Nosocomial Outbreak of Infection With Pan—Drug-Resistant *Acinetobacter baumannii* in a Tertiary Care University Hospital •

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Source: *Infection Control and Hospital Epidemiology*, Vol. 30, No. 3 (March 2009), pp. 257-263
Published by: The University of Chicago Press on behalf of The Society for Healthcare Epidemiology of America
Stable URL: http://www.jstor.org/stable/10.1086/595977
Accessed: 05/06/2014 03:58

ORIGINAL ARTICLE

Nosocomial Outbreak of Infection With Pan–Drug-Resistant *Acinetobacter baumannii* in a Tertiary Care University Hospital

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OBJECTIVE. To describe what is, to our knowledge, the first nosocomial outbreak of infection with pan–drug-resistant (including colistin-resistant) *Acinetobacter baumannii,* to determine the risk factors associated with these types of infections, and to determine their clinical impact.

DESIGN. Nested case-control cohort study and a clinical-microbiological study.

SETTING. A 1,521-bed tertiary care university hospital in Seville, Spain.

PATIENTS. Case patients were inpatients who had a pan–drug-resistant *A. baumannii* isolate recovered from a clinical or surveillance sample obtained at least 48 hours after admission to an intensive care unit (ICU) during the time of the epidemic outbreak. Control patients were patients who were admitted to any of the "boxes" (ie, rooms that partition off a distinct area for a patient's bed and the equipment needed to care for the patient) of an ICU for at least 48 hours during the time of the epidemic outbreak.

RESULTS. All the clinical isolates had similar antibiotic susceptibility patterns (ie, they were resistant to all the antibiotics tested, including colistin), and, on the basis of repetitive extragenic palindromic–polymerase chain reaction, it was determined that all of them were of the same clone. The previous use of quinolones and glycopeptides and an ICU stay were associated with the acquisition of infection or colonization with pan–drug-resistant *A. baumannii.* To control this outbreak, we implemented the following multicomponent intervention program: the performance of environmental decontamination of the ICUs involved, an environmental survey, a revision of cleaning protocols, active surveillance for colonization with pan–drug-resistant *A. baumannii*, educational programs for the staff, and the display of posters that illustrate contact isolation measures and antimicrobial use recommendations.

CONCLUSIONS. We were not able to identify the common source for these cases of infection, but the adopted measures have proven to be effective at controlling the outbreak.

Infect Control Hosp Epidemiol 2009; 30:257-263

Acinetobacter baumannii has become one of the most important pathogens responsible for healthcare-associated infections and particularly affects patients admitted to intensive care units (ICUs).[1] *A. baumannii* is mainly related to ventilator-associated pneumonia, bacteremia, surgical site infection, secondary meningitis, and urinary tract infection.[1,2] It may cause infections as a result of an endemic situation and/or epidemic outbreak, because this bacteria can be found on human skin and can survive for long periods on dry inanimate surfaces in hospital environments.[3,4] Patients are one of the main reservoirs of *A. baumannii* because they contaminate the hands of hospital staff, which, in turn, results in the subsequent risk of cross-transmission.[2,5,6] There is controversy over whether infections caused by *A. baumannii* have attributable mortality rates.[1,7,8] However, they have secondary morbidity and are usually found in patients with serious underlying diseases,[1] and their treatment is often difficult as a result of *A. baumannii* resistance to multiple antibiotics, including carbapenems.[9,10]

A. baumannii frequently shows resistance to a number of antimicrobial drugs.[1,11] This resistance is especially common in environments of high antibiotic pressure, such as ICUs, where resistance to multiple antibiotics has left colistin as the only therapeutic option.[12,13] The in vitro[14,15] and in vivo activity of colistin suggests that it could be an effective antimicrobial agent against *A. baumannii.*[13-20]

From the Preventive Medicine and Public Health Service (R.V., M.C., J.M.A.), the Clinical Microbiology Service (L.A.A., J.A.), the Intensive Care Service (J.G.-M., C.O.), and the Infectious Diseases Service (J.M.C., J.P.), Virgen del Rocío University Hospitals, and the Departments of Preventive Medicine (R.V., M.C.), Microbiology (M.-J.T., F.F.-C., J.A.), and Medicine (J.P.), the University of Seville, Spain.

Received February 1, 2008; accepted October 27, 2008; electronically published January 28, 2009.

