antibiotic therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value for patients receiving:</th>
<th>95% Confidence interval for odds ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral gentamicin only (n = 23)</td>
<td>Oral gentamicin plus CSAT (n = 27)</td>
<td></td>
</tr>
<tr>
<td>No. (%) male</td>
<td>15 (65)</td>
<td>20 (74)</td>
<td>0.710</td>
</tr>
<tr>
<td>Median age, yr, ± SD</td>
<td>67 ± 12</td>
<td>61 ± 15</td>
<td>0.108</td>
</tr>
<tr>
<td>No. (%) of ICU patients</td>
<td>1 (4)</td>
<td>9 (33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. (%) obtaining gut decontamination</td>
<td>14 (11–19)</td>
<td>18 (12–29)</td>
<td>0.311</td>
</tr>
<tr>
<td>No. (%) with KPC-Kp infection</td>
<td>22/23 (96)</td>
<td>12/27 (44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. (%) died</td>
<td>5/23 (22)</td>
<td>10/27 (37)</td>
<td>0.406</td>
</tr>
</tbody>
</table>

a In the 6-month follow-up period.

### Table 3: Univariate logistic regression for gut decontamination event

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio</th>
<th>95% Confidence interval for odds ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSAT*</td>
<td>0.036</td>
<td>0.002–0.213</td>
<td>0.002</td>
</tr>
<tr>
<td>KPC-Kp infection*</td>
<td>0.057</td>
<td>0.011–0.231</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU stay*</td>
<td>0.062</td>
<td>0.008–0.305</td>
<td>0.002</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.697</td>
<td>0.163–2.548</td>
<td>0.598</td>
</tr>
<tr>
<td>Age</td>
<td>1.028</td>
<td>0.985–1.076</td>
<td>0.200</td>
</tr>
<tr>
<td>Duration of gentamicin treatment</td>
<td>0.966</td>
<td>0.913–1.015</td>
<td>0.198</td>
</tr>
</tbody>
</table>

a Significant predictor.
The virtual lack of any systemic activity of oral gentamicin (only 2 patients had blood levels of >1 mg/liter) underscored why the oral regimen was associated with a good safety profile in our study, with no evidence of nephrotoxicity, ototoxicity, or drug interruption due to adverse effects.

Finally, a limitation of this pilot study was the lack of a control group and blinding by physicians caring for patients. An additional limitation was the potential overestimation of gut decontamination due to the lower sensitivity of the culture method than of PCR (15).

Low-level carriage may not be detectable with culture-based methods, but two consecutive negative results are certainly suggestive either of true decontamination or of a significant reduction of the gut colonization burden and have been used as the basis for relaxation of strict contact precautions in infection control programs (14).

However, given our experience, which suggests that selective oral decontamination therapy of KPC-Kp with oral gentamicin is safe and possibly effective, we believe that larger-scale prospective, randomized trials should be considered to evaluate this promising approach for reducing the risk of severe infection of blaKPC producing carbapenem-resistant Enterobacteriaceae: who is prone to become clinically infected? Clin. Microbiol. Infect. 19:451–456. http://dx.doi.org/10.1111/j.1469-0691.2012.03888.x.


