

ORIGINAL ARTICLE

Potential Role of Active Surveillance in the Control of a Hospital-Wide Outbreak of Carbapenem-Resistant *Klebsiella pneumoniae* Infection

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BACKGROUND. The recent emergence of carbapenem resistance among Enterobacteriaceae is a major threat for hospitalized patients, and effective strategies are needed.

OBJECTIVE. To assess the effect of an intensified intervention, which included active surveillance, on the incidence of infection with carbapenem-resistant *Klebsiella pneumoniae*.

SETTING. Sheba Medical Center, a 1,600-bed tertiary care teaching hospital in Tel Hashomer, Israel.

DESIGN. Quasi-experimental study.

METHODS. The medical records of all the patients who acquired a carbapenem-resistant *K. pneumoniae* infection during 2006 were reviewed. An intensified intervention was initiated in May 2007. In addition to contact precautions, active surveillance was initiated in high-risk units. The incidence of clinical carbapenem-resistant *K. pneumoniae* infection over time was measured, and interrupted time-series analysis was performed.

RESULTS. The incidence of clinical carbapenem-resistant *K. pneumoniae* infection increased 6.42-fold from the first quarter of 2006 up to the initiation of the intervention. In 2006, of the 120 patients whose clinical microbiologic culture results were positive for carbapenem-resistant *K. pneumoniae*, 67 (56%) developed a nosocomial infection. During the intervention period, the rate of carbapenem-resistant *K. pneumoniae* rectal colonization was 9%. Of the 390 patients with carbapenem-resistant *K. pneumoniae* colonization or infection, 204 (52%) were identified by screening cultures. There were a total of 12,391 days of contact precautions, and of these, 4,713 (38%) were added as a result of active surveillance. After initiation of infection control measures, we observed a significant decrease in the incidence of carbapenem-resistant *K. pneumoniae* infection.

CONCLUSIONS. The use of active surveillance and contact precautions, as part of a multifactorial intervention, may be an effective strategy to decrease rates of nosocomial transmission of carbapenem-resistant *K. pneumoniae* colonization or infection.

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The spread of carbapenem resistance among Enterobacteriaceae is mediated by the *Klebsiella pneumoniae* carbapenemase (KPC) and represents an emerging threat because Enterobacteriaceae are resistant to almost all available antimicrobial agents and spread rapidly. Since the first description of carbapenem-resistant *K. pneumoniae* in North Carolina in 2001,¹ a number of outbreaks of infection have been reported.²⁻⁶ In a report from New York City, carbapenem-resistant *K. pneumoniae* accounted for one-quarter of all invasive *K. pneumoniae* infections during a period of 2 years.⁷ Infections due to carbapenem-resistant *K. pneumoniae*

are associated with increased morbidity and mortality.^{7,8} Patients with an infection caused by carbapenem-resistant *K. pneumoniae* were 3 times more likely to die during their hospital stay, compared with patients with an infection caused by a susceptible strain.⁷ Despite growing concern about the emergence of carbapenem-resistant *K. pneumoniae*, optimal strategies for preventing its spread in a healthcare facility are unknown. Reports of the successful containment of outbreaks of carbapenem-resistant *K. pneumoniae* infection are rare.⁹

In 2006, carbapenem-resistant *K. pneumoniae* spread in several acute care facilities in Israel,^{3,10} causing several hun-

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dred infections. We describe the outbreak in our institute and report the results of the intensified infection control program during a 19-month period (June 2007–December 2008).

METHODS

Setting

Sheba Medical Center is a 1,600-bed tertiary care teaching hospital in Tel Hashomer, Israel, with approximately 90,000 annual admissions. There are 5 intensive care units and 4 step-down units that are designed as open wards, with curtains separating the patients. Most patients in the general wards are hospitalized in rooms with 3 beds.

Study Period and Infection Control Measures

The study period included a preintervention period from January 2006 through May 2007 and an intervention period from June 2007 through December 2008.