 0899-823X/2009/3003-0008$15.00. DOI: 10.1086/595977

In 2002, Hsueh et al.[21] described a nosocomial outbreak of infection that involved 73 hospitalized patients and that was caused by what they referred to as pan–drug-resistant *A. baumannii* (PDRAB), although they had not tested the isolates recovered from the patients for susceptibility to colistin. Several authors reported that some isolates of *A. baumannii* were resistant to polymyxin B and colistin, but they did not identify the risk factors or the clinical repercussions.[22-24] The aim of the present study was to describe what is, to our knowledge, the first nosocomial outbreak of infection with PDRAD, to study the risk factors associated with these infections, and to determine their clinical impact.

METHODS

Setting

Our study was carried out at one of the Virgen del Rocío University Hospitals, a 1,521-bed tertiary care university hospital in Seville, Spain, which consists of 5 buildings. It provides medical and surgical assistance to a population of 587,103, with an average of 54,367 admissions per year. Its 4 ICUs treat patients from all over southwestern Spain who have severe comorbidities. Two of these ICUs were affected by this outbreak, namely, the ICU of the Medical Adult Center (hereafter referred to as ICU A) and the ICU of the Center for Rehabilitation and Traumatology (hereafter referred to as ICU B). ICU A has 6 rooms, but only 2 of them were involved in this outbreak; these 2 rooms have 8 beds each and treated 138 and 154 patients, respectively, in 2002. ICU B has 3 rooms, all of which were affected by the outbreak; these 3 rooms have 11, 6, and 5 beds, respectively, and received a total of 479 admissions in 2002. Every unit is run by its own independent staff.

Study Design

The epidemic period was defined as the time that elapsed from the presentation of the first case (April 9, 2002) until 3 months after the last isolation of the strain of PDRAB (March 9, 2003). During this period, a prospective identification of all the clinical isolates of PDRAB in the microbiology service was performed on a daily basis. In addition, active surveillance for PDRAB colonization was performed, with rectal and pharyngeal swab specimens collected from patients hospitalized in the rooms in which a new case of colonization or infection had been detected.

To study the risk factors associated with infection or colonization with PDRAB, we conducted a nested case-control cohort study. There were 12 case patients. A case patient was defined as any inpatient who had a pan–drug-resistant *A. baumannii* isolate recovered from a clinical or surveillance sample obtained at least 48 hours after ICU admission during the epidemic period. There were 72 control patients. A control patient was defined as any patient admitted to any of these ICU rooms during the epidemic period for at least 48 hours. We selected 6 control patients per 1 case patient by use of incidence density sampling without matching,[25] for an expected odds ratio (OR) of the prevalence of control patients who were treated with antibiotics of 2 (ie, 78% of control patients; $\alpha = .05$), with 11.6% sample power. The Centers for Disease Control and Prevention criteria were used to classify nosocomial infections.[26,27]

The following patient data were collected: age; sex; reason for ICU admission; length of hospital and ICU stay; receipt of mechanical ventilation; a history of tracheostomy, surgery, or other invasive procedure (such as the placement of a central venous catheter, urinary catheter, or arterial line); receipt of parenteral nutrition and/or antibiotics; and underlying chronic diseases (such as diabetes, cancer, pulmonary or renal disease, and immunosuppression).[28] For the case patients, previous antibiotic therapy was defined as the receipt of antibiotics during the period from ICU admission to the recovery of the first PDRAB isolate from a clinical sample. For control patients, previous antibiotic therapy was defined as the receipt of antibiotics during the period from ICU admission to ICU discharge. The defined daily dose, which was established by the Nordic Council on Medicine, was used to measure antibiotic prescriptions.[29] The survival or death of a patient was recorded only during hospitalization.

Microbiological Methods

Clinical samples were cultured according to standard guidelines. Isolates were identified as *A. baumannii* by means of Gram staining, by observation of their colonial morphology and motility, by use of cytochrome oxidase reaction analysis, by determination of whether there was growth at 44°C, as well as by the use of a semiautomated microbiology system (MicroScan Walk-Away; Dade-Behring). All strains were confirmed as *A. baumannii* by the use of amplified ribosomal DNA restriction analysis.[30]

Conventional antimicrobial susceptibility testing was performed, according to Clinical and Laboratory Standards Institute guidelines, by the use of the semiautomated microbiology system on the following antibiotics: ampicillin-sulbactam, piperacillin-tazobactam, aztreonam, ceftriaxone, ceftazidime, cefotaxime, cefepime, imipenem, meropenem, ciprofloxacin, ofloxacin, cotrimoxazol, tetracycline, minocycline, gentamicin, tobramycin, and amikacin.

