Rev. salud pública. 13 (4): 691-702, 2011

The emergence of multidrug-resistant *Acinetobacter baumannii* in Colombia: A time-series analysis, 2001-2007

Surgimiento de Acinetobacter baumannii multirresistente en Colombia: Un análisis de series de tiempo 2001-2007

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Received 3rd August 2010/Sent for Modification 25th May 2011/Accepted 15th June 2011

ABSTRACT

Objective This study was aimed at analyzing the phenotypical behavior of *Acinetobacter baumannii* resistance to antibiotics currently available in Colombia for its treatment.
Methods An ecological time-series study was conducted based on information regarding *A. baumannii* resistance to available antibiotics gathered through a Colombian surveillance system involving 33 reference hospitals. Descriptive analysis and modeling forecasting were also carried out.
Results The sample included 5.415 *A. baumannii* isolates collected from 33 hospitals throughout Colombia. This microorganism was the eighth most frequently isolated pathogen in hospital settings, having 3.8 % isolation frequency in intensive care units (ICUs).The study recorded the presence of multidrug-resistant *A. baumannii* strains since 2001, as well as a dramatic increase in *A. baumannii* strains having decreased susceptibility to the antibiotics currently available on the market (30 % to 70 %).
Conclusion *A. baumannii* has shown a clear transition to a multidrug resistance profile in Colombia during recent years which includes resistance to important second-line antibiotics, such as carbapenems.

Key Words: *Acinetobacter baumannii*, method, anti-bacterial agent, drug resistance, multiple (*Source: MeSH, NLM*).

RESUMEN

Objetivo Analizar la conducta fenotípica de resistencia del *Acinetobacter baumannii* a los antibióticos disponibles para su tratamiento en Colombia.
Métodos Se llevó a cabo un estudio ecológico de series de tiempo basado en la información de resistencia del *A. baumannii* a los antibióticos, a partir del sistema de vigilancia colombiana de 33 hospitales de referencia. Se realizaron análisis descriptivos y un modelo de pronóstico.
Resultados Se incluyeron 5 415 aislamientos de *A. baumannii* recolectados en 33 hospitales a través del país. Este microorganismo fue el octavo patógeno más aislado en el escenario hospitalario, con una frecuencia de aislamiento de 3,9 % en unidades de cuidado intensivo (UCIs). Se registra la presencia de cepas de *A. baumannii* multirresistentes desde el año 2001, así como un dramático incremento de cepas de *A. baumannii* con menor susceptibilidad a los antibióticos disponibles en el mercado, con una variación del 30 al 70 %.
Conclusión En los últimos años, en Colombia, el *A. baumannii* ha mostrado una clara transición hacia un perfil multirresistente que incluye la resistencia a antibióticos de segunda línea como los carbapenems.

Palabras Clave: *Acinetobacter baumannii*, métodos, agentes antibacterianos, farmacorresistencia bacteriana múltiple (*fuente: DeCS, BIREME*)

Multi-resistant microorganisms' emergence and dissemination has become a major public health issue. Members of the *Acinetobacter calcoaceticus-baumannii* complex are currently considered an important cause of infection in healthcare systemsall over the world (1,2). *A. baumannii* was consideredto be a microorganism having low clinical importance for a long time. However, it has emerged as an important nosocomial pathogen during recent years due to its ability to develop and combine resistance mechanisms against multiple antimicrobials which, added to its ability to survive in inanimate environments, hinders its treatment, follow-up and control (3). A. baumannii is typically associated with hospital-acquired infections (HAI) affecting seriously-ill patients, mostly those being treated in intensive care units (ICUs) (4). Up to 3 % of infections associated with this microorganism in Colombia have been registered in elderly care facilities (5).

Some of the mechanisms through which *A. baumannii* strains can acquire resistance to antimicrobial compounds include beta-lactamase-mediated hydrolysis, alteration of membrane proteins and penicillin-binding proteins, and increased efflux pump activity (6). Such diversity of drug resistance mechanisms has led to the emergence of *A. baumannii* strains which are resistant to almost all antimicrobial drugs currently available for their treatment, including

broad-spectrum amino glycosides, quinolones and beta-lactams. The situation has been further aggravated by the rapid emergence and proliferation of carbapenem resistance, an issue of major concern for health care systems since it confirms *A. baumannii* as being a multidrug-resistant microorganism and limits therapeutic options for its treatment; it thus raises public health surveillance system awareness regarding this important marker (7).

