A National Intervention to Prevent the Spread of Carbapenem-Resistant Enterobacteriaceae in Israeli Post-Acute Care Hospitals

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ORIGINAL ARTICLE

A National Intervention to Prevent the Spread of Carbapenem-Resistant Enterobacteriaceae in Israeli Post-Acute Care Hospitals

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OBJECTIVE. Patients hospitalized in post-acute care hospitals (PACHs) constitute an important reservoir of antimicrobial-resistant bacteria. High carriage prevalence of carbapenem-resistant Enterobacteriaceae (CRE) has been observed among patients hospitalized in PACHs. The objective of the study is to describe the impact of a national infection control intervention on the prevalence of CRE in PACHs.

DESIGN. A prospective cohort interventional study.

SETTING. Thirteen PACHs in Israel.

INTERVENTION. A multifaceted intervention was initiated between 2008 and 2011 as part of a national program involving all Israeli healthcare facilities. The intervention has included (1) periodic on-site assessments of infection control policies and resources, using a score comprised of 16 elements; (2) assessment of risk factors for CRE colonization; (3) development of national guidelines for CRE control in PACHs involving active surveillance and contact isolation of carriers; and (4) 3 cross-sectional surveys of rectal carriage of CRE that were conducted in representative wards.

RESULTS. The infection control score increased from 6.8 to 14.0 ($P < .001$) over the course of the study period. A total of 3,516 patients were screened in the 3 surveys. Prevalence of carriage among those not known to be carriers decreased from 12.1% to 7.9% ($P = .008$). Overall carrier prevalence decreased from 16.8% to 12.5% ($P = .013$). Availability of alcohol-based hand rub, appropriate use of gloves, and a policy of CRE surveillance at admission to the hospital were independently associated with lower new carrier prevalence.

CONCLUSION. A nationwide infection control intervention was associated with enhanced infection control measures and a reduction in the prevalence of CRE in PACHs.

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Over the past decade, long-term care hospitals providing acute care (long-term acute care hospitals [LTACHs]) have increased in number, and it is increasingly common for patients to be discharged to LTACHs after episodes of critical illness. The pivotal role of LTACHs in the epidemiology of multidrug resistance has recently been recognized.[1,2] High prevalences of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and multidrug-resistant gram-negative bacteria have been observed among patients hospitalized in these facilities.[3,4] The transfer of colonized patients from acute care facilities to LTACHs is probably the primary mode of introduction of resistant pathogens to the latter environment.[1,5,6] Persistence of resistance in LTACHs has been linked to both individual and institutional characteristics.[7-10] Consequently, LTACHs may become reservoirs of multidrug-resistant organisms (MDROs), contributing to the reintroduction of the organisms to acute care facilities at subsequent admissions. In Israel, the LTACH model is most closely exemplified by the post-acute care hospitals (PACHs). Similar to LTACHs, the PACHs provide skilled nursing care as well as care for patients who receive long-term mechanical ventilation. In addition, rehabilitation care is provided in most of these facilities.

In recent years, carbapenem-resistant Enterobacteriaceae (CRE) have emerged as a major public health problem throughout the world.[11,12] The global spread of CRE has largely been attributed to dissemination of *Klebsiella pneumoniae* that produce the serine β-lactamase KPC.[13] A single clone

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TABLE 1. Compliance with Infection Control Guidelines in 13 Post-Acute Care Hospitals as Noted on 3 Site Visits

Variable	2008	2010	2011	*P*
Infection control consultant	62	85	92	.055
Hand hygiene[22]				
Presence of ABHR in each room	85	92	100	.146
ABHR at site of care	15	54	85	<.001
Presence of antiseptic soap	15	92	85	<.001
Presence of sink in each room	23	31	46	.164
Paper towel availability	69	85	100	.032
Compliance audits	0	46	77	<.001
Appropriate use of barrier precautions in context of standard precautions[23]				
Gloves	31	69	92	.001
Gowns	54	77	77	.208
Masks	38	62	69	.118
CRE prevention program				
Placement of colonized patients in single rooms or cohorting	77	85	100	.082
Use of gown and gloves in contact isolation	46	92	100	.001
Designated medical equipment	92	100	100	.221
Admission screening cultures	15	69	77	.002
Contact screening	38	77	100	.001
Discontinuation of isolation per standard protocol	15	46	100	<.001
Total infection control score (average, out of possible 16)	6.8	11.6	14.0	<.001

