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Acinetobacter Baumannii Antibiotic Multiresistance Evolution in Hospital Acquired Infections, Clinical Data from a Six Year Study in Mexico

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Abstract

Introduction: As T. Dobzhansky said, since "nothing in biology makes sense except in the light of evolution", the increasing diseases and deaths caused by hospital acquired infections by multiresistant germs such as *Acinetobacter baumannii* cannot be understand or fought efficiently without an evolutionary approach.

Methods: A clinical and epidemiological study between 2012 and 2017 was conducted surveying hospital records about patient, time and place information for 2175 cases of hospital acquired infections and culture and antibiograms of each sample.

Results: We found an increased number and tendency of A. baumannii hospital acquired infections, and a widened diversity of those infections types. Also, there was a increased resistance toward several antibiotics.

Conclusions: Acinetobacter baumanni showed an increased importance and diversification in the incidence of hospital acquired infections. This relevance is result of its evolutionary process of genetic variation that enabled it to evade hospital hygiene, to overcome microorganism competitions, to diversify and amplify its virulence, and to develop antibiotic multiresistance.

Keywords: *Acinetobacter baumannii*; Anitibiotic multiresistance; Evolution; Hospital acquired infections

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Introduction

"The post-antibiotic age -when common infections and minor wounds could kill-, far from being an apocalyptic fantasy, is a very realistic possibility in the 21st century" [1,2]. This is a warning from the World Health Organization (WHO) about the huge development of Antibiotic Multiresistance (AMR) from pathogenic germs, mainly bacteria. Facing this complex global public health challenge, there is no standalone strategy that can contain the emergency of the propagation of these infectious agents. Note even increasing the bactericidal duty or widening the drug spectra; paradoxically, its inadequate use is the main cause for AMR. Every antimicrobiotic substance, being unable to exterminate all of the populations, causes the selection of resistant subpopulations. Therefore, the wide use of antibiotics, provoques resistance against them; a natural phenomenon, but "accelerated by the selective pressure exerted by the use and misuse of antibiotics in humans and other animals" [2].

Antibiotic resistance changed and escalated since the industrial production and wide medical use of the first antibiotics, penicillin and sulphonamide, in the 1930 decade. With the arrival of wide spectrum antibiotics in the years of 1950 and 1960, the pathogens were not exterminated, but got stronger against these drugs. In the decades of 1970 and 1980, was decided to make chemical modifications to the original molecules of antibiotics; expecting and increased efficiency, and reducing or avoiding resistance and secondary effects. In the 21st century, just the opposite of what was expected is more evident and the generation of new antibiotics is practically stagnated. Since the beginning of this century, WHO has pointed: "Resistance of infectious agents to their indicated drugs goes almost to 100% and in some cases, the same happens to resistance to the second and third optative drugs" [3]. This obliges to search for alternatives to combat multiresistance.

In the development of microbial resistance, hospitals played a main role; on one hand, in their spaces converge the favorable factors for transmission, colonization, and reproduction of

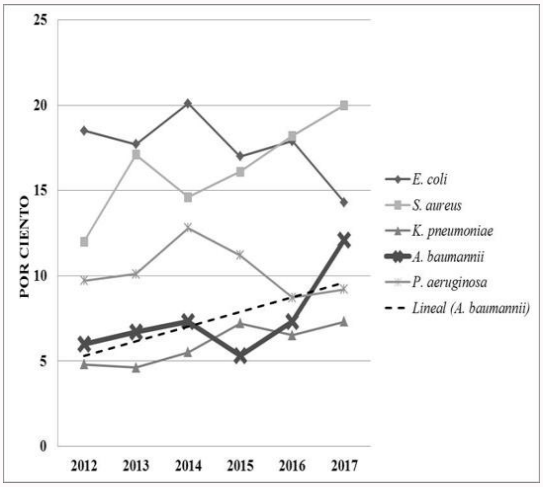

Figure 1: Annual percentages and *A. baumanni* trend of the main etiological agents of nosocomial infection at HGR1 (2012-2017).