Antimicrobial resistance surveillance systems play an important role in monitoring and reporting the sensitivity patterns for this and other microorganisms. Methods such as time-series analysis mean that information can be processed taking into account important considerations regarding data independence and behavior as time elapses. Furthermore, time-series analysis has been described as being the most suitable data-mining and forecasting tool, especially for historical data such as that provided by surveillance networks (8).

The present study analyses the phenotypical behavior of *A. baumannii* resistance to the antibiotics currently available for its treatment in Colombia, particularly to carbapenems, and describes multiresistance marker behavior in an antimicrobial resistance surveillance network covering several Colombian hospitals.

METHODS

This was an ecological analytical study that included all *A. baumannii* isolates obtained by the Bogota Antimicrobial Resistance Control Group (GREBO) from January 2001 to December 2007. The network included33 third-level hospitals (hospital capacity ranging from 100 to 800 beds) from five regions of Colombia.

Laboratories in the hospitals involved in the program made use of an external quality control program supported by the of National Institute of Health's Microbiology Department (Bogota, Colombia). More detailed information regarding the network's functioning and notification is available through a previous report (9).

Data collection. Information regarding bacterial isolates processed by each institution's microbiology laboratory was gathered monthly. Micro Scan (Dade Behring, California, USA) and Vitek (Biomerieux, Lyon, France) automated systems were used for bacteriological analysis, according to Clinical Laboratory Standard Institute's (CLSI) standards set for 2007. The data collected from

each institution was transferred to WHONET software (version 5.4,WHO,Geneva,Switzerland)using BacLink 2.0 software (WHO, Geneva, Switzerland).

Data analysis. Bacterial resistance data was analyzed by using the one per patient option, which only includes the first isolate per patient. The sensibility profile was descriptively analyzed during the study period, considering just *A. baumannii* isolates collected from ICUs or non-ICU areas. Multiresistance was defined as resistance to at least three antibiotics. *A. baumannii* percentage resistance to imipenem and meropenem was selected for time series analysis (84 periods).The time series was differentiated and simple and partial auto correlograms were analyzed. A second stage involved using Box-Jenkins methodology for model estimation (10). The models' fit was evaluated by using error and bias (mean error, mean percentage error, mean absolute percentage error, mean absolute error, and root mean squared error). Models were diagnosed by analyzing the residuals' simple and partial autocorrelograms and Box-Pierce tests. Twelve-month predictions were based on the best fitting model, considering 95 % confidence intervals for statistical predictions. All analysis was carried out using Statgraphics Centurion (15.1.02, Virginia, USA).

RESULTS

A total of 5,415 *A. baumannii* isolates were recorded from January 2001 to December 2007. According to the hospital ward in which they had been isolated, 47 % were collected from ICUs and 53 % from non-ICU areas. According to clinical sample type, most isolates were obtained from blood samples (22 %), non-specific secretions (19 %),catheters (13 %), urine (8 %) and abdominal liquids (6 %).

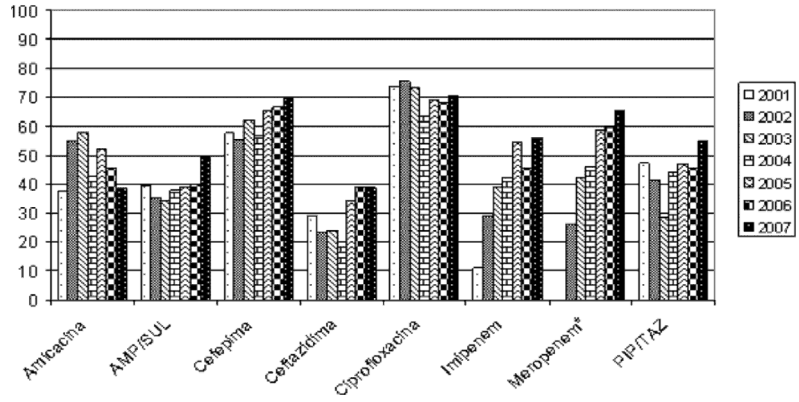
A. baumannii was among the ten microorganisms most frequently isolated by the surveillance network during the study period, accounting for 2.3 % of all microorganisms isolated in 2001 and 2.6 % of all being isolated in 2007. A. baumannii occupied eighth place in ICUs (3.8 % frequency) by contrast with non-ICU areas where it occupied eleventh place (1.7 % frequency).

