Gastrointestinal colonization by KPC-producing *Klebsiella pneumoniae* following hospital discharge: duration of carriage and risk factors for persistent carriage

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Abstract

The natural history of KPC-producing *Klebsiella pneumoniae* (KPC KP) carriage is unknown. We aimed to examine the duration of KPC KP carriage following hospital discharge and to study the risk factors for persistent carriage. A cohort of 125 KPC KP carriers was followed monthly for between 3 and 6 months after discharge from an acute-care hospital. Rectal swabs and data were collected at baseline and at each visit. KPC KP was detected by culture and direct bla_{KPC} PCR. Acquisition time was regarded as the earliest date of KPC KP isolation. Resolution of carriage was defined as a negative KPC KP test in at least two consecutive samples. Analyses were separated for recent (<4 months) (REC, 75 patients) and remote ($\geq$4 months) (REM, 50 patients) acquisition groups. Risk factors for persistent carriage were examined by survival analyses for the REC group and by prevalence methods for the REM group. The mean age of patients was 67.5 years and 49.6% were male. Forty-six (61%) patients in the REC group and 14 (28%) in the REM group were persistent carriers ($p < 0.001$). A significant risk factor for persistent carriage identified in both the REC and REM groups was the presence of any catheter ($p < 0.05$). Unique risk factor groups included long-term care facility (LTCF) residence ($p < 0.01$) and a low functional status as measured by the Barthel's index ($p < 0.05$) in the REC group and high Charlson's score in the REM group ($p < 0.05$). Out of the entire 100 patients who had at least one negative sample, only 65 remained negative on subsequent cultures. In conclusion, persistent carriage of KPC KP is associated with catheter use and a low functional status; it is more common in patients with recent acquisition and is related to LTCF stay. A single negative KPC KP test is insufficient to exclude persistent carriage.

Keywords: Carbapenem resistance, Charlson's score, colonic carriage, enterobacteriaceae, KPC-producing *Klebsiella pneumoniae*, long-term care facilities

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Introduction

The first cases of *Klebsiella pneumoniae* carbapenemase (KPC)-*Klebsiella pneumoniae* were reported from the mid-Atlantic region of the United States between 1997 and 2000 [1–3]. Since then, KPC-producing *K. pneumoniae* (KPC KP) have spread and become endemic in several countries in Europe, the Middle East, Asia and South America [4,5]. This epidemic is caused by a predominantly monoclonal dissemination of the Sequence-Type (ST)-258 and its Clonal Complex (CC) [6–8], which is still by far the dominant clone in Israel [9].

Carriage of KPC KP in the gastrointestinal tract is important for several reasons. First, it may precede and possibly serve as a source for subsequent clinical infection in approximately 9% of carriers [10,11]. Second, carriers may serve as an important reservoir for dissemination of KPC KP in healthcare facilities [12–14]. Consequently, active surveillance for carriage of KPC KP and other carbapenem-resistant Enterobacteriaceae (CRE) has become an integral part of local and national programmes designed to control the spread of CRE in the healthcare setting [14–17].

Very little is known about the duration of carriage of KPC KP and of the risk factors associated with persistent carriage. We have recently published a study on a cohort of 59 known CRE carriers and found that 23 of them (38%) were positive at their subsequent hospital admission [18]. Persistent carriers were more likely to be admitted from another healthcare facility, had a higher rate of recent antibiotic exposure and had a shorter duration of time from first detection of CRE to admission [18]. This study sampled patients at their second hospital admission and therefore did not examine the overall natural history of CRE carriage.

In the current study, we followed systematically a cohort of previously known KPC KP carriers following their hospital discharge. Our aims were (i) to examine the duration of carriage of KPC KP and (ii) to study the risk factors for persistent carriage.

Methods

Setting, patient selection and collection of surveillance specimens

The study was conducted at the Tel Aviv Sourasky Medical Center (TASMC), a 1200-bed tertiary care hospital, and at the Reut Hospital, a 300-bed long-term care facility (LTCF), both in Tel Aviv, Israel. In this prospective, observational, cohort study, previously known carriers of KPC KP were identified using the computerized database of the TASMC and the National registry of KPC-KP carriers [17]. Patients were asked to enroll and provide a written informed consent. Patients who were unable to give an informed consent (e.g. critically ill patients) were not approached. Surveillance KPC KP rectal cultures were collected as previously described [19] at five time-points: before discharge, and at 2 weeks, 1, 2 and 3 months following hospital discharge (Fig. S1). A selected group of persistently KPC KP positive patients (positive on their 4 or 5th tests) was sampled also at a sixth time period. Data were collected at enrollment and at each time-point by a patient's enrollment form that included demographics, exposures to antibiotics, underlying conditions and invasive devices, as well as the Barthel's (ADL) index [20] and the Charlson's co-morbidities score [21], and a follow-up form that included questions regarding recent (<1 month) use of an invasive device or antibiotics and LTCF residence. The study was approved by the institutional ethical committee.