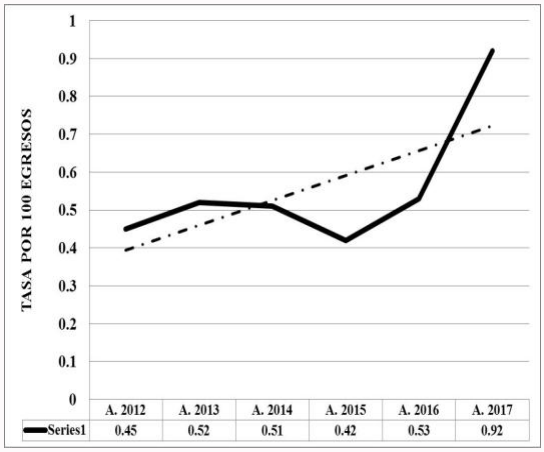

Figure 2: Annual rate and trend of *A. baumanni* nosocomial infections for every 100 hospital releases from HGR1 (2012-2017).

pathogenic germs: the most severe infections, the most susceptible patients, a controlled ambient (temperature, humidity, among other factors), efficient means of direct and crossed transmission by the contact between patients and health staff, and invasive procedures for diagnostics and treatments (punctures, venoclysis, catheters, probes, surgery, etcetera). On the other hand, the methods and substances used for cleaning, asepsia and antisepsia, and antibiotics contribute to combat and reduce microorganisms; but paradoxicaly, help to the selection and development of strong subpopulations resistant to those resources [3].

The historical development of antibiotic resistance cannot be thoroughly comprehended without knowing the biologic evolution of microorganisms. In 1934, there was a discussion about genetic variation by mutation and the hereditary ability of bacteria; "several supported a Lamarckian mechanism of bacteria heredity, while others support a Darwinian vision". By experiments with Escherichia coli in the 1940 decade, it was showed that "natural selection determines the path of evolution by keeping mutations that are beneficial for their carriers, while discarding others that are harmful" [4]. In the 1970s, it was proved that "pathogenic bacteria that were successfully treated with antibiotics, usually develop resistance against those same drugs; meanwhile, other microbes could became pathogens by the acquisition of new abilities". Commenting about it, Richard Dawkins said: "If only every one of us were educated in the Darwinian way of thinking, we were aware early of the dangers of the selection of resistant strains" [5].

As R. Dawkins points out, evolutionary changes happen through spontaneous mutations and environmental adaptation by natural selection, and originate diverse patterns inside and between populations. "Natural selection only subtracts, but mutations could add", their joint actions, in an accumulative manner, build and develop complex beings in two ways: "coadapted genotypes" and "arms race" [6]. The main features of evolution are: genetic variation, species and population divergences between them and their ancestors, and the adaptation to their environment. About bacteria, R. Lenski has described their current evolutionary process through experimental observation [7], and can be summarized as follows:

First, "the adaptation process through natural selection requires the genetic variation of characters that influence survival and reproduction". Genetic variation occurs through spontaneous mutation and genetic mixing (mixis), and both of them depend on the properties of the "genetic system": the whole factors and features about the physiology, biochemistry and reproduction of the organism. On the asexual lineages, such as bacteria, the Muller's ratchet phenomena occur: the accumulation of small DNA changes across generations with probable lethal capacity. Even so, gene mixing could purge the load of harmful mutations.

Evolution implies the insertion and adaptation to an environment (fitness). Genes "are not selected according to their intrinsic qualities, but because of their interactions with the environment… Genes alone do not evolve, just survive or not in their own genetic pool. The whole network evolves in cooperation towards the solution of problems", such as antibiotics [6].

Adaptation to the environment by natural selection is not a lineal process, but periodical, with ups and downs, and an ascendant tendency. This is caused because the frequency of beneficial mutations is discontinuous and disjointed; while some genes are developing, others are delayed.

An "organism it is not specifically determinate by their genes, but is the unique product of an ontogenic process associated with the environment". Four fundamental points must be considered about this relationship: 1) "organisms determine which elements of the external world will constitute their environment"; 2) "organisms alter continuously their environment"; 3) furthermore, "build up the world in their surroundings"; and 4) "external conditions become part of the organism environment" [8].