Resistance profiles

Figure 1 shows the annual microorganism resistance pattern regarding currently available therapeutic options during the study period; high resistance percentages were recorded for all antibiotics during the time the study lasted.

Imipenem had the lowest resistance during 2001 (10.9 %), followed by ceftazidime (29 %), amikacin (37 %), ampicillin/sulbactam (39 %), piperacillin/tazobactam (47 %) and cefepime (57 %), ciprofloxacin having the highest resistance percentage for this year (73.6 %).

Figure 1. *A. baumannii* resistance tendency, 2001-2007



* Meropenem was not regularly tested in 2001 (n = 5 415 isolates)

Resistance percentages remained stable for all antibiotics during the follow-up years, except for carbapenem. A marked increase was observed for carbapenems, varying from 2002 to 2007 for imipenem (10.9 % to 55 %) and meropenem (26.1 % to 65 %).When resistance to these two carbapenems was analyzed jointly (imipenem+meropenem), isolates having higher susceptibility to these two antibiotics was evidenced during 2002 (70.6 %), a notably increase from 2001 (33.3 %); simultaneous resistance to both antibiotics increased from 23.5 % in 2002 to 63.7 % in 2007.

Table 1 summarises the susceptibility profiles of isolates collected inside and outside ICUs; higher resistance was consistently observed in ICU isolates. Analyzing the relative differences between antibiotic resistance percentages revealed a higher rate for imipenem (28.4 %), followed by meropenem (23.9 %), ceftazidime (21.2 %), amikacin (13.8 %), cefepime (13.2 %), piperacillin/tazobactam (8.6 %), ciprofloxacin (3.3 %) and ampicillin/sulbactam (0.5 %).

All antibiotics showed resistance percentages above 30 %. In ICUs, the higher level of susceptibility was registered for imipenem (44.2 %), followed by amikacin (35.8 %), meropenem (35.7 %) and piperacillin/tazobactam (34.1 %). On the contrary, imipenem reported the highest level of susceptibility in non-ICU

areas (60.6 %), followed in decreasing order by meropenem (50.8 %), piperacillin/tazobactam (40.4 %) and amikacin (40.1 %).

Trends regarding multiresistance phenotype

The percentage of isolates susceptible to all antibiotics remained stable during the years being reviewed, varying from 14 % to 16 %. Multiresistance (defined as resistance to three or more of the nine antibiotics available for the treatment of *A. baumannii* infections which were being tested in this study) was high throughout the whole study period (79.4 % in 2001 to 76.3 % in 2007). Table 2 shows that when the multiresistance profile was analyzed according to the number of antibiotics, the germ's resistance pattern became more multi-resistant due to the circulation of a higher percentage of *A. baumannii* isolates which were resistant to more than five antibiotics since 2003 and to more than seven antibiotics having been used since 2004. This transition was also seen in the more frequent circulation of pan-resistant strains (resistant to all tested antibiotics).

Table 1. Drug-resistant Acinetobacter baumannii isolated from ICUs and non-ICU areas during 2001-2007

Antibiotics	Non-ICU areas				ICUs			
	N	% R	% I	% S	N	% R	% I	% S
Amikacin	2 597	42.4	17.4	40.1	2 380	49.2	15	35.8
Ampicillin/sulbactam	2 554	40.1	22.5	37.4	2 310	40.3	27.2	32.5
Cefepime	2 248	59.2	11.1	29.7	2 028	68.5	8	23.4
Ceftazidime	2 581	2..8	34.3	38.8	2 316	34	33.1	32.8
Ciprofloxacin	2 712	69.1	1.5	29.4	2 380	71.5	0.8	27.7
Imipenem	2 652	35	4.4	60.6	2 360	48.9	6.9	44.2
Meropenem	1 612	47.8	1.4	5..8	1 650	62.8	1.5	35.7
Piperacillin/tazobactam	1 244	43.5	16.2	40.4	927	47.6	18.3	34.1