NOTE. Data are percentage of compliant hospitals ($n = 13$), unless otherwise indicated. ABHR, alcohol-based hand rub; CRE, carbapenem-resistant Enterobacteriaceae.

of this organism, sequence type (ST) 258, has become endemic in hospitals in the United States, Israel, and Greece and has spread elsewhere throughout the globe.[12,14-16]

Since 2006, Israel has been facing a nationwide outbreak of CRE caused primarily by ST258 throughout the healthcare system.[15,17] Between 2006 and 2007, over 1,000 hospitalized patients acquired this strain, and the proportion of invasive nosocomial *K. pneumoniae* isolates exhibiting carbapenem resistance reached 21.9%.[18] Consequently, the Israel Ministry of Health formed a task force to confront the spread of CRE. A nationwide intervention to decrease CRE transmission was implemented, resulting in a significant decrease in new CRE acquisitions in acute care facilities.[19]

Approximately 10% of CRE carriers discharged from acute care hospitals were transferred to PACHs, resulting in a potential growing reservoir of CRE in these facilities. To determine the prevalence and risk factors for carbapenem-resistant *K. pneumoniae* (CRKP) carriage and to assist with the extension of the nationwide intervention to these facilities, a cross-sectional prevalence survey was conducted in Israeli PACHs during 2008.[20] The prevalence of rectal carriage among patients without a history of CRKP carriage was 12%. Independent risk factors for carriage were prolonged length of stay, sharing a room with a known carrier, and increased prevalence of known carriers on the ward. A policy of screening for carriage at hospital admission was protective.

On the basis of these findings, we designed an intervention to limit the transmission of CRE in PACHs. The objectives of this report are to describe the intervention and analyze its impact on infection control and the prevalence of CRE in PACHs.

METHODS

Setting

The intervention was conducted in Israeli PACHs. In 2008, there were a total of 13 PACHs in Israel. The 12 that participated in the point prevalence survey that year comprised 2,451 beds (median, 209 beds; range, 104–320 beds). The patient population is hospitalized in 4 distinct ward types: skilled nursing, long-term mechanical ventilation, subacute medical, and rehabilitation. The period analyzed in this report is January 1, 2008, through December 31, 2011.

Site Visits

Periodic site visits were performed at all PACHs by staff of the National Center for Infection Control (NCIC). A standardized assessment of infection control policies and resources was conducted. A 16-element score was devised to measure standards of infection control in each facility. The score evaluated the facility on the basis of the presence or absence of the following: a physician specializing in infectious diseases responsible for infection control, implementation of the World Health Organization multimodal hand hygiene strategy,[22] implementation of standard precautions,[23] and CRE containment policies. The 16 elements of the score are summarized in Table 1.

Weekly Reports

All PACHs were required to send weekly census reports to the NCIC. The reports included data on transfers of CRE carriers from other facilities; new CRE acquisitions; mode of detection (screening and/or clinical culture); total prevalence of hospitalized colonized patients in the facility; and compliance with isolation guidelines. The PACH reports were considered in coordination with daily reports arriving from the acute care hospitals, enabling real-time communication between facilities regarding carrier movements.

Targeted Guidelines

On the basis of the results of the initial cross-sectional CRE prevalence survey,[20] we developed national guidelines for prevention of CRE targeted to the PACH setting. Requirements varied by ward type (Table 2). In skilled nursing, long-term mechanical ventilation, and subacute wards, the guidelines mandated admission rectal screening for CRE and cohorting of carriers. In contrast, in rehabilitation wards, modified contact precautions alone were mandated, whereby carriers were permitted to perform activities in common areas and to share rooms with noncolonized patients. Routine admission screening was not mandated in these wards, because the likelihood of new carriage detection was considered to be low.

Prevalence Surveys

To assess the impact of the multifaceted intervention outlined above, 2 follow-up prevalence surveys were conducted, one in 2010 and the other in 2011. The methodology was similar to that of the first survey: in all surveys, screening cultures were obtained from all patients hospitalized in a representative sample of wards, determined by selection of at least 1 ward of each type contained in the facility surveyed. The characteristics of the facility and the demographic data of the patients surveyed were collected using structured questionnaires. Patient data recorded included age, sex, duration of hospital stay before recovery of CRE, ward type, and history of previous CRE carriage. Data recorded regarding the facilities included the prevalence of CRE carriers on each ward and the infection control score.