The minimum inhibitory concentrations (MICs) of colistin were first determined by the use of the Etest (AB Biodisk) and subsequently confirmed by the use of the broth microdilution method, as described elsewhere.[31,32] For colistin, an MIC of at least 4 μg/mL was used as the cutoff point to determine resistant isolates.[31,33] All isolates were stored at −70°C until the assays were performed. Colistin resistance was determined by the use of *Escherichia coli* ATCC 25922 as a quality control strain during susceptibility testing and by the use of *A. baumannii* ATCC 19606 as a quality control strain during amplified ribosomal DNA restriction analysis.

Molecular Typing

The clonal relationship of isolates was analyzed by the use of the repetitive extragenic palindromic–polymerase chain reaction (REP-PCR) method, as described by Snelling et al.[34] REP-PCR patterns were compared by visual inspection, as described elsewhere.[35]

Infection Control Intervention Program

We implemented the following multicomponent intervention program: the performance of environmental decontamination of the ICUs involved, an environmental survey, a revision of cleaning protocols, active surveillance for PDRAD colonization, educational programs for the staff, and the display of posters that illustrate contact isolation measures and antimicrobial use recommendations. Because *A. baumannii* carriage at different body sites, such as the digestive or respiratory tract, may develop into *A. baumannii* infection,[36] active surveillance for colonization, identified by culture of rectal and pharyngeal swab specimens, was prospectively performed for patients hospitalized in the same room in which a new case of colonization or infection had been detected.

Statistical Analysis

In the bivariate analysis, we compared the following variables of case and control patients: variables related to the patient (ie, age and sex), variables related to comorbidity (ie, reason for ICU admission and presence of underlying chronic diseases), variables related to the procedures used in the ICU and their duration (eg, receipt of mechanical ventilation, placement of central venous catheter, and receipt of antibiotic therapy), and variables related to the ICU stay. Bivariate analysis of categorical variables was performed using the χ^2 test or the Fisher exact test, as appropriate. Continuous variables were compared by the use of the Student *t* test or the Mann-Whitney *U* test. ORs and 95% confidence intervals (CIs) were also calculated for all significant ($P < .05$) variables in univariate analysis and for all significant variables in multivariate analysis, and other variables with clinical significance were included in the logistic regression model for multivariate analysis. A step-by-step selection process was applied. The outcome for the logistic regression model was the acquisition of infection or colonization with PDRAB. Statistical analysis was performed by the use of EPI Info software, version 6.04a (Centers for Disease Control and Prevention), and SPSS software, version 11.5 (SPSS).

RESULTS

Of the 1,882 inpatients admitted to the ICUs at our hospital during the epidemic period, we identified 12 case patients infected or colonized with PDRAB: 6 patients from ICU A and 6 patients from ICU B. The global attack rate was 0.64%, with a higher attack rate in ICU B than in ICU A (0.88% vs 0.5% of cases of infection or colonization per 100 ICU admissions; $P = .48$).

A total of 19 PDRAB isolates were recovered from the 12 case patients. All these isolates showed identical REP-PCR patterns, and we concluded that one clone was responsible for the outbreak. All the isolates were resistant to the following antimicrobials: ampicillin-sulbactam, piperacillin-tazobactam, aztreonam, ceftriaxone, ceftazidime, cefotaxime, cefepime, imipenem, meropenem, ciprofloxacin, ofloxacin, cotrimoxazol, tetracycline, minocycline, gentamicin, tobramycin, and ami-

TABLE 1. Data on Patients Infected or Colonized With Pan–Drug-Resistant *Acinetobacter baumannii* During a Nosocomial Outbreak at a Tertiary Care University Hospital in Seville, Spain, April 9, 2002–March 9, 2003