Table 2. Trends (%) shown by antimicrobial resistance phenotypes, 2001-2006

Resistance per number of antibiotics	Year						
	2001 (n=574)	2002 (n=651)	2003 (n=572)	2004 (n=580)	2005 (n=662)	2006 (n=739)	2007 (n=1 031)
0	14.81	13.98	10.84	19.66	14.65	15.70	16.78
1	0.00	5.22	4.37	5.17	4.38	4.74	3.78
2	5.75	3.99	2.45	4.31	2.11	4.74	3.10
3	14.98	9.06	5.59	4.66	6.04	3.65	3.01
4	24.56	11.37	9.27	4.31	4.53	2.57	2.91
5	26.13	23.81	13.81	7.59	5.29	5.68	4.27
6	7.49	14.90	13.81	8.62	7.10	9.88	9.02
7	4.36	13.06	11.01	11.90	15.71	14.34	20.37
8	1.92	4.15	14.34	17.41	28.55	31.39	25.51
9	*	0.46	14.51	16.38	11.63	7.31	11.25

* No data was available on routine sampling of meropenem resistance reported for this year

Carpapenem resistance time series

The carpapenems had the largest change in resistant strainisolation frequency

amongst the antibiotics being studied. Data was collected over a 84-month period for developing a time series model for imipenem and 60 months for meropenem; such difference in the number of months was due to the absence of regular sampling for meropenem resistance during the first years of observation. Aλ=1.5 Box-Cox transformation was applied given that imipenem series variance tended to become modified as time elapsed.

The imipenem series had an increasing trend until month 50, followed by a trend towards resistance stabilization while a constantly increasing trend was identified for meropenem. Both trends became more evident once the series became smoothed by using a moving average (i.e. 5).

An ARIMA (0,1,1) having a constant term was the imipenem series model that best fit the series with Box-Cox transformation (Figure 2). MA (1) was 0.8 and proved to be statistically significant (t=11.3; p=0.000), the constant term was 0.55, which was also statistically significant (t=2.2; p=0.03). The meropenem series fit an ARIMA (0,1,1) model having MA (1)=0.962 and 0.43 constant, both being statistically significant (t=-46.7; p=0.000 and t=4.4; p=0.000, respectively) (Figure 3).The models were tested by "runs", Box-Pierce and variance ratio tests; none of them proved significant (p>0.05), there by confirming that the models were adequate for the data. The residuals' autocorrelograms showed no significant values. A 12-month prognosis was produced on the basis of the proposed model which showed increasing multiresistance prevalence for both antibiotics (Figure 3).

Figure 2. One-year forecastmodelfor theimipenem series.
Box Cox transformation with λ=1.5 ARIMA (0.1.1) with constant term

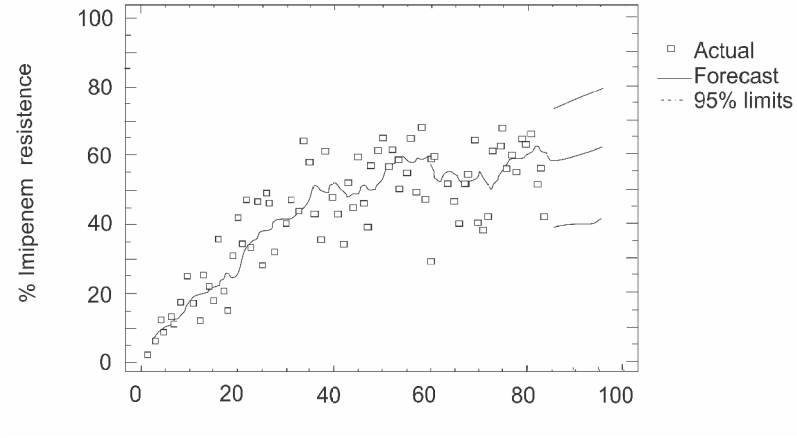
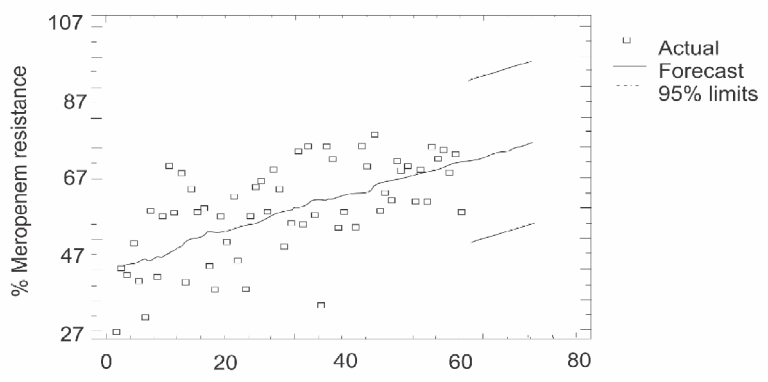