Preintervention period. In 2006, an outbreak of carbapenem-resistant *K. pneumoniae* infection spread throughout Sheba Medical Center. The medical records of all patients who acquired carbapenem-resistant *K. pneumoniae* infection were reviewed for clinical and epidemiological data, including patient demographics, reason for hospital admission, anatomical sites where carbapenem-resistant *K. pneumoniae* was isolated, and whether patients had any underlying diseases, were exposed to antimicrobials within the past 2 months, and/or stayed in an intensive care unit. Nosocomial infections caused by carbapenem-resistant *K. pneumoniae* were defined according to definitions from the Centers for Disease Control and Prevention.¹¹ Contact precautions were implemented for the management of patients with clinical isolates of carbapenem-resistant *K. pneumoniae*. During this period, detection of carbapenem-resistant *K. pneumoniae* was based on culture of clinical samples only.

Intervention period. In May 2007, an enhanced national infection control program was added to the baseline protocol. The national program included the following components: contact precautions were used for the care of all patients with carbapenem-resistant *K. pneumoniae* colonization or infection; the prevalence of colonization or infection was reported daily, and this information was mailed to the hospital management and the national coordinator; and patients infected with carbapenem-resistant *K. pneumoniae* had their names entered into a database so that they could be identified at hospital readmission. In addition to the measures taken in accordance with the national infection control program, an active surveillance program was initiated at our institution and included obtaining rectal culture samples from patients hospitalized in intensive care units and in step-down units, at admission to the unit and once weekly until the patient was discharged. In other departments, surveillance culture samples were only obtained from patients with epidemio-

logic links to persons from whom a carbapenem-resistant *K. pneumoniae* isolate had been recovered.

Incidence of infection with carbapenem-resistant *K. pneumoniae* was expressed as the number of clinical microbiologic cultures performed per 10,000 patient-days. Only the first positive culture result was included in the analysis.

Microbiologic Methods

Clinical isolates were identified by use of standard laboratory methods from Clinical and Laboratory Standards Institute (CLSI) guidelines.¹² Antibiotic susceptibility was determined by use of the disk diffusion method. Minimum inhibitory concentrations (MICs) of carbapenems were determined by use of the Etest (AB Biodisk). MIC breakpoints were defined according to CLSI guidelines.¹² Isolates of carbapenem-resistant *K. pneumoniae* with elevated MICs of carbapenems or with reduced disk diffusion zone sizes were tested for the presence of carbapenemases by use of the modified Hodge test.¹³

For rectal screening, surveillance culture samples were obtained by use of Copan Amies sterile transport swabs (Copan Diagnostics) and transported to the microbiology laboratory for the detection of carbapenem-resistant *K. pneumoniae*. These rectal swab samples were streaked onto MacConkey agar plates (Hy Laboratories) with meropenem (10 µg) and ertapenem (10 µg) disks and were incubated overnight at 35°C in ambient air. Bacterial colonies in the area surrounding either disk were isolated and identified, as described above. The swab samples were also placed in brain-heart infusion broth, initially with a disk of ertapenem and thereafter without any selective substances. All broth cultures were incubated overnight at 35°C in ambient air. After overnight incubation, a subculture of all the broths was placed onto a MacConkey agar plate (Hy Laboratories), and all 3 disks (Oxoid)—ertapenem (10 µg), meropenem (10 µg), and imipenem (10 µg)—were placed on the plate and incubated for another 18–24 hours. Any suspicious bacterial colony was identified.

Clonal Analysis

The genetic relatedness of carbapenem-resistant *K. pneumoniae* strains was determined by use of pulsed-field gel electrophoresis (PFGE) analysis. Isolates were obtained during the preintervention period. DNA was prepared as described elsewhere,¹³ and chromosomal restriction fragments obtained after *Xba*I and *Spe*I cleavage were documented and compared. Isolates were screened for *bla*_{KPC} by use of polymerase chain reaction (PCR), as described elsewhere.¹⁴ Approval was obtained from the institutional review board.

