



Clinical Features and Epidemiology of *Acinetobacter baumannii* Colonization and Infection in Spanish Hospitals

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Source: Infection Control and Hospital Epidemiology, Vol. 25, No. 10 (October 2004), pp. 819-824 Published by: Cambridge University Press on behalf of Society for Healthcare Epidemiology of

Stable URL: http://www.jstor.org/stable/10.1086/502302

Accessed: 29-01-2016 17:58 UTC

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# CLINICAL FEATURES AND EPIDEMIOLOGY OF ACINETOBACTER BAUMANNII COLONIZATION AND INFECTION IN SPANISH HOSPITALS

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### ABSTRACT -

**OBJECTIVE:** To investigate the clinical features and the epidemiology of *Acinetobacter baumannii* in Spanish hospitals.

**DESIGN:** Prospective multicenter cohort study.

**SETTING:** Twenty-seven general hospitals and one paraplegic center in Spain.

**METHODS:** All cases of *A. baumannii* colonization or infection detected by clinical samples during November 2000 were included. Isolates were identified using phenotypic and genotypic methods. The molecular relatedness of the isolates was assessed by pulsed-field gel electrophoresis.

**RESULTS:** Twenty-five (89%) of the hospitals had 221 cases (pooled rate in general hospitals, 0.39 case per 1,000 patient-days; range, 0 to 1.17). The rate was highest in intensive care units (ICUs). Only 3 cases were pediatric. The mean age of the patients in the general hospitals was 63 years; 69% had a

chronic underlying disease and 80% had previously received antimicrobial treatment. Fifty-three percent of the patients had an infection (respiratory tract, 51%; surgical site, 16%; and urinary tract, 11%). Crude mortality was higher in infected than in colonized patients (27% vs 10%; relative risk, 1.56; 95% confidence interval, 1.2 to 2.0; P = .003). Molecular analysis disclosed 79 different clones. In most hospitals, a predominant epidemic clone coexisted with other sporadic clones. Imipenem resistance was present in 39% of the hospitals.

**CONCLUSIONS:** *A. baumannii* was present in most participating Spanish hospitals (particularly in ICUs) with different rates among them. The organisms mainly affected predisposed patients; half of them were only colonized. Epidemic and sporadic clones coexisted in many centers (*Infect Control Hosp Epidemiol* 2004;25:819-824).

Multidrug-resistant *Acinetobacter baumannii* has become an important cause of nosocomial infection worldwide. This gram-negative organism mainly affects predisposed patients, particularly those in intensive

care units (ICUs), thus behaving as a nosocomial opportunistic pathogen.<sup>2</sup> One of its main features is its ability to develop resistance to multiple antimicrobial agents. During recent years, dissemination of carbapenem-

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Supported in part by a research grant from Merck Sharp & Dohme, Spain, and by the Red Española de Investigación en Patología Infecciosa (Instituto de Salud Carlos III, C03/14).

The authors thank the Grupo para el Estudio de la Infección Hospitalaria (GEIH), from the Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC), for supporting the study.

Presented in part at the 42nd International Conference on Antimicrobial Agents and Chemotherapy, September 27-30, 2002; San Diego, CA.

TABLE 1
CHARACTERISTICS OF THE 28 SPANISH HOSPITALS PARTICIPATING IN THE STUDY

			No. of Cases			
Hospital	No. of	Type of	No. of	per 1,000	No. of	
No.	Beds	Hospital	Cases	Patient-Days	Clones	
1	220	R	27	5.19	15	
2	200	G	1	0.31	1	
3	240	G	3	0.50	3	
4	266	G, U, P	0	0	-	
5	308	G, P	1	0.14	1	
6	343	G, P	0	0	-	
7	424	G, T	1	0.08	1	
8	517	G, T	10	0.71	1	
9	500	G, T	1	0.7	1	
10	540	G, U	3	0.23	3	
11	540	U, T	12	0.67	1	
12	601	G	7	0.44	3	
13	650	G, T	9	0.56	3	
14	727	G, U, T	1	0.05	1	
15	873	G, U, T	5	0.22	4	
16	931	G, U	5	0.19	1	
17	940	G, U, T	0	0	-	
18	960	G, U, T	37	1.17	9	
19	1,054	G, U, T	1	0.07	1	
20	1,075	G, T	1	0.04	1	
21	1,085	G, U, T	15	0.54	1	
22	1,126	G, U, T	12	0.50	2	
23	1,176	G, T	7	0.23	4	
24	1,300	G, T	4	0.13	1	
25	1,300	G, T	3	0.09	3	
26	1,442	G, U, T	12	0.32	3	
27	1,550	G, U, T	2	0.05	2	
28	1,606	G, U, T	42	1.04	14	