Microbiological Methods

CRE identification and susceptibility testing for the first 2 surveys were performed as described elsewhere.[20] For the third survey, rectal swab samples were collected and plated onto MacConkey agar with imipenem 1 mg/L (HyLabs). Colonies suspected to be CRE visualized after 24 hours of incubation at 37°C were subcultured onto MacConkey agar plates and introduced into the Vitek-2 automated system (bioMérieux) using the AST-GN09 card for identification and susceptibility testing. Susceptibility was determined using the 2010 minimum inhibitory concentration breakpoint criteria of the Clinical and Laboratory Standards Institute.[21] Polymerase chain reaction (PCR) for bla_{KPC} and bla_{NDM} was performed on all isolates identified in the third survey.

Statistical Analysis

The data were analyzed with SPSS, version 17.0 (SPSS). Categorical variables were compared using the χ^2 or Fisher exact tests. Mean age was compared using Student *t* test. Infection control scores were calculated in each year for the principal categories: infectious disease consultant, hand hygiene, stan-

TABLE 2. Israeli National Guidelines for the Care of Patients with Carbapenem-Resistant Enterobacteriaceae in Acute Care versus Post-Acute Care Hospitals

		Post-acute care hospitals	
Variable	Acute care hospitals	Skilled nursing/chronic ventilated/subacute wards	Rehabilitation wards
Room assignment	Private or cohorting with other CRE carriers	Private or cohorting with other CRE carriers	No regulation regarding room assignment
Dedicated nursing staff for CRE carriers	Required	Not required	Not required
Use of gloves and gowns in care of CRE carriers	Mandatory on room entrance	Mandatory on room entrance	According to standard precautions
Admission CRE screening of high-risk groups[a]	Required	Required	Not required, except in outbreak setting
CRE screening of patient contacts	Required	Required	Required
Participation in group activities	Prohibited	Allowed	Allowed
Standard protocol for discontinuation of contact isolation	Yes	Yes	Yes
Regular mandatory census reporting to NCIC	Yes	Yes	Yes

NOTE. CRE, carbapenem-resistant Enterobacteriaceae; NCIC, National Center for Infection Control.

[a] High-risk groups were defined as patients transferred from other facilities or patients with earlier hospitalization within the previous 6 months.

TABLE 3. Newly Discovered Carriers, by Ward Type, in 3 Carbapenem-Resistant Enterobacteriaceae Screening Surveys

	First survey 2008		Second survey 2010		Third survey 2011		
Ward type	Patients screened	No. (%) of patients with positive results	Patients screened	No. (%) of patients with positive results	Patients screened	No. (%) of patients with positive results	*P*
Skilled nursing care	291	76 (26.1)	252	49 (19.4)	257	33 (12.8)	.001
Mechanical ventilation	126	15 (11.9)	134	17 (12.7)	209	29 (13.9)	.86
Subacute care	229	22 (9.6)	209	19 (9.1)	203	12 (5.9)	.33
Rehabilitation	359	9 (2.5)	360	6 (1.7)	351	7 (2.0)	.73
Total	1,005	122 (12.1)	955	91 (9.5)	1,020	81 (7.9)	.008

dard precautions, and implementation of a CRE control program. Mean scores were compared using the 2-tailed Mann-Whitney *U* test and 1-way ANOVA. Comparison of CRE carrier prevalence in the 3 surveys was conducted using the χ^2 test for proportions. Risk factors for newly discovered CRE carriage were assessed by univariate analysis. Wards were classified into high-risk and low-risk categories on the basis of type of ward and carrier prevalence. The impact of individual elements of the infection control score on the risk of newly discovered CRE carriage was evaluated via a conditional logistic regression model, following matching by ward risk category. For all analyses, $P < .05$ was considered statistically significant. The study was approved by the jurisdictional institutional review board.