Statistical Analyses

To compare the preintervention and intervention periods, we used an interrupted time-series design, which is particularly suited to address secular trends and to evaluate interventions

in a quasi-experimental design.¹⁵ A segmented Poisson regression model was used, accounting for time trend to assess the change in incidence of infection with carbapenem-resistant *K. pneumoniae* (measured as cases per 10,000 patient-days) during a 17-month preintervention period and during a 19-month intervention period. Two measurements are determined when using time-series analyses: changes in level of the outcome and change in trend of the outcome (change between the outcome's preintervention slope and its slope across the entire intervention), while controlling for secular trend. The statistical method recommended to analyze the impact of interventions in quasi-experimental studies is to estimate the change in the preintervention and postintervention slopes.^{15,16} Here, we report the impact of the interventions as the change in slope of incident cases during the preintervention period, compared with that during the intervention period. Because adjacent outcome measurements can be correlated when evaluating the outcome of an infectious agent, we also adjusted for the outcome in the previous month. All analyses were 2 tailed and were performed using SAS, version 9.1 (SAS Institute).

RESULTS

Description of Outbreak

The number of clinical cases of infection with carbapenem-resistant *K. pneumoniae* increased gradually from 3–5 cases each month (ie, 1.08 cases per 10,000 patient-days) during the first quarter of 2006 to 22–24 cases each month (ie, 6.93 cases per 10,000 patient-days) during the last quarter, before the intervention was implemented (Figure 1). In 2006, there were 120 patients who were identified by use of clinical microbiologic culture as being either colonized or infected. Their median age was 72 years (range, 16–99 years). Sixty-seven patients (56%) were male, 87 (73%) were identified after 72 hours of hospitalization, and 33 (28%) were identified during their first 72 hours of hospitalization. However, all patients had a prior hospitalization or were transferred from another healthcare facility. Carbapenem exposure during the previous 2 months was observed in only 28 patients (23%). The median time of acquisition of carbapenem-resistant *K. pneumoniae* was 13.3 days (range, 0–147 days). Of the 120 patients, 48 (40%) acquired carbapenem-resistant *K. pneumoniae* in medical departments, 24 (20%) in intensive care units, 23 (19%) in the rehabilitation departments, and 13 (11%) in general surgical departments; less than 1% of patients acquired carbapenem-resistant *K. pneumoniae* in the hematology and bone marrow transplantation department. Carbapenem-resistant *K. pneumoniae* isolates were predominantly recovered from urine (55%) and blood samples (36%). Nosocomial infections due to carbapenem-resistant *K. pneumoniae* developed in 67 (56%) of 120 patients: 44 patients had primary bloodstream infections, and 19 patients had urinary tract infections. Crude in-hospital mortality was 55%.

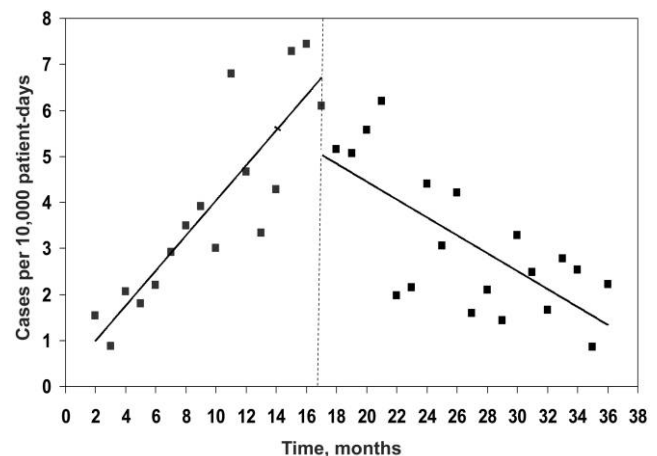


FIGURE 1. Scatterplots showing the change in the number of clinical cases of infection with carbapenem-resistant *Klebsiella pneumoniae* per 10,000 patient-days, before and after the intervention, implemented in month 17. Solid lines represent the linear regression fits across all cases.