Figure 3. One-year forecastmodel for the meropenem series. ARIMA (0.1.1) with constant term



DISCUSSION

Bacterial resistance is considered nowadays to be an unavoidably progressive public health problem in healthcare services. The World Health Organization's recommendation to follow-up important drug resistance markers has promoted surveillance system development and implementation. The available information regarding frequently reported outbreaks of hospital infection (11) indicates that Acinetobacter baumannii is an endemic pathogen in Colombia (5,12).Indeed, common clones have been reported to be circulating amongst hospitals and even between different cities (13).

A. baumannii was amongst the ten most frequently isolated pathogens in the hospitals included in this study, this being similar to the statistics reported by the SENTRY antimicrobial surveillance program (14,15).

A. baumannii accounts for around 6.5 % of bacteraemia-associated pathogens in Latin-America(16); this is considerably higher than the 3.9 % reported in the USA and Canada (15) and similar to the 7.1 % reported in Spain (17). The present study reports around 3 % isolation frequencies for all isolates, thereby agreeing with available information regarding infection-associated microorganisms reported in Colombia's capital (5).

Nosocomial infections caused by *A. baumanniia* remain confined to critically-ill, immuno suppressed patients having severe underlying conditions requiring invasive life-support measures and higher exposure to broad-spectrum

antibiotics (18), this being consistent with the higher percentage of multi-resistant and carbapenem-resistant *A. baumannii* isolates found in ICUs in our study.

European countries' surveillance systems have also shown a trend for *A. baumannii* strains to acquire a multidrug resistant phenotype, even though the magnitude of the increases registered by the present study was smaller (14). Such differences could be due to regional variations intrinsic to the multidrug resistance phenomenon. There has been reports of multi-resistant *A. baumannii* strains circulating in North America, Europe, Latin-America (Argentina, Brazil), Taiwan, Korea and Hong-Kong to date. Evidence has even been presented regarding the emergence of these pathogens in countries which have historically presented low drug resistance percentages, such as Norway (1).

This report shows the rapid emergence of imipenem and meropenem resistance(around 60 %). Such rate might reflect the frequent use of imipenem since 2001 and the more recent increase in meropenem administration in most hospitals involved in this study. It is worth noting that such increased resistance might have been promoted by national drug policies, including resistance to antimicrobials in the national drug use handbook, but without including other molecules such as cefepime or cefoperazone/sulbactam, since it guarantee that healthcare insurance companies will cover their prescription.

Carbapenem resistance is mainly conferred at molecular level by a loss of outer membrane porin protein expression thereby enabling the antibiotics' entry, this being secondary to decreased expression of a 33-36 kDa outer membrane protein, alteration of penicillin binding protein 2 (PBP-2) and the emergence of carbapenem-hydrolyzing enzymes. These carbapenem resistance mechanisms can act together, as has been shown by studies reporting a combination of OXA-24 and reduced porin protein expression (6,19,20). OXA-23 (13,21,22), OXA-72 (13), OXA-64 and OXA-69 have been reported as being the prevalent enzymatic resistance mechanisms in Colombia (22).

Aminoglycoside and quinolone resistance suggests the existence of other mechanisms, such as the presence of inactivating enzymes and reduced topoisomerase II and IV affinity for fluoro quinolones, respectively. Resistance rates for these antimicrobials recorded during the first years of observation in the present study may have been reflecting previous consumption.

Given the current situation, it becomes evident that the limited treatment options represent one of the most difficult challenges in treating infections

caused by multidrug-resistant *A. baumannii*. Options include the use of ampicillin/sulbactam, polymyxins, combination therapy and the use of natural and synthetic peptides.