Case patient	Type of infection or colonization	Treatment	Clinical outcome
1	Keratoconjunctivitis	Topical aminoglycosides	Death, unrelated
2	Intra-abdominal infection	Colistin, glycopeptides, aminoglycosides, and carbapenems	Death, probably related
3	Tracheobronchitis	Intravenous and intrathecal colistin; glycopeptides and 3G cephalosporins and carbapenems; rifampicim	Death, probably related
4	Meningitis	Intrathecal and intravenous colistin and glycopeptides	Death, probably related
5	Skin and soft-tissue infection	Topical polimixin B	Recovered
6	Tracheobronchitis	Colistin, glycopeptides, and carbapenems	Death, probably related
7	Pneumonia	Colistin, glycopeptides, and 4G cephalosporins and carbapenems, rifampicim	Death, probably related
8	Intra-abdominal infection	None[a]	Death, probably related
9	Ventriculitis	Intravenous and intrathecal colistin, aminoglycosides, glycopeptides, and carbapenems	Death, probably related
10	Skin and soft-tissue infection	None[a]	Death, unrelated
11	Meningitis and CVC-related bacteremia	Intravenous and intrathecal colistin, aminoglycosides, and 3G cephalosporins and glycopeptides	Recovery
12	Colonization of the pharynx	None	Recovery

NOTE. CVC, central venous catheter; 3G, third generation; 4G, fourth generation.

[a] Strain was isolated after death of patient.

TABLE 2. Risk Factors for Infection or Colonization With Pan–Drug-Resistant *Acinetobacter baumannii* During a Nosocomial Outbreak at a Tertiary Care University Hospital in Seville, Spain, April 9, 2002–March 9, 2003

Risk factor	Case patients ($n = 12$)	Control patients ($n = 72$)	OR (95% CI)
Underlying condition			
COPD	2 (16.7)	9 (12.7)	1.4 (0.3–7.4)
Diabetes mellitus	2 (16.7)	11 (15.3)	1.1 (0.2–5.8)
Neoplasia	2 (16.7)	12 (16.9)	1 (0.2–5.1)
Hepatic failure	1 (8.3)	2 (2.8)	3.2 (0.3–38.1)
Inmunosuppression	0 (0)	3 (4.2)	0 (0–9.5)
Other	8 (66.7)	47 (68.1)	0.9 (0.3–3.6)
Total parenteral nutrition	6 (50)	6 (8.3)	11.2 (2.7–45.6)
Tracheostomy	6 (50)	9 (12.5)	7.1 (1.9–26.9)
Mechanical ventilation	12 (100)	38 (52.8)	12 (1.5–257.9)
Use of urinary catheter	12 (100)	64 (87.5)	2 (0.2–45.3)
Receipt of nasogastric feeding tube	12 (100)	48 (66.7)	6.6 (0.8–143.4)
Use of peripheral venous catheter	8 (72.7)	44 (62)	1.7 (0.4–7)
Use of central venous catheter	12 (100)	71 (97.2)	0.5 (0.1–14.6)
Use of arterial catheter	4 (33.3)	11 (15.3)	2.8 (0.7–10.9)
Drainage of CNS	4 (33.3)	6 (8.3)	5.6 (1.3–24.1)
Abdominal drainage	2 (16.7)	13 (18.1)	0.9 (0.2–4.7)
Receipt of thoracic tube	5 (41.7)	18 (25)	2.2 (0.6–7.7)
Surgery	10 (83.3)	28 (38.9)	8 (1.6–39.4)
Antibiotic use	12 (100)	56 (77.8)	3.9 (0.5–85)

NOTE. Data are no. (%) of patients. A P value of .05 was considered statistically significant. CI, confidence interval; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; OR, odds ratio.

kacin. The colistin MIC_{90} value was 64 μg/mL (range, 4 to greater than 128 μg/mL).

Only one of the 12 case patients was colonized (in the pharynx), without any evidence of clinical infection, and 1 case patient had 2 cases of infection. There were 5 case patients who had an organ-space surgical site infection (2 had meningitis, 2 had an intra-abdominal infection, and 1 had ventriculitis). There were 3 case patients who had a respiratory infection (2 had tracheobronchitis, and 1 had pneumonia). There were 2 patients who had skin and soft-tissue infection. There was 1 case patient who had central venous catheter–related bacteremia, and there was 1 case patient who had keratoconjunctivitis (Table 1).