Lewontin et al noticed the dialectics of the evaluative process: "It is not the genes or the environment alone what determines an organism, but the particular combination of both the organism depends on their surroundings just as much as on their genes all organisms are not only the product, but also the creators of their own environment". That is why, "identical genotypes will evolve in dissimilar ways in different environments, and different genotypes will evolve differently in the same environment [9]".

"Anywhere those antibiotics are used, unavoidably; there will appear resistance [10]". That shows "a fast bacterial adaptation and evolution, implicated in resistance development and an increase in its virulence and transmission". Particularly, "the host susceptibility,

Table 1: *Acinetobacter baumanni* nosocomial infections percentages at HGR1 (2012 and 2017).

NOSOCOMIAL INFECTION	2012	~ 2017 (%)
~ Pneumonia	37.9	40
~ From surgery site	34.5	24
~ Insertion tunnel for central venous catheter	13.8	14
~ Urinary tract	10.3	8
~ *Decubitus* Ulcers	3.5	4
~ Bacteremia	0	8
~ Respiratory tract	0	2

sick or immunocompromised individuals, plays a main role in the emergence of new strains resistant ones because of the selective pressure in the of healthcare field, probably favors the emergency of new multiresistant strains [11]", or "superbugs".

The superbug designation includes "microbes with heavy morbidity and mortality, and high resistance to antibiotics conferred by several mutations… and had acquired higher virulence and enhanced their transmissibility". These multiresistant pathogens had emerged as the main etiological agents in nosocomial infections [12]. In 2014, WHO highlighted "nine bacterial species of international significance" [2]; being the top six those that make up the ESKAPE acronym: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp [13,14].

Current taxonomy groups the Genus Acinetobacter as a Gammaproteobacteria in the Pseudmonadales Order and Moraxellaceae Family. These genus groups' strictly aerobic bacteria, non-fermenting, non-motile, non-sporulating, catalase and oxidase negative Gram-negative coccobacillus [15]. There are 26 Acinetobacter species, from which *A. baumannii*, *A. iwoffi*, *A. haemolyticus*, and *A. calcoaceticus* are of medical relevance [16]. Because of three main reasons, Acinetobacter (Greek for "non motile bacteria") acquired medical relevance worldwide: its growing potential to cause severe nosocomial infections; its development from merely multiresistance to extreme resistance; and its verotoxins production [17].

Antibiotics are substances that disrupt some bacterial vital processes; especially the ones that use enzymes or structures absent or different from those in eukaryotic cells. There are four main targets: cell wall synthesis (beta lactams), protein production (amynoglicosids, tetracyclins, lincosamids...), folates and nucleic acids synthesis (sulfonamides and fluoroquinolones). Those targets and process define the bacterial resistance against them [18,19]. Bacteria resist the antibiotics because of estructural (chormosomal) or acquired (mutation, conjugation or transfer) genetic mechanisms. There are five fundamental mechanisms of bacterial resistance: (1) inactivation by enzymes, (2) modification of targets, (3) changes in membrane permeability, (4) DNA polymerase mutation, and (5) biofilm formation [1,14,20-22].

Methods

At the Hospital General Regional No. 1 (HGR1) of Chihuahua, Mexico, the Epidemiologic Clinical Surveillance Unit develops the active monitoring, detection, register, and analysis of nosocomial infections incidences; and coordinates the institutional program to reduce and prevent these diseases. Based on information gathered by the Surveillance Unit and obtained by the Microbiology Laboratory,

Table 2: Antibiotics resistance percentage of *Acinetobacter baumannii* at HGR1 (2012 and 2017).