However, the introduction of a new antibiotic often entails the concomitant emergence of resistance. Recent articles have reported polymyxin B-resistant clinical isolates (23), as well as the emergence of tigecycline-resistant strains (24). Several multimodal strategies targeted at restraining the spread of A. baumannii infection in hospitals have been described; they would include surveillance of antimicrobial susceptibility profiles in clinical isolates, establishing policies for the rational use of antibiotics, the identification and isolation of colonized/infected patients, training healthcare personnel, hand-washing, decontamination of hospital environments, using molecular tools for determining clonality, screening tests for detecting beta-lactamases and even restricting access to hospital areas (3,25-27).

Taken together, the data reported by this study stresses the key importance of reinforcing policies for the rational use of antimicrobial drugs aimed at detaining multiresistance development. Furthermore, such policies must be combined with strong surveillance and infection control programs and regular clinical studies to guide pan-resistant microorganism-infected patients' therapeutic management ♣

Acknowledgements: We would like to thank the Bogota Antimicrobial Resistance Control Group(GREBO): Martha Lucia Salinas, Norma Montoya (Clínica de Occidente), Mauricio Luna Ortiz, Martha Martínez (Clínica del Niño), Álvaro Ignacio Arango, Jaime Alberto Patiño, Martha Isabel Álvarez, Zenaida Montañez, Shirley Acosta (Fundación Cardio Infantil), YanizHernandez, Claudia Calderón, Jaime Saravia (Fundación San Carlos), Guillermo Prada, Clara Luz Rico, Blanca Stella Vanegas (Fundación Santa Fe de Bogotá), Gerson Arias, Nubia Escobar (Hospital Occidente de Kennedy), Elkin Lemos, Narda Olarte, Alberto Valderrama, Julia Stella Quijano, Martha Isabel Garzón (Hospital el Tunal), Carlos Gómez, MariaNilse González (Hospital Militar Central), Carlos Arturo Álvarez, Claudia Linares, José Roberto Tamara, Beatriz Ariza, Sandra Valderrama (theSan Ignacioteaching hospital), Tailandia María Rodríguez Gutiérrez, Felipe Zamora, Constanza Correa (Hospital Simón Bolívar), Carlos Alquichire, Martha Ruiz (Clínica San Pedro Claver), Adriana Jiménez, Henry Mendoza, Claudia Fajardo Uribe (Hospital de San Jose), Luz Mila López, Gloria Inés Gallo (Hospital Santa Clara), Carlos Humberto Saavedra Trujillo, Clemencia Ávila, Claudia Clavijo (theClínica San Rafaelteaching hospital), Myriam Lucia Galeano, Johana Montes (La Misericordiateaching hospital), Carlos Pérez, Beatriz Cuevas, Lucy Guzmán Cruz (La Samaritanateaching hospital), Sonia Isabel Cuervo, Claudia Patricia Arroyo (Instituto Nacional de Cancerología), Catherine Rojas, Nidia Stella Moya, Margarita Cardona (Centro Policlínico El Olaya),

Giovanni Rodríguez Leguizamón, Claudia Cifuentes Lopez (Clínica Infantil Colsubsidio), Johana Avila, Claudia Cifuentes (ClinicaVidelmédica), Tailandia Rodríguez, Luz Stella Gomez (Clinica Colsubsidio Orquídeas), Henry Mendoza, Martha Meléndez (Hospital Central de la Policía Nacional), Amparo Ovalle Garzón, Claudia Echeverri, (Hospital Federico Lleras Acosta), Ana Maria Pérez Fernández, Melba Sofía (Clinica Central del Quindío), Sandra Gualtero, Luis Fernando Duran, Dagoberto Santofimio Sierra (Hernando Moncaleno Perdomoteaching hospital), Claudia Pilar Botero, Inés Elena Montoya (Clínica la Presentación de Manizales) and Carlos Alquichire, Giovanni Peña (Clínica Jorge Piñeros Corpas - SaludCoop). This research was possible thanks to financial support by COLCIENCIAS (grant 110134319310) and the Universidad Nacional de Colombia'sResearch Division, Bogota.

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