Antibiotic Susceptibility and Clonality

All isolates recovered from patients during the outbreak were resistant to carbapenems, β -lactam and β -lactamase inhibitor combinations, cephalosporins, trimethoprim-sulfamethoxazole, and fluoroquinolones. These isolates were susceptible only to coliracin, gentamicin, and tigecycline. PFGE analysis of 41 random isolates demonstrated that they all belonged to the same clone (Figure 2). PCR results showed the presence of *bla*_{KPC-3} in all isolates.

Active Surveillance Cultures

From June 2007 through 31 December 2008 (ie, the intervention period), 4,456 surveillance cultures were performed for 2,251 patients. Of these cultures, 2,686 (60%) were performed for patients in high-risk units. The rate of rectal colonization with carbapenem-resistant *K. pneumoniae* was 9% (ie, 204 of 2,251 cultures). Of the 1,172 patients who were screened at hospital admission, 42 (4%) were found to be colonized. Most acquisitions were identified among patients who were screened 48 hours after hospitalization (162 [12%] of 1,323 patients). Among the 204 patients who were identified by screening, the median duration of their prior hospitalization was 12 days (range, 0–65 days).

During the intervention period, 390 patients were identified as being colonized or infected with carbapenem-resistant *K. pneumoniae*; of these patients, 204 (52%) were identified by use of active surveillance cultures, and 186 (48%) were identified by use of clinical microbiologic cultures. Of the 204 patients identified by use of surveillance cultures, 50 (26%) were subsequently identified by use of clinical microbiological cultures as well. Carbapenem-resistant *K. pneumoniae* was detected a median of 9 days (range, 2–66 days) earlier