Microbiological and molecular methods

A nylon flocked swab system with liquid Amies medium (eSwab; Copan, Brescia, Italy) was used for rectal sampling, and was immediately transferred to the laboratory and processed. Swabs were streaked onto CHROMagar-KPC Plates (HyLabs, Rehovot, Israel) and into a 3-mL Brain-Heart Infusion (BHI) broth tube and were incubated overnight at 36°C. CRE suspicious colonies were identified and processed, including a bla_{KPC}-PCR, as previously described [19], with the exception that a manual biochemical kit (Enterotest; HyLabs) was used for species identification. In addition, bla_{KPC}-PCR was performed from the BHI broth [22].

Data analysis

Clearance of KPC KP carriage was defined as at least two consecutive negative cultures and bla_{KPC}-PCR tests without any subsequent positive test in accordance with the Israeli National Guidelines [23]. The time to clearance was determined as the time from first detection of KPC KP until first negative KPC KP test of the two consecutive negative tests. For the analyses, patients were divided into two groups, according to the time from first identification of KPC KP, by either surveillance or clinical cultures, to the time of hospital discharge: acquisition of KPC KP at less or more than 4 months from discharge was considered recent (REC) or remote (REM), respectively (see Fig. 1). This division was undertaken as survival analysis was deemed inappropriate for the patients with remote acquisition. Associations between REC/REM groups and other baseline demographic and clinical variables were evaluated with analysis of variance, Kruskal–Wallis or chi-squared tests. In the REC group, the association between the baseline demographic and clinical variables and time to KPC KP clearance is presented as Kaplan–Meier curves and compared using the Log Rank test. Cox proportional hazards models were constructed to evaluate the adjusted effects as hazard ratios (HRs) and 95% confidence intervals (CIs). Variables with p value of < 0.1 in the univariate

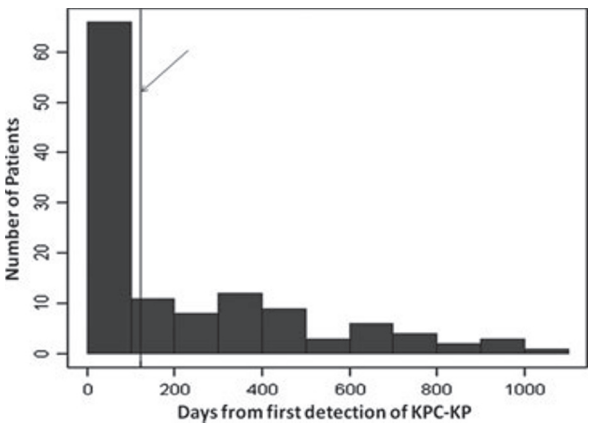

FIG. 1. Time interval from initial detection of KPC-producing *Klebsiella pneumoniae* (KPC KP) to enrollment. The 4-month time-point is marked by an arrow.

analysis entered the multivariate model. In addition, variables that were considered to be critical factors (age, log of the time from first KPC KP detection to enrollment and recent use of antibiotics) were also added. Use of an invasive device, use of antibiotics and LTCF residence were treated as time-dependent variables.

In the REM group, the association between the baseline demographic and clinical variables and KPC KP clearance was compared using similar methods to those described for REC/REM group comparisons. Multivariate analysis was constructed with similar criteria to those described above, using a binary logistic regression model. The 95% CI for the HR of the Charlson's score was incalculable due to the low number (n = 1) of the reference group.