Target Synthesis	Antibiotic	2012	2017	Diference
Cell Wall	β Lactam	63.9	87.4	23.5
	~ Penicillins	72.1	75.2	3.1
	~ Cephalosporins	57	91.9	34.9
	~ Carbapenems -	61.8	84	22.2
	Meropenem			
Folates	~ Sulfonamides -	76.4	94	17.6
	Trimetropim/			
	Sulfamethoxazole			
Proteins	~ Tetracyclines	9.1	21.2	12.1
	~ Aminoglycosides	57.2	64.9	7.7
Nucleic Acids	~ Fluorquinolones	78.2	86.9	8.7
Total		61.9	78.8	16.9

we made an observational, longitudinal, and retrospective clinical-epidemiological analysis from 2016 to 2012 and a prospective study during 2017. The database was build collecting date, place, and patient info for every detected case of nosocomial infection, focusing on the cultures and antibiograms results associated with each case. These were performed by properly trained and qualified team of Chemists, Biologists; Parasitologists with years of experience in the use of the equipment VITEK® 2 Compact, an advanced technology system for the microbial identification and its sensibility to antimicrobial, totally automated. Because of technical limitations, identification and classification of the etiological agents was restricted to routine tests; and genomic tests were not performed.

Empirical observations showed the increasing importance of nosocomial infections by *S. aureus*, *A. baumannii*, and *K. pneumoniae*. Since *S. aureus* infections concentrate the research spotlight worldwide [2,10,11,13,14,23], to generate more original data, we decide to focus on Acinetobacter, instead.

We observed *A. baumannii* evolution; through their insertion and colonization in the clinical environment; a population remained a prolonged time (adaptation), outperformed other bacterial species (natural selection), and showed a divergence with the original strains by the development of an increased and diversified morbidity and widened resistance to antibiotics. These observations are direct evidence of an evolutionary process.

Results

From 2012 to 2017, out of 79,480 hospitalized patients at HGR1, 5,989 cases of nosocomial infections were detected; with an incidence annual rate of 4.1 to 8 nosocomial infections and a global 7.5 per 100 hospital releases. Microbiological culture and antibiogram were performed for 2,175 cases (36.3%); founding 52 species as etiological agents; mostly bacteria: 2,016(92.7%); and 159 cases (7.3%) of Candida yeast infections.

Frequency and types of the identified bacterial species fluctuated during the inspected period. In 2012, *Citrobacter koseri* and *Citrobacter fascium* were found once but never again. Something similar occurred with *Vibrio furnissi* in 2013 and with *Providencia rittgeri* in 2015. Burkholderia cepacia was identified once in 2015 and again in 2016. Four cases of Flavimonas oryzihabitans infections were detected, all in 2016. Without previous cases, Chryseomonas luteola

Table 3: *Acinetobacter baumannii* resistance percentages by infection type HGR1-2017.

BLANCO	FAMILIA	TIPO	FARMACO	NEWMONIA	SITO QX	TUNEL CVC	BACTERIEMIA	OTRAS	TOTAL
I~Sintesis de la pared celuar	β Lactamicos	A~Penicilinas	Ampiclina	100	100	100	100	100	100
			Ampiclina/Sulbactam	25	33.3	14.3	25	71.4	32
			Piperacilina/ Tazobactam	100	83.3	71.4	75	85.7	88
			Ticracilina/Ac. Clavulanico	~	~	~	100	100	100
		Subtotal		75	72.2	61.9	75	89.3	75.3
		B~Cefalosporians	Cefazolina	100	100	100	100	100	100
			Cefriaxona	100	91.7	71.4	50	100	90
			Ceftazidime	~	~	~	100	100	1100
			Cefepime	95	91.7	71.4	25	71.4	82
			Cefotaxime	~	~	~	100	100	100
		Subtotal		98.3	94.4	80.9	75	94.3	91.9
		D~Monobactamicos	Aztreonam	100	100	100	100	100	100
	Subtotal			88.1	86.5	75	79.2	92.9	86
	Nitrofurantoina			100	100	100	100	100	100
TOTAL				89.4	88	77.8	80.8	93.4	87.4
II~Sintesi de proteinas	1~Aminoglucosidos		Amikacina	~	~	~	50	85.7	72.7
			Gentamicina	70	66.7	14.3	100	57.1	62
			Tobramicina	70	66.7	42.9	100	57.1	66
	Subtotal			70	66.7	28.6	83.3	66.7	64.9
	2~Tetraciclinas		Tigeciclina	0	0	0	0	0	0
TOTAL				46.7	44.4	19	62.5	50	44.7
III~Sintesis de acido muclieico	Fluorquinolonas	2a generacion	Ciprofloxacina	100	91.7	71.4	75	100	92
			Levofloxacina	~	~