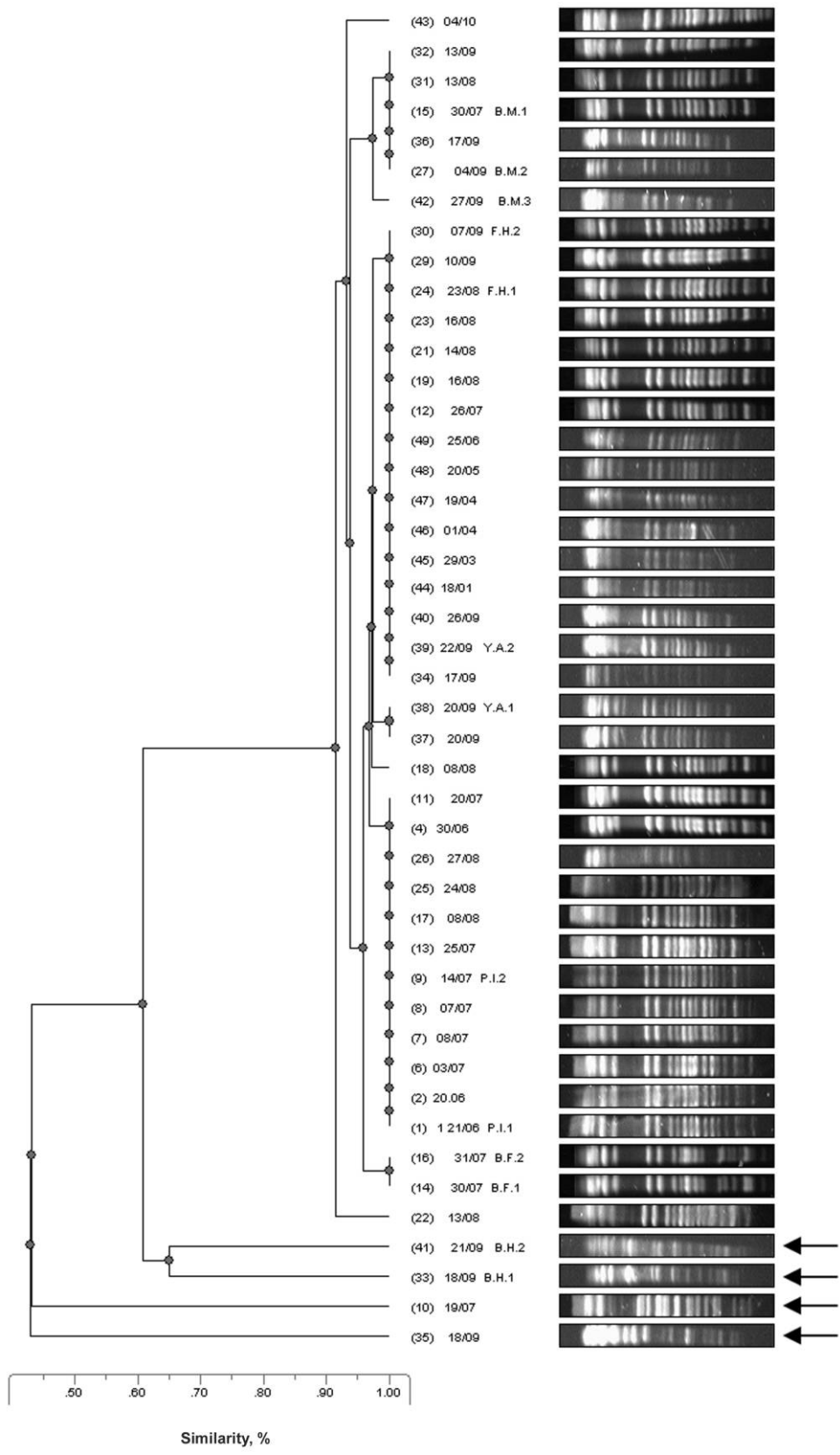


FIGURE 2. Dendrogram showing genetic relatedness of 41 *Klebsiella pneumoniae* isolates producing carbapenemase in 2006, based on pulsed-field gel electrophoresis patterns and compared with 4 controls (arrows).

in patients who were screened by use of active surveillance cultures than in patients who were screened by use of clinical microbiologic cultures. Carbapenem-resistant *K. pneumoniae* was detected only by use of active surveillance cultures in 154 patients, accounting for 39% of all carbapenem-resistant *K. pneumoniae* isolates. There were a total of 12,391 days of contact precautions, and of these, 4,713 (38%) were added as a result of active surveillance during the intervention period.

Effect of the Intervention

The incidence of clinical infection with carbapenem-resistant *K. pneumoniae* has decreased 4.7-fold, from 6.93 cases per 10,000 patient-days during the last quarter of the preintervention period to 1.8 cases per 10,000 patient-days during the last quarter of 2008 ($P < .001$). The change in the number of cases of infection per 10,000 patient-days over time, before and after the intervention (implemented in month 17), is shown in Figure 1. The change in slope was from 0.12 to -0.07 during the preintervention and intervention periods, respectively ($P < .001$).

DISCUSSION

Outbreaks of nosocomial infection due to multidrug-resistant gram-negative bacteria have been increasingly reported during recent years. Despite the increasing amount of data on the risk factors for acquisition,¹⁷⁻¹⁹ their molecular epidemiology,^{20,21} the laboratory methods for identification and assessment of antimicrobial therapy,²² there are only a limited number of studies describing effective strategies that limit the spread of multidrug-resistant gram-negative pathogens.²³⁻²⁷ The recent emergence of carbapenem resistance among Enterobacteriaceae is a major threat for hospitalized patients, and effective strategies are needed.

In 2006, the incidence of infection with carbapenem-resistant *K. pneumoniae* at our institution increased, and a hospital-wide outbreak was identified. To demonstrate the burden of illness and the rapid spread in several wards, we described the clinical characteristics of the patients who acquired carbapenem-resistant *K. pneumoniae* during the first 12 months of the outbreak. Primary bacteremia was the most frequent infection. The crude mortality rate (55%) was high among patients infected with carbapenem-resistant *K. pneumoniae*, similar to other studies.^{4,7} A single clone was detected, demonstrating that cross-transmission was the main route of acquisition at our institution as well as in the nationwide spread in Israel.⁶ Despite routine infection control measures that were implemented during the preintervention period, the outbreak was not contained but spread further. Only after implementing an intervention that included active surveillance and intensified monitoring by a national task group did the incidence of infection with clinical carbapenem-resistant *K. pneumoniae* significantly decrease.