Results

Patients' and isolates' characteristics

The study was conducted from December 2008 through to January 2011, enrolling 125 patients with previous identification of KPC-KP 1. All patients that were approached had agreed to participate in the study and had completed the initial sampling and data collection. Of these, 83 have completed the five follow-up tests and 42 patients did not: 28 have died and 14 have dropped out. An additional sixth test was performed in 30 persistently positive patients. The time intervals between first detection of KPC KP and enrollment are presented in Fig. 1. Accordingly, 75 and 50 patients were included in the REC and REM groups, respectively. The clinical and demographic characteristics of these patients are presented in Table 1. Compared with the REM group, patients in the REC group had a higher rate of positive KPC KP test at enrollment (71 vs. 20%, $p < 0.001$), higher rate of antibiotic treatment in the preceding month (80% vs. 56%, $p < 0.01$), higher rate of LCTF discharge (70.7 vs. 51%, $p < 0.05$) and a higher post-discharge mortality rate (32 vs. 12%, $p = 0.01$). Patients in the REC group tended to have an overall higher Charlson's score, but the difference was not statistically significant ($p = 0.08$). In addition to KPC KP, KPC-producing *E. coli* was isolated in five samples, taken from four patients.

TABLE 1. Demographic and clinical characteristics of patients at enrollment

Variable	REC group[a] (n = 75)	REM group[b] (n = 50)	p-value
Male (%)	36 (48.0)	26 (52.0)	0.661
Mean age (SD)	69.8 (18.0)	64.2 (20.9)	0.099
Median time (days) from KPC KP[c] identification to enrollment (25–75% interval)	26 (11–46)	419 (333–662)	p < 0.001
Negative KPC KP test at enrollment (%)	22 (29.3)	40 (80.0)	<0.001
ADL[d] (Barthel's) index, no. (%)			
0–5	35 (46.6)	22 (44.0)	0.958
5–50	20 (26.7)	14 (28.0)	
>50	20 (26.7)	14 (28.0)	
Charlson's score, no. (%)			
0 (%)	11 (14.7)	15 (30.0)	0.080
1–5 (%)	40 (53.3)	25 (50.0)	
>5 (%)	24 (32.0)	10 (20.0)	
Invasive device present (%)	45 (60.0)	27 (55.1)	0.589
Surgical procedure in the last year (%)	35 (46.7)	19 (38.0)	0.338
Admission from an LTCF[e] (%)	41 (54.7)	21 (42.0)	0.165
Carriage of resistant bacteria[f] (%)	12 (16.0)	9 (18.0)	0.770
Antibiotic treatment during the month before enrollment (%)	60 (80.0)	28 (56.0)	0.004
Specific antibiotic during the month before enrollment			
Penicillin (%)	19 (25.7)	8 (16.0)	0.200
β-lactams/β-lactamase inhibitors	3 (4.1)	3 (6.1)	0.614
Cephalosporin (%)	27 (37.0)	11 (22.4)	0.089
Carbapenem (%)	11 (15.1)	3 (6.1)	0.129
Quinolones (%)	10 (13.7)	7 (14.3)	0.927
Aminoglycosides (%)	13 (17.8)	8 (16.3)	0.832
Metronidazole (%)	10 (13.7)	4 (8.2)	0.347
Macrolides (%)	10 (13.7)	2 (4.1)	0.121
Median duration of hospitalization, days (25–75% interval)	19 (7–44)	11 (7-218)	0.780
Discharge to an LTCF[e] (%)	53 (70.7)	25 (51.0)	0.027
Early drop-out (%)	11 (14.7)	6 (12.0)	0.670
Deceased (%)	25 (33.3)	6 (12.0)	0.007

[a]REC, the recent KPC KP acquisition group (<4 months prior to enrollment).
[b]REM, the remote KPC KP acquisition group (more than 4 months prior to enrollment).
[c]KPC KP, KPC-producing *Klebsiella pneumoniae*.
[d]ADL, activities of daily living index.
[e]LTCF, long-term care facility.
[f]Resistent bacteria, including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and carbapenem-resistant *Acinetobacter baumannii*.

Duration of KPC KP carriage following hospital discharge

Overall, 544 rectal samples were collected, of which 225 (41%) were positive. The percentages of KPC KP positive tests as a function of the time from first detection of KPC KP and sampling schedule are presented in Fig. 2. The percentage of positive results declined with increased time from first KPC KP detection (Fig. 2a). The percentage of positive results also declined from the first (enrollment) test up to the fifth (3 months) test (Fig. 2b). The sixth sample was taken from 30 persistent carriers (median time from the fifth sampling, 61 days; interquartile range (IQR), 38–63); 21 tests (70%) were found to be positive.