The median age was 55 years (range, 30–78 years) for the case patients and 51 years (range, 19–83 years) for control patients ($P = 0.5$). The sex distribution was similar for both case patients (8 [67%] of 12 were male) and control patients (47 [65%] of 72 were male). No differences were observed between case and control patients with regard to indications for ICU admission. For the 12 case patients, the most frequent indications for ICU admission were cardiovascular disease (5 patients [42%]), traumatologic disorder (2 patients [17%]), and cancer (2 patients [17%]); for the 72 control patients, they were traumatologic disorder (22 patients [30%]) and cardiovascular disease (17 patients [23%]). Case patients were intubated more frequently (eg, for receipt of mechanical ventilation with or without tracheostomy) and usually required parenteral nutrition, drainage of the central venous system, and major surgery during their ICU stay ($P < .05$; Table 2). The median ICU stay was 34 days (range, 10–95 days) for case patients and 6 days (range, 2–60 days) for control patients ($P < .05$). Previous exposure to aminoglycosides, colistin, carbapenems, quinolones, and/or glycopeptides was more frequent in case patients than in control patients ($P \leqslant .05$; Table 3).

The best-fitting model for the risk factors for infection or colonization with PDRAB explained 62.4% (by Nagelkerke R^2) of the variance observed in the outcome variable. In this model, there was a statistically significant correlation between PDRAB infection and 3 variables (ie, use of quinolones, use of glycopeptides, and ICU stay) ($P < .05$; Table 4).

For the case patients, the mortality rate from the outbreak was 75% (9 of 12 case patients), with death occurring between a minimum of 1 day and a maximum of 59 days after the first PDRAB isolate was recovered (median, 6.5 days); for the control patients, the mortality rate was 18.1% (13 of 72 control patients) (OR, 13.6 [95% CI, 2.8–75.12]). The clinical information was reviewed independently by 2 clinicians, to assess whether mortality was related to PDRAB infection. For 2 case patients, it was determined that mortality was not related to PDRAB infection; for 7 case patients, it was determined that mortality was probably related to PDRAB in-

TABLE 3. Data on the Antimicrobial Agents Used and Their Association With a Nosocomial Outbreak of Infection or Colonization With Pan–Drug-Resistant *Acinetobacter baumannii* at a Tertiary Care University Hospital in Seville, Spain, April 9, 2002–March 9, 2003

Agent	Mean defined daily dose		Student *t* test	*P*
	Per case patient	Per control patient		
Penicillins	25.1	13.1	1	.2
Aminoglycosides	7.9	1.7	2.2	.04
Cephalosporins				
2nd generation	0.2	0.5	−0.5	.6
3rd generation	9.1	0.9	1.5	.2
4th generation	5.2	1.3	1.4	.2
All	14.5	2.7	1.9	.07
Colistin	13.4	0.4	2.7	.02
Carbapenems	11.8	3.2	3.2	.02
Glycopeptides	13.4	0.5	4.5	.001
Quinolones	8.4	1.5	2.2	.05
Antifungals	1.7	0.03	0.9	.3

fection. In Table 1, we show the clinical outcome of each case patient and the treatment used for each case of infection.

The data on the active surveillance of patients hospitalized in the ICUs after the outbreak took place showed that 4 (19.1%) of 21 patients from ICU A and 27 (35.1%) of 77 patients from ICU B were colonized with multidrug-resistant *A. baumannii.* However, all of these isolates were susceptible to colistin. After the performance of the environmental decontamination of the ICUs involved in the outbreak, the environmental survey did not detect any further PDRAB isolates.

DISCUSSION

Our study describes what is, to our knowledge, the first nosocomial outbreak of infection with PDRAB. The resistance of the isolates (recovered from the case patients) to an extremely large number of antibiotics and the clinical outcome of the case patients confirm the importance of this outbreak, despite the moderate number of patients affected (which is reflected in the low statistical power of our study), even with the increase in the number of control patients per case patient (ie, a 6 : 1 ratio). The outbreak shows the alarming capacity of *A. baumannii* to develop antibiotic resistance, not only to carbapenems but also to other antibiotics, such as colistin, which is one of the last available antibiotics used for the treatment of multidrug-resistant *A. baumannii* infection.

A previous study, conducted in Spain, described a rate of colonization or infection with carbapenem-resistant *A. baumannii* of 1.36 cases of infection or colonization per 1,000 hospital admissions,[37] whereas the rates in our ICUs during 2001–2003 were in the range of 0–15.7 cases of infection or colonization per 1,000 ICU admissions for ICU A and 8.4–29.3 cases of infection or colonization per 1,000 ICU admissions for ICU B (authors' unpublished data). Although the inclusion of data on asymptomatically colonized patients could seem inappropriate, we decided to use a case definition that was more sensitive than that specified: we defined a case patient as any inpatient who had a PDRAB isolate recovered from a clinical or surveillance sample obtained at least 48 hours after admission to an ICU during the the time of the epidemic outbreak. We did so because of the newness of the PDRAB isolate and because of the effect the outbreak had on our hospital.

The mechanism of acquisition of resistance was unknown, but we suspected that it could be closely related to the previous antimicrobial pressure and/or inappropriate antimicrobial treatment. In our institution, there was a situation in which the disease was endemic: in a previous study conducted in our ICU, the cases of nosocomial *A. baumannii* bacteremia were polyclonal, and 20% of them were resistant to all classes of antimicrobial agents tested, except for colistin.[38] In both ICU A and ICU B, the outbreak coincided with an increase from the previous month in the number of *Acinetobacter* isolates with resistance patterns associated with increased consumption of broad-spectrum antimicrobial agents (ie, ampicillin-sulbactam, carbapenem, quinolone, and third-generation cephalosporins). To study the possible effect of antibiotic pressure on the development of the outbreak, the antibiotic prescription during the ICU stay was included in the analysis. Despite the few reports on the use of defined daily dose as a unit of measure, it is considered to be an adequate method to measure antibiotic administration in these ICUs, where dosage and duration of prescription usually vary widely. The results of our study were compatible with those of previous studies: the identification of 2 risk factors—previous antimicrobial therapy with quinolones and aminoglycosides and a longer length of stay in an ICU with a high density of infected or colonized patients—for the development of the outbreak.[1,39] Although the estimate of risk found in our model is very low, because of the low number of cases, we believe this information could be relevant to the importance of correctly managing these patients.

For cases of *A. baumannii* infection, it is difficult to assess the influence of antibiotic resistance on the clinical outcome,[10]

TABLE 4. Multivariate Analysis of Risk Factors Associated With Infection or Colonization With Pan–Drug-Resistant *Acinetobacter baumannii* During a Nosocomial Outbreak at a Tertiary Care University Hospital in Seville, Spain, April 9, 2002–March 9, 2003

Risk factor	OR (95% CI)
ICU stay	1.07 (1.01–1.13)
Use of quinolones	1.15 (1.01–1.3)
Use of glycopeptides	1.17 (1.04–1.32)

NOTE. CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

and, although the virulence of the strains of endemic multidrug-resistant *A. baumannii* in these ICUs was unknown, we observed a higher mortality rate for this outbreak (75%) than for the one described by Garcia-Garmendia et al.[40] (49%). The attributable mortality could not be calculated because the control patients were not matched by severity of the underlying disease; thus, in our case patients, we observed more severe underlying conditions (Table 2), and, after reviewing the clinical information, we have detected an increased death rate that could possibly be related to PDRAB infection. We did not routinely use imipenem and rifampicin to treat patients with PDRAB infection, because, at that time, there was no sufficient evidence of its effectiveness.

The strategies followed over the past decades for controlling outbreaks of infection with multidrug-resistant *A. baumannii* have been different in every hospital. In those institutions in which the epidemics are limited to a single area, such as ICUs, the origin of the outbreak is usually located in a contaminated object, and the implementation of contact isolation measures and the modification of cleaning protocols have usually been effective in controlling the outbreaks.[10] The present outbreak affected 2 different ICUs that did not share any common element that could explain the transmission of the infection between the 2 ICUs. Despite the epidemiological research, we could not detect a common source for these cases of infection, although new cases of colonization were usually the result of a mistake made during the implementation of hygienic measures, which resulted in an increased incidence of cross-transmissions among patients via the contaminated hands of the hospital staff.[41] However, the measures adopted to control the outbreak were effective at controlling PDRAB transmission,[1] although they probably had a low impact on the clinical outcomes of the case patients, because of the limited therapeutic alternatives. Selective intestinal decontamination was not included among our infection control measures, because of the wide resistance profiles observed in the isolates of *A. baumannii*.[10]

In summary, we described an outbreak of infection with PDRAB that resulted in a high mortality rate in a clinical setting. This outbreak was due to a high rate of colonization or infection with multidrug-resistant *A. baumannii* and high antibiotic pressure. To avoid these types of outbreaks of infection with pan–drug-resistant bacteria (with no available treatment) in the future, we must implement an adequate antibiotic strategy as well as the strict observation of the measures for controlling infection.

ACKNOWLEDGMENTS

The authors thank R. Fernández Pascual for her review and comments on statistics.

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

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