RESULTS

Evaluation of Infection Control Policies

Thirty-nine site visits were conducted in the 13 PACHs during the study period. In each visit, all components of the infection control score were evaluated. An improvement was noted in all 4 principal categories over the study period: infection control consultant, hand hygiene, standard precautions, and implementation of a CRE control program (Table 1). The overall infection control score increased progressively from 6.8 in 2008 to 11.6 in 2010 and 14.0 in 2011 ($P < .001$).

Point Prevalence Surveys

Twelve of the 13 PACHs participated in the point prevalence surveys. The thirteenth PACH, with a patient population and bed distribution similar to that of the other facilities, elected not to participate. A total of 3,516 patients (2,980 not known to be CRE carriers and 536 known carriers) were screened in the 3 surveys. The breakdown by year was as follows: 1,147 patients in 2008 (39 wards), 1,131 patients in 2010 (39 wards), and 1,238 patients in 2011 (44 wards). Patient characteristics were similar in the 3 surveys, with the exception that, among patients included in the third survey (2011), median length of stay was greater (44, 38, and 56 days in the 3 surveys, respectively), and there was a higher proportion of patients with long-term mechanical ventilation (14.2%, 16.7%, and 24.6% of patients in the 3 surveys, respectively). Among all patients participating in the surveys, including known CRE carriers, CRE carriage was detected in 193 patients (16.8%) in 2008, 160 (14.1%) in 2010, and 155 (12.5%) in 2011 ($P = .013$). *K. pneumoniae* was the most common CRE species identified (95.3% of all isolates). Results of PCR performed on the isolates obtained in the 2011 survey demonstrated bla_{KPC} in all *K. pneumoniae* isolates (149 of 149). bla_{NDM} was not detected.

CRE Carriage among Patients Not Known to Be Colonized

In the 2008 survey, CRE carriage was detected in 122 of 1,005 patients (12.1%) who were not known to be CRE carriers. In 2010, this figure was 91 (9.5%) of 955, and in 2011 it was 81 (7.9%) of 1,020 ($P = .008$). A significant decrease in CRE carriage was noted among patients hospitalized in skilled nursing care wards, from 26.1% in 2008 to 12.8% in 2011 ($P = .001$; Table 3).

Risk factors for newly discovered CRE carriage are shown in Table 4. Type of ward, colonization pressure, length of stay, and lower infection control score were found to be associated with CRE carriage. When specific components of the infection control score were examined, multiple components were found to be inversely associated with carriage. The infection control score was dichotomized into low (3–12) and high (13–16) categories. High infection control score correlated with lower individual risk of CRE carriage, after stratifying by ward risk category (Table 5). Multivariable analysis, matched for ward risk category, revealed the presence of alcohol-based hand-rub (ABHR) in each patient room (odds ratio [OR], 0.63 [95% confidence interval (CI), 0.44–0.93]; $P = .019$), appropriate use of gloves in standard precautions (OR, 0.74 [95% CI, 0.57–0.96]; $P = .023$), and an active admission CRE screening policy (OR, 0.69 [95% CI, 0.52–0.93]; $P = .014$) as independent institutional factors predicting decreased risk of CRE carriage.

DISCUSSION

Few infection control interventions reported to date have shown an impact in decreasing the prevalence of MDROs in long-term care facilities (LTCFs).[24,25] In this study, we have demonstrated that a nationwide, centrally coordinated intervention succeeded in improving compliance with infection

TABLE 4. Univariate Analysis of Risk Factors for Newly Discovered Carbapenem-Resistant Enterobacteriaceae (CRE) Carriage