Overall, resolution of carriage (e.g. two consecutive negative tests with no subsequent positive test) was documented for 65/125 (52%). Resolution of carriage was documented in 29/75 (39%) and 36/50 (72%) of the REC and REM patients, respectively ($p < 0.001$). The rates of resolution were similar in the 83 patients that had completed the five-point follow-up: 21/45 (46%) and 30/38 (79%) in the REC and REM patients, respectively. To evaluate the validity of this criterion, we examined the number of patients who fulfilled it but subsequently had positive testing and compared it to using one or three consecutive negative tests as criteria (Table 2). Overall, KPC KP clearance was correctly defined (e.g. no subsequent positive test) at higher rates in the REM group than in the REC group; the rates increased with increased number of negative

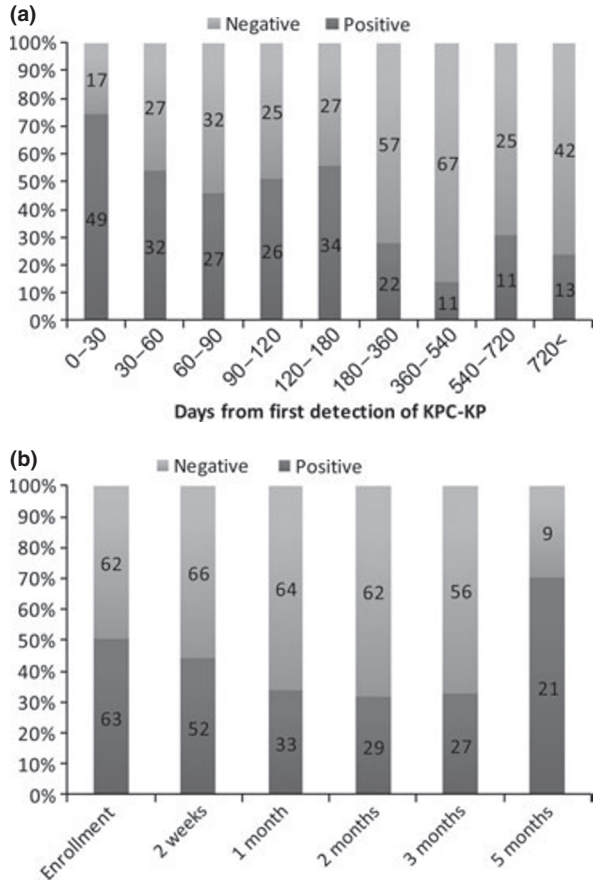

FIG. 2. The rates of KPC-producing *Klebsiella pneumoniae* (KPC KP)-positive samples. (a) The rates of KPC KP-positive samples according to the time from initial identification of KPC KP. (b) The rates of KPC KP-positive samples according to the sampling schedule. The numbers of patients are indicated inside the bars. The time of the sixth test reflects the median time interval.

TABLE 2. Validity of different criteria for defining clearance of KPC KP carriage

Criteria[a]	Study group	Total number of patients, *n*	Patients with negative tests, *n*	Patients with KPC KP[b] clearance, *n* (%[c])
1		≥2 tests	≥1 negative test	
	REC[d]	69	54	29 (54)
	REM[e]	49	43	36 (84)
2		≥3 tests	≥2 negative tests	
	REC	55	31	25 (81)
	REM	42	36	32 (89)
3		≥4 tests	≥3 negative tests	
	REC	52	19	16 (84)
	REM	39	31	29 (94)

[a]Criteria, number of consecutive negative tests (without subsequent positive test) necessary for defining clearance of KPC KP carriage.
[b]KPC KP, KPC-producing *Klebsiella pneumoniae*.
[c]%, ratio of the number of patients with KPC KP clearance to the number of patients with negative tests.
[d]REC, recent (<4 months) KPC KP acquisition group.
[e]REM, remote (>4 months) KPC KP acquisition group.

tests, although the number of patients available for the analysis had declined.

Risk factors for persistent KPC KP carriage following recent acquisition

The rate of persistent KPC KP carriage was studied in the REC group and included all the variables detailed in Table 1 by survival analysis. Significant risk factors at enrollment included low ADL (Barthel's) index, the presence of an invasive device, admission from an LCTF and discharge to an LTCF (Fig. 3). Recent use of antimicrobials, either at enrollment or during the follow-up period, was not associated with persistent carriage. In all of these variables, persistence of KPC KP carriage at the end of the follow-up was found in *c.* 50% of patients with the unfavourable characteristics, compared with *c.* 20% of patients with the favourable characteristics. The ADL index correlated significantly with the place of residence and the presence of an invasive device. A multivariate analysis that included the significant variables from the unadjusted analysis as well as the three critical variables (see in 'Methods') was constructed. Taken apart, the ADL index, LTCF residence and the presence of an invasive device were identified as significant risk factors (Table S1a–c). However, none of these variables remained statistically significant in the joint model, as a result of significant correlation between the variables (data not shown).