The use of contact precautions prevents the transmission of multidrug-resistant microorganisms. However, colonized

patients may be undetected by use of clinical cultures, and therefore they may not be subjected to contact precautions. Consequently, unidentified colonized patients may serve as a potential reservoir for transmission of multidrug-resistant organisms. Several reports have suggested that the use of active surveillance cultures, in combination with the use of contact precautions, for colonized patients has resulted in a persistent reduction in the incidence of infections with methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci.²⁸⁻³⁰ In contrast, the role of active surveillance cultures in the control of multidrug-resistant gram-negative bacteria is less established. A few studies have described the use of surveillance cultures as part of efforts to control the spread of multidrug-resistant gram-negative bacteria in outbreak settings.^{23,24} During a 6-year period, Troche et al³¹ reported a successful reduction in the rate of colonization with extended-spectrum β -lactamase-producing Enterobacteriaceae by use of a multifaceted control program that included use of surveillance cultures. In contrast, another report demonstrated that, in an endemic nonoutbreak setting, active surveillance and isolation of patients did not have any significant impact on either colonization or infection rates.³² In the present study, early identification of colonized patients and their isolation led to the containment of a hospital-wide outbreak. As we have shown, one-third of the days of contact precautions were added as a result of active surveillance. Previous studies have also shown that use of clinical cultures may fail to detect colonization with multidrug-resistant gram-negative bacteria.^{33,34} Calfee et al³³ have recently reported that 37% of patients with carbapenem-resistant *K. pneumoniae* colonization were first identified by use of active surveillance cultures. In our institution, 52% of patients were initially identified by use of surveillance cultures. Furthermore, 39% of the patients were identified by active surveillance only. In addition, active surveillance resulted in the early identification of patients who later had isolates recovered from clinical microbiologic culture samples.

The optimal timing of active surveillance and the interval between the performance of one culture and the next are not well defined. Most institutions obtain admission culture samples as well as weekly culture samples.^{28,30,35} In other institutions, surveillance culture samples were obtained only at the time of admission to the hospital or to the intervention unit.³⁶ In our institution, most patients acquired carbapenem-resistant *K. pneumoniae* colonization more than 48 hours after admission, which suggests in-hospital transmission and emphasizes the importance of weekly surveillance cultures. As our data demonstrate, during a hospital-wide outbreak (ie, more than 20 cases a month), limiting active surveillance to only admission screening would have failed to identify a sizable proportion of colonized patients who may serve as a source of transmission. The recent Centers for Disease Control and Prevention guidelines also support weekly periodic surveillance until no new cases are identified in the health-care facility.³⁷

Our study has several limitations. The study design was a quasi-experimental design without a control group. Because of the rapid spread of carbapenem-resistant *K. pneumoniae* in our institution and the high mortality rates associated with nosocomial infections due to carbapenem-resistant *K. pneumoniae*, we decided to implement aggressive infection control measures to mitigate the further spread of carbapenem-resistant *K. pneumoniae*. On the basis of prior reports demonstrating high rates of undetected multidrug-resistant gram-negative bacteria among hospitalized patients in endemic institutions,^{24,34} we believed that screening cultures may have an important role to play in the intervention program. Therefore, it is impossible to exclude other unmeasured factors that have contributed to the control of the outbreak. Furthermore, during the intervention period, in addition to active surveillance, a national task group implemented an intensified monitoring program. The intensified monitoring could have contributed to better compliance with contact precautions. Therefore, it is impossible to determine the relative contribution of each intervention. Nevertheless, because half of the cases of colonization with carbapenem-resistant *K. pneumoniae* were identified by use of active surveillance culture, the role that active surveillance plays in the early identification of colonized patients is apparent.

In conclusion, we have shown that, by use of surveillance cultures, carbapenem-resistant *K. pneumoniae* was detected in a substantial number of patients who may serve as an important reservoir for transmission. The use of active surveillance and contact precautions, as part of a multifactorial intervention, may be an effective strategy to decrease rates of nosocomial transmission of carbapenem-resistant *K. pneumoniae* colonization or infection.

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Potential conflicts of interest. All authors report no conflicts of interest relevant to this article.

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