Variable	CRE negative (n = 2,686)	CRE positive (n = 294)	P
Male sex	1,192 (44.5)	126 (43.0)	.58
Age, years, mean (±SD)	73.5 ± 15.2	75.1 ± 16.3	.097
Length of stay, days, median (IQR)	33.0 (12.0–122.3)	95.0 (26.5–437.5)	<.001
Type of ward			<.001
Chronic mechanical ventilation	408 (15.2)	61 (20.8)	
Skilled nursing care	642 (23.9)	158 (53.9)	
Subacute care	588 (21.9)	53 (18.0)	
Rehabilitation	1,048 (39.0)	22 (7.5)	
Patients with previous CRE carriage, median (IQR)	4.3 (0–11.8)	11.1 (0–27.6)	<.001
Infection control score, mean (±SD)	10.9 (4.0)	9.7 (4.2)	<.001
Infection control consultant	2,172 (80.9)	219 (74.5)	.009
Presence of ABHR in each room	2,556 (95.2)	263 (89.5)	<.001
ABHR at site of care	1,574 (58.6)	141 (48.1)	.01
Presence of antiseptic soap	1,762 (65.6)	158 (53.7)	<.001
Presence of sink in each room	946 (35.9)	101 (34.5)	.63
Paper towel availability	2,327 (86.6)	248 (84.4)	.28
Compliance audits	1,147 (42.7)	107 (36.4)	.038
Appropriate use			
Gloves	1,826 (68.0)	154 (52.4)	<.001
Gowns	1,789 (66.6)	198 (67.2)	.798
Masks	1,670 (62.2)	156 (53.1)	.002
Placement of colonized patients in single rooms or cohorting	2,314 (86.2)	237 (80.6)	.01
Use of gown and gloves in contact isolation	2,118 (78.9)	208 (70.7)	.001
Designated medical equipment	2,607 (97.1)	272 (92.5)	<.001
Admission screening cultures	683 (41.7)	75 (27.6)	<.001
Contact screening	1,965 (73.2)	178 (60.5)	<.001
Discontinuation of isolation per standard protocol	1,473 (54.8)	124 (42.2)	<.001

NOTE. Data are no. (%) of patients, unless otherwise indicated. ABHR, alcohol-based hand rub; CRE, carbapenem-resistant Enterobacteriaceae; IQR, interquartile range; SD, standard deviation.

control standards in PACHs. Furthermore, the intervention was associated with a significant reduction both in newly discovered CRE carriage and in overall CRE carrier prevalence as found in serially conducted point prevalence surveys during the course of the intervention. By performing a stratified analysis, we were able to show that an individual patient's risk of newly identified CRE carriage was inversely correlated with the institution's infection control score, independent of ward-based risk factors. Elements of the infection control score independently associated with decreased risk of newly discovered CRE carriage included presence of ABHR in each room, appropriate use of gloves in the context of standard precautions, and a policy of active surveillance for CRE at admission.

Infection control interventions in LTCFs are important not only to contain the spread of MDROs in these institutions themselves, but also to protect acute care hospitals, because LTCFs can serve as a reservoir of ongoing carriage, amplification, and dissemination of MDROs into acute care facilities.[1,2,4,5,26] Several recent studies have reported a high prevalence of CRE carriage among patients hospitalized in LTCFs,[25,27] and outbreak investigations conducted in acute care hospitals have identified previous hospitalization in a LTCF as an important risk factor for CRE carriage.[28-30] Point prevalence studies conducted among LTCF residents have detected colonization prevalence as high as 12%–49%.[20,25] Of note, patients hospitalized in LTACHs, which in the Israeli medical system most closely resemble PACHs, may have a higher risk for CRE carriage than patients hospitalized in other LTCFs.[31]

The Israeli PACH intervention was multifaceted and included general improvement in infection control practices in addition to implementation of measures targeted to contain the spread of CRE. The CRE-targeted interventions included carrier cohorting, active surveillance of high-risk patients, and real-time notification of new-carrier identification and interfacility carrier transfers to verify proper isolation. The intervention was part of a national program that initially involved all acute care hospitals and was later expanded to include all healthcare facilities in the country.[32] The intervention strategy was based on an understanding of the importance of coordinated regional intervention to control the spread of MDROs, as has been demonstrated in controlling regional spread of vancomycin-resistant enterococci,[25] and

TABLE 5. Association between Infection Control Score and Newly Discovered Carbapenem-Resistant Enterobacteriaceae Carriage, Stratified by Ward Risk Category

	Percentage (proportion) of patients with newly discovered carbapenem-resistant Enterobacteriaceae carriage		
Ward risk category	Low infection control score (3–12)	High infection control score (13–16)	*P*
Low	5.3 (34/638)	2.2 (17/770)	.002
High	17.4 (180/1033)	11.7 (63/539)	.003
Total	12.8 (214/1671)	6.1 (80/1309)	<.001

more recently of methicillin-resistant *S. aureus*.[33] National and regional programs that include both acute care facilities and LTCFs enable centralized communication between receiving and discharging facilities. This strategy allows early implementation of infection control practices at the time of admission and conduction of contact investigation in the case of newly reported cases from different facilities.