Risk factors for persistent KPC KP carriage following remote acquisition

The rate of persistent KPC KP carriage was studied in the REM group and included all the variables detailed in Table 1. Persistent carriers ($n = 14$) were more likely to have an invasive device at enrollment (10/14 (76.9%) vs. 17/36 (47.2%), $p = 0.065$). Persistent carriers had a higher Charlson's score compared with non-carriers: score 0–1 (7%) vs. 14 (39%), scores 1 to 5–9 (64%) vs. 16 (44%) and scores higher than 5–4 (29%) vs. 6 (17%) ($p = 0.087$). Interestingly, persistent carriers were less likely to have a surgical procedure in the preceding year (2/14 (14%) vs. 17/36 (47.2%), $p = 0.031$). In multivariate analysis, the presence of an invasive device (HR = 7.69, 95% CI, 1.03–50; $p = 0.046$) and high Charlson's score (HR = 111.11 and 200 for scores of 1–5 and >5 compared with 0, respectively; $p < 0.05$; the 95% CI was incalculable due to the small reference value) were identified as independent risk factors.

Discussion

Very little is known about the duration of and the risk factors for persistent gastrointestinal carriage of KPC KP, as well as

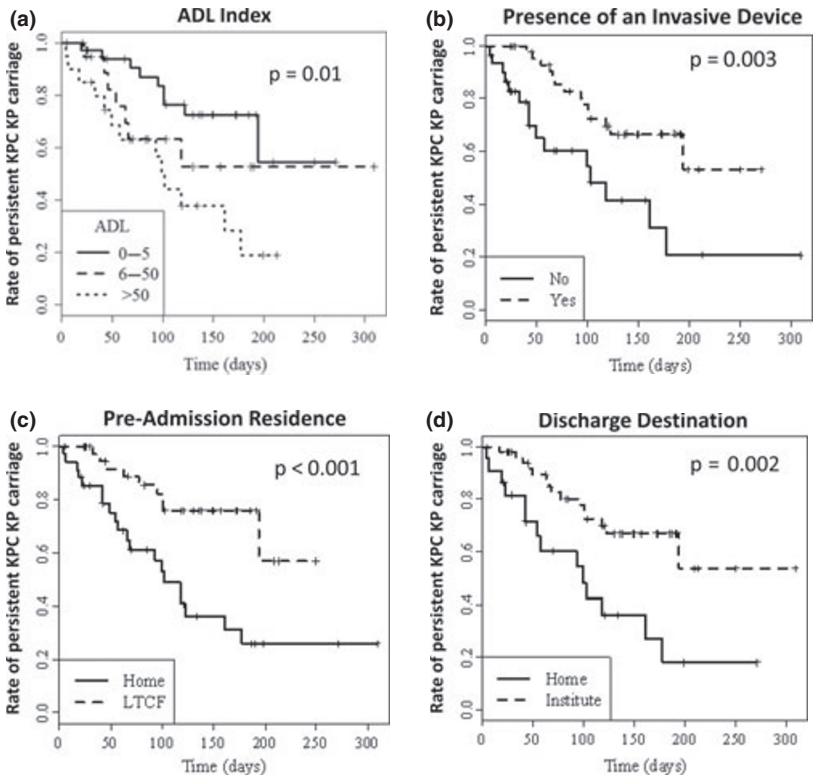

FIG. 3. Risk factors for persistent carriage of KPC-producing *Klebsiella pneumoniae* (KPC KP) in the recent acquisition (<4 months) group (n = 75). Kaplan–Meier estimates for cumulative survival function for clearance of KPC KP. (a) The Barthel's (ADL) index (presented here in three categories); (b) the presence of an invasive device; (c) pre-admission residence (home vs. long-term care facility (LTCF)); (d) discharge destination (home vs. LTCF).

other types of resistant gut bacteria, in non-hospitalized patients. In the present study, a cohort of previously known KPC KP carriers was followed-up by serial rectal cultures for 3 months after hospital discharge. We found that the rate of positivity is highest (74%) when the test is carried out within 30 days of first KPC KP isolation, but declines to <30% once the time interval is over 6 months (Fig. 2b). Accordingly, patients with remote acquisition of KPC KP were less likely to remain positive in subsequent samplings, as was also reported by Schechner [18] and Ben-David [24]. These patients also had lower Charlson's score, had a lower mortality rate and were more likely to be discharged to their homes. The difference in the rates of persistent carriage at the time of enrollment between the two acquisition groups, is probably a reflection of the fact that patients that had survived long enough following the initial KPC KP acquisition, are healthier in general and thus less likely to be exposed to the various risk factors for persistent carriage.