R = paraplegic reference center; G = general hospital; U = university hospital; P = private hospital; T = active transplantation program.

resistant strains has been described in many countries.<sup>3,4</sup>

Many outbreaks caused by this organism have been described in the literature. Although in some centers a single clone predominates, in others the epidemiologic situation is more complex, with coexistence of epidemic and sporadic strains.<sup>5</sup> Although most studies on the epidemiology of *A. baumannii* have been performed in single hospitals, some of the scarce multicenter studies performed to date have shown interinstitutional spread of resistant strains,<sup>69</sup> thus raising the possible need for control of interhospital transmission.<sup>8,9</sup>

The objective of this study was to describe the clinical and molecular epidemiology of *A. baumannii* and the clinical features of *A. baumannii* infections in a wide sample of Spanish hospitals.

# METHODS Setting

The members of the Hospital Infection Study Group (GEIH) from the Spanish Society on Infectious Diseases and Clinical Microbiology were asked to participate in the GEIH-Ab 2000 project, promoted by the GEIH with the objective of investigating the epidemiology, mechanisms of resistance, and clinical implications of *A. baumannii* in Spanish hospitals. Members from 28 hospitals agreed to participate.

The 28 participating hospitals serve a population of 11 million inhabitants (approximately 25% of the Spanish population). Twenty-seven are general hospitals and one is a specialized reference center for paraplegic patients. Twenty-six (92.8%) are public hospitals, 14 (50%) are university hospitals, and 19 (67.8%) have active transplant programs. Eleven hospitals (39.3%) have 500 to 999 beds, 10 (35.7%) have more than 1,000 beds, and 7 (25%) have fewer than 500 beds (Table 1).

### **Patients**

Every new case of colonization or infection due to A. baumannii detected from clinical samples during November 2000 in the participating hospitals was included in the study. Cases detected only from surveillance samples were excluded as surveillance policies differ from hospital to hospital. All of the isolates presumptively identified as A. baumannii in each participating hospital were sent to a reference laboratory (Hospital Clinic, Barcelona), where identification was performed following phenotypic and genotypic methods. For each case, only one isolate (the first) was studied. Only those cases in which the organism was finally identified as A. baumannii were included. For each case, the following variables were recorded: hospital ward (ICU, medical, surgical, and pediatric), gender, age, type of sample, type and severity of underlying disease (according to McCabe classification),<sup>10</sup> invasive procedures, and previous antimicrobial treatment. A. baumannii was considered to have been nosocomially acquired if the sample had been obtained more than 2 days after the patient's admission. Patients colonized or infected during the first 2 days of admission and who had been directly moved from another center were considered to be imported cases. The clinical significance (colonization or infection) of the A. baumannii isolation and type of infection in each case were assessed according to Centers for Disease Control and Prevention criteria. 11,12 Sepsis, severe sepsis, septic shock, and multi-organ failure were defined according to standard criteria.<sup>13</sup> Patients were observed until discharge or death, or until 30 days after the sample had been obtained if the patient was still hospitalized.

### Microbiological Studies

Identification of *A. baumannii* was performed by traditional phenotypic methods and amplified ribosomal DNA restriction analysis.<sup>14</sup> Genotyping of isolated organisms was performed by pulsed-field gel electrophoresis

TABLE 2
RATES OF ACINETOBACTER BAUMANNII COLONIZATION OR
INFECTION IN 27 TERTIARY-CARE SPANISH HOSPITALS DURING THE
1-MONTH STUDY PERIOD\*

	Pooled Rate	Median (Range)
Global	0.39	0.22 (0-1.17)
Medical wards <sup>†</sup>	0.14	0 (0-0.73)
Surgical wards <sup>†</sup>	0.22	0 (0-0.94)
Intensive care units <sup>†</sup>	4.55	1.96 (0-13.2)

<sup>\*</sup>New cases per 1,000 patient-days. †The 3 pediatric cases are not included

(PFGE) analysis. Genomic DNA was prepared in agarose plugs, as described elsewhere.<sup>15</sup> DNA inserts were restricted with *SmaI*, according to the manufacturer's instructions (New England BioLabs, Beverly, MA). Isolates were assigned to clonal groups, according to the criteria of Tenover et al.<sup>16</sup> Antimicrobial susceptibility was studied by microdilution following the recommendations of the National Committee for Clinical Laboratory Standards.<sup>17</sup>

### Statistical Analysis

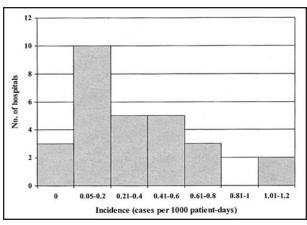
Rates were estimated by dividing the number of new cases by the number of patient-days in the study period. Categorical and continuous variables were compared using chi-square and the Mann-Whitney U test, respectively. For continuous dependent variables, correlations with independent variables were assessed by analysis of variance. For dichotomous dependent variables, relative risk (RR) or odds ratio (OR) and 95% confidence interval (CI $_{\rm q5}$ ) were calculated.

## RESULTS

During the study period, 240 isolates presumptively identified as *A. baumannii* by the local laboratories were sent to the reference laboratory. Nineteen cases were excluded: 1 was not an *Acinetobacter* species, 15 were identified as *Acinetobacter* genospecies 3, and 3 were another *Acinetobacter* species. Thus, 221 isolates and cases of *A. baumannii* colonization or infection were included.

Twenty-five of the 28 participating hospitals (89.2%) had cases of *A. baumannii* colonization or infection (range per hospital, 0 to 42 cases) during the study period (Table 1). The 221 cases were distributed as follows: 104 (47%) were in ICUs, 57 (26%) were in medical wards, 54 (24%) were in surgical wards, and 3 (1%) were in pediatric wards (only 1 case in a neonatal unit). These data were not available for 3 (1.3%) of the patients.

In the 27 general hospitals, the pooled rate of *A. baumannii* colonization or infection was 0.39 case per 1,000 patient-days (range, 0 to 1.17 cases) or 0.30 case per 100 admissions (range, 0 to 1.48 cases). The median rate



**FIGURE.** Distribution of rates of *Acinetobacter baumannii* colonization and infection in 27 general hospitals in Spain.

was 0.22 case per 1,000 patients-days, and the 75th percentile was 0.50. ICUs had higher rates than did medical or surgical wards (Table 2). The frequency distribution of tertiary-care hospitals according to the incidence is shown in the figure. There were no geographic trends in the distribution of the incidence and no relation between the rates and the size of the hospitals (number of beds) ( $r^2 = 0.04$ ; P = .2) or other hospital features (data not shown). The rate in the paraplegic center was 5.19 cases per 1,000 patient-days.

A. baumannii was isolated from respiratory samples in 87 (39.3%) of the patients, exudates or abscesses in 52 (23.5%), urine cultures in 51 (23%), vascular catheter tips in 8 (3.6%), blood cultures in 7 (3.1%), cerebrospinal fluid in 4 (1.8%), and other samples in 3 (1.3%). Data were unavailable in 9 (4%) of the cases.

Overall, 206 (93.2%) of the cases were nosocomially acquired and 8 (3.6%) were community acquired; 7 nosocomially acquired cases were considered to be imported from other centers. These data were unavailable in 7 (3.2%) of the cases. Predisposing conditions of the colonized or infected patients were available for 206 (93.2%) of the cases and are summarized in Table 3; no significant differences in the frequency of these conditions were found among hospitals in different areas (data not shown). There were 203 adult and 3 pediatric patients. Among these 206 patients, 109 (52.9%) had an infection due to A. baumannii and the rest were only colonized. The types of infections among the 102 infected patients in general hospitals were as follows: respiratory tract infections, 52 (pneumonia, 36); incisional surgicalsite infections, 16; urinary tract infections, 11; nonsurgical skin and soft tissue infections, 9; phlebitis, 5; meningitis, 4, primary bacteremia, 3; and intra-abdominal infections, 2. Among the 7 infected patients in the paraplegic center, 6 had a urinary tract infection and 1 had a non-surgical skin and soft tissue infection. Regarding systemic response, 51 (46.8%) of the patients with infection presented with sepsis, 12 (11%) with severe sepsis, 9

TABLE 3
CHARACTERISTICS OF THE 206 PATIENTS COLONIZED OR INFECTED WITH ACINETOBACTER BAUMANNII IN SPANISH HOSPITALS

	General	Paraplegic	
Characteristic	Hospitals	Hospital	
No. of patients	183	23	
Median age, y (range)	63 (0-91)	34 (14-67)	
Male	129 (70.5%)	20 (87%)	
Chronic underlying disease			
Nonfatal	85 (46.4%)	21 (91.3%)	
Ultimately fatal	37 (20.2%)	2 (8.7%)	
Rapidly fatal	4 (2.2%)	0	
Diabetes mellitus	30 (16.4%)	2 (8.7%)	
Neoplasia	35 (19.1%)	0	
Chronic pulmonary disease	27 (14.8%)	1 (4.3%)	
Chronic renal insufficiency	9 (4.9%)	1 (4.3%)	
Transplantation	4 (2.2%)	0	
Central venous catheter	134 (73.2%)	4 (17.4%)	
Current or previous ICU stay	142 (77.6%)	14 (60.9%)	
Bladder catheter	144 (78.7%)	17 (73.9%)	
Cerebrospinal fluid shunt	13 (7.1%)	0	
Parenteral hyperalimentation	52 (28.4%)	0	
Mechanical ventilation	103 (56.3%)	11 (47.8%)	
Surgical procedure	94 (51.4%)	5 (21.7%)	
Previous antimicrobial treatment	148 (80.9%)	16 (69.6%)	
Aminopenicillins	39 (21.3%)	6 (26.1%)	
Piperacillin/tazobactam	26 (14.2%)	5 (21.7%)	
Carbapenems	30 (16.4%)	3 (13%)	
Cephalosporins	72 (39.3%)	5 (21.7%)	
Aminoglycosides	60 (32.8%)	6 (26.1%)	
Fluoroquinolones	30 (16.4%)	4 (17.4%)	

ICU = intensive care unit.

(8.3%) with septic shock, and 8 (7.3%) with multi-organ failure syndrome.

Thirty-nine patients died (crude mortality, 18.9%). Mortality was higher among patients with infection than among those with colonization (26.6% vs 10.4%; RR, 1.56;  $\text{CI}_{95}$ , 1.2 to 2.0; P = .003). The mean duration of hospitalization after A. baumannii isolation in the surviving cases was 21 days (range, 1 to > 30 days), and was significantly longer among patients with infection than among those with colonization (mean, 23.1 vs 19.2 days; P = .02).

Molecular analysis disclosed 79 different PFGE types among the 221 isolates of *A. baumannii* included in the study. A PFGE type could not be obtained in 1 isolate. Fifty-two (65.8%) of the clones were each isolated from a single patient, 18 (22.7%) from 2 to 5 patients, 5 (6.3%) from 6 to 10 patients, and 4 (5%) from more than 10 patients. No clones were present in more than one hospital. The number of clones in an individual hospital ranged from 1 to 4 except in the 3 hospitals with higher rates, where there were 9, 14, and 15 clones, respectively (Table

1). A predominant clone (ie, a clone that caused more than 50% of the cases) was observed in the 14 hospitals with 4 or more cases; in 5 of them, all of the cases were caused by that clone.

In 4 of the 8 cases considered to be community acquired, the isolates belonged to clones that were epidemic in the centers where the cases were detected. Similarly, in 5 of the 7 cases considered to be imported from other hospitals, the isolates belonged to epidemic clones in the centers where the cases were detected.

Among the 221 isolates, 91 (41.2%) were imipenem resistant and 14 (6.3%) had intermediate susceptibility. Seventy isolates (31.6%) showed high-level imipenem resistance (minimum inhibitory concentration  $\geq$  64 mg/L). Imipenem-resistant strains were detected in 11 hospitals (39.3%). Imipenem resistance was more frequent among university hospitals than among non-university hospitals  $(57.1\% \text{ vs } 15.4\%; \text{ OR, } 7.3; \text{ CI}_{95}, 1.1 \text{ to } 46.2; P = .04). \text{ No other}$ hospital features (ie, the number of beds or having a transplantation program) were associated with imipenem resistance. Imipenem-resistant isolates belonged to 28 (35.4%) of the 79 clones; in 11 of these clones there were isolates showing different imipenem susceptibility. Imipenem-resistant clones were more frequently epidemic (isolated from more than one patient) than were imipenem-susceptible clones (63% vs 21.2%; OR, 6.3;  $\text{CI}_{95}$ , 2.2 to 17.6; P < .001). The mean number of isolates (± standard deviation) in each clone was 4.5 (± 5.3) for imipenem-resistant clones and 1.8 ( $\pm$  2.3) for imipenem-susceptible clones (P = .01). Also, ciprofloxacin-resistant clones were more frequently epidemic than were ciprofloxacin-susceptible clones (88.9% vs 11.1%; OR, 3.8;  $CI_{95}$ , 1.02 to 14.7; P = .03).

# **DISCUSSION**

A. baumannii is an important cause of nosocomial infections in most countries. Many outbreaks have been described in the literature, and the organism has become endemic in many centers. <sup>5,8,18-20</sup> Multicenter studies on the epidemiology of A. baumannii colonization and infection are scarce.

Our study was performed in a wide sample of Spanish hospitals. Because participation was voluntary, this sample cannot be considered a representative sample of Spanish centers. It is possible that those hospitals with A. baumannii-related problems might have been more prone to participate. Nevertheless, the participating hospitals included small and large university and non-university centers, were located in small and large towns, provided healthcare to more than 25% of the Spanish population, and had different rates of A. baumannii colonization or infection during the study period. Due to the nature of our objectives (which included the use of appropriate methods for the identification of A. baumannii and the performance of molecular analysis), it was necessary to limit the number of isolates to be investigated and, consequently, the study period was necessarily short. Thus, seasonal variations could not be investigated. However, we believe our data are indicative of the incidence of A.

baumannii colonization and infection in most Spanish hospitals.

A. baumannii was present in almost 90% of the hospitals. The rate of colonization and infection in the month studied was different among general hospitals. We did not find any relationship between size, teaching condition, or existence of transplantation programs in the hospitals and the rates. Although clinical practice is probably similar in the participating hospitals, a bias due to different frequency of submission of samples for culture among the hospitals cannot be discarded. However, we do not think that this could explain the differences in the rates. Thus, local epidemiologic circumstances, such as differences in infection control programs and compliance with infection control measures, are probably more important than the general features of the hospitals in the rates of A. baumannii. As expected, the rates were highest in ICUs (median, 1.93 cases). In U.S. hospitals, the median annual rate of Acinetobacter infections in ICUs between 1987 and 1996 was 0.72 case per 1,000 patient-days.<sup>21</sup> However, comparison of these data is not possible as we included colonized patients and excluded non-baumannii species of Acinetobacter. It is remarkable that only 3 cases were pediatric and that only 1 occurred in a neonatal unit. Outbreaks of A. baumannii in neonatal units have been described, <sup>22-25</sup> but it seems that this organism does not affect these units as frequently as do other multidrugresistant, gram-negative bacilli such as extended-spectrum beta-lactamase-producing Klebsiella pneumoniae.

The rate in the reference center for paraplegic patients was high. This hospital receives patients from other Spanish hospitals, including many of the participating ones. In this center, *A. baumannii* was mostly isolated from urine samples in catheterized patients, suggesting that urine of catheterized patients was an important reservoir of the organism. Some outbreaks of *Acinetobacter* infections have been previously described in spinal cord units. <sup>26-28</sup>

Our data confirm that *A. baumannii* is still confined to hospitals and only rarely causes community-acquired infections. The fact that some so-called "community-acquired" cases were caused by a clone that was epidemic in the institutions might suggest that those patients could have acquired the organism during a previous admission or, alternatively, that the nosocomial acquisition of *A. baumannii* occurred during the first 48 hours of admission, which has been reported in colonization studies of ICU patients in the context of an outbreak.<sup>29</sup> This also could have occurred in a patient transferred from another center, whose isolate was clonally related to an epidemic clone in the institution that he or she was transferred into.

In our study, half of the patients were considered to be only colonized. A similar rate has been described for *Stenotrophomonas maltophilia*.<sup>30</sup> These data underscore the importance of adequately interpreting the clinical significance of these organisms when isolated from clinical samples to avoid unnecessary use of antimicrobials. The

relevance of patients' colonization in the epidemiology of *A. baumannii* is well known.<sup>29</sup>

Regarding the molecular epidemiology, a wide heterogeneity was found among the isolates, although surveillance samples were not included. The heterogeneity was more evident in hospitals with higher rates, in most of which sporadic and epidemic clones coexisted, as described by Villers et al.<sup>5</sup> However, a predominant clone was observed in all centers with 4 cases or more. Imipenem-resistant or quinolone-resistant clones were more frequently epidemic, in accordance with the results of Koeleman et al.<sup>31</sup> Our data support the hypothesis that antimicrobial resistance may favor the epidemic behavior of some *A. baumannii* clones.

Interinstitutional spread of *A. baumannii* clones has been reported in some areas, <sup>6,8,9</sup> suggesting that the epidemiology of *A. baumannii* cannot be viewed as merely a local problem. We could not demonstrate interinstitutional spread of *A. baumannii* clones, even in hospitals close to one another or in the paraplegic center. Interinstitutional transfer of patients and healthcare workers among hospitals is probably less frequent in Spain than in other countries. However, our study has limitations that need to be considered when interpreting these data: the study period was short and surveillance samples were not included. A longer study including surveillance cultures would be necessary for adequately evaluating interinstitutional spread of *A. baumannii* in Spain and for having a more profound knowledge of the spread of endemic strains.

A. baumannii was present in most of the participating Spanish hospitals, but the rates were different among them; interinstitutional spread of A. baumannii clones was not found, and in many centers, epidemic and sporadic clones coexisted. The organisms mainly affected predisposed patients and mainly caused respiratory tract infections.

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