Infection control interventions in LTCFs must take into account the nature of care in these facilities. In contrast to the acute care setting, patients in LTCFs remain in the facility for prolonged periods of time, ranging from weeks to years. Taking into consideration the prolonged length of stay and the need for rehabilitation and socialization, strict isolation may not be feasible or even ethical in these facilities.[34] Implementing control measures identical to those in the acute care setting may result in less effective rehabilitation as well as in undesirable psychological and social consequences. On the basis of data obtained early in the intervention,[20] we were able to adapt the guidelines according to the risk of transmission by ward type. The adapted guidelines allowed patients to go outside their rooms for individual or group activities and for participation in rehabilitation programs.

We found that an institutional policy of active surveillance for CRE at admission was independently associated with reduced likelihood of newly discovered CRE carriage for PACH patients undergoing CRE screening. Previous reports have shown that clinical cultures may fail to identify intensive care unit patients colonized by multidrug-resistant gram-negative bacteria. Calfee et al[35] have reported that 37% of intensive care unit patients with CRKP were first identified by active surveillance cultures.[35] Recently, several studies have implemented active surveillance as a major element of CRE control programs in both acute and long-term care facilities.[25,36-38] An aggressive intervention conducted during a prolonged outbreak in a LTCF included biweekly CRE prevalence surveys, education and auditing of staff, and isolation and cohorting of CRE carriers with dedicated nursing staff.[25] In a healthcare setting in which CRE-infected patients have recently been recognized, screening of high-risk patients (eg, those with prolonged lengths of stay, increased severity of illness, or antimicrobial use) at the time of interfacility transfer may prevent the unrecognized dissemination of CRE-colonized patients to multiple facilities. This in turn may prevent the development of an unrecognized reservoir of CRE-colonized patients and minimize CRE amplification and transmission within and between healthcare facilities. Once local spread has occurred, CRE becomes an infection control challenge for all healthcare facilities within the region.[19,28]

Our study has a number of limitations. First, it is an observational study, lacking a control group. Therefore, the statistically significant association between the decrease in CRE prevalence and our control program can only imply causality, not prove it. Other factors not associated with the intervention, such as trends in medical severity and complexity of the population, may also be associated with a change in MDRO prevalence. However, in the third survey, in which the lowest CRE carrier prevalence was found, the population screened was in fact more medically complex than the populations screened in previous surveys, with a higher proportion of patients with long-term mechanical ventilation and a greater median length of stay. Alternatively, the simultaneous intervention introduced in acute care hospitals may have resulted in decreased export of carriers to other facilities and consequently decreased the risk of CRE transmission in PACHs. However, during the study period, we did not observe a reduction in the number of transfers of known CRE carriers to the PACHs (data not shown).

Second, we assessed infection control resources and polices. However, actual compliance with the guidelines within each facility was not systematically measured. Furthermore, we did not collect data on degree of compliance with screening policies throughout the intervention period. Therefore, incremental improvements in compliance with admission screening policies and resultant early detection of carriers may have yielded a reduction in the proportion of new carriers detected in the surveys. However, the fact that we observed a significant decrease in the overall carrier prevalence during the study period, despite similar rates of transfer of CRE carriers from acute care hospitals, suggests a true decrease in CRE transmission in the PACHs.

Finally, we used a rectal swab sample as the exclusive means of CRE carriage detection. A recent study has reported that the addition of inguinal skin swab cultures increased sensitivity from 88% to 100%.[39] It is therefore possible that we have underestimated the CRE reservoir. However, if so, the effect is likely to be small and nondifferentially distributed among the 3 surveys.

In summary, a centrally coordinated intervention in Israeli

PACHs has succeeded in improving the implementation of infection control measures and was associated with decreasing CRE carrier prevalence in these facilities. This intervention has been performed in the context of a broader, nationwide intervention that began in the acute care hospitals and extended to LTCFs and the rest of the healthcare system. The demonstrated potential for rapid dissemination of CRE within and between healthcare facilities, the high rates of mortality associated with these pathogens, and the need for strict compliance to patient population–based carrier isolation guidelines necessitate a regional or national control program to ensure containment of spread.

PACH CARBAPENEM-RESISTANT ENTEROBACTERIACEAE WORKING GROUP

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