Hypothetically, repeated positive KPC KP testing may result from either persistent carriage in the individual patient or from reacquisition from other patients. The latter is especially of great concern in Israel, as our national policy is to group previously known carriers in a single ward [17]. A supporting finding for the role of reacquisition, is the association between residence at an LTCF and persistence carriage in the REC group, which was also reported by Schechner *et al.* [18]. The average prevalence of KPC KP carriage in the major LTCFs in Israel was reported to be 17% [24], much higher than the prevalence reported in two general hospitals in Israel even at the peak of the KPC KP epidemic [13,25]. New acquisition of KPC KP was detected in 12% of LTCF patients, and was especially common in institutions with high prevalence of KPC KP carriage or in patients that shared a room with a known carrier [24]. Hence, it is likely that even following resolution of carriage in an individual patient, patients may still get re-infected during their subsequent admission, especially if they are admitted to an LTCF with a high prevalence of KPC KP carriage.

Low functional status (ADL index), high co-morbidity index (Charlson's score) and the presence of an invasive device were identified as risk factors in the REC group, the REM group and in both groups, respectively. These factors were not identified as risk factors for persistent carriage by Schechner *et al.* [18], but they were identified as risk factors

for KPC KP acquisition [13,26]. Although ADL and an invasive device were correlated with residence in an LTCF in the REC group, their association with persistent KPC KP carriage is not entirely clear, as residence in an LTCF was not identified as a risk factor in the REM group. This suggests that patients with poor functional status and co-morbidity conditions are more likely to remain colonized by hospital-acquired organisms, such as KPC KP.

An intriguing difference between our study and previous reports [18,24] is the lack of association between persistent carriage and recent antibiotic therapy. This was also reported in a study that looked into the duration and risk factors for persistent carriage of ESBL-producing Enterobacteriaceae [27]. A likely explanation is the very high rate of recent antibiotic therapy in all of our patients, especially in the REC group (80%).

Accurate and reliable determination of resolution of carriage is important for both the individual patient and the medical institution, especially when a policy of carriers cohorting is implemented. Our findings indicate that a single negative test cannot serve as a reliable indication for resolution, as only 65 patients out of 97 with two tests (67%) did not have a subsequent positive test. This rate increased with increased number of negative tests and in patients with remote acquisition. The total number of tests and the duration of follow-up in our study are not sufficient to determine the exact number of tests that are required for defining KPC KP clearance. However, our risk factor analyses can indicate patients that are less likely to remain carriers (e.g. patients admitted from home, with good functional status and with remote acquisition, in whom testing for resolution of carriage is likely to be beneficial).

Our study has several limitations. First, we were unable to distinguish between persistence of carriage and re-infection. In theory, the use of a molecular epidemiology tool might have allowed us to answer this question. However, due to the predominantly monoclonal nature of the KPC KP epidemic in Israel (as shown in our recent report [9]), such a distinction would have been impossible in the vast majority of patients. Also, the distinction between persistence and re-acquisition is further complicated by the fact that the KPC gene may be transmitted *in-situ* by the transfer of mobile genetic elements from one strain to another strain or a different species altogether [28,29]. Thus, even the isolation of a different species of KPC-producing Enterobacteriaceae, as was found in four patients, may not provide a definite proof of re-acquisition.

Second, there might have been a selection bias toward relatively healthier patients, as patients who were unable to give an informed consent (e.g. critically ill patients) were not approached.

Third, there might have been a selection bias in the REM group, toward the selection of relatively sicker patients, as patients with remote acquisition that were healthier were less likely to be admitted and thus were not recruited. It is noteworthy that even with this potential bias, this group was basically healthier than the REC group (Table 1) and had a higher rate of KPC KP clearance.

In conclusion, our study shows that although resolution of carriage occurs in the majority of patients with remote acquisition, it is uncommon in patients with recent acquisition, especially those with poor functional status who reside in an LTCF. Repeat KPC KP testing in this population is likely to be futile or misleading.

Acknowledgements

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Transparency Declaration

Nothing to declare.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Study design. Rectal cultures for KPC-producing *Klebsiella pneumoniae* (KPC KP) were performed at enrollment and at each time-point.

Table S1. Multivariate analysis of factors associated with resolution of carriage in the recent acquisition (<4 months) group (n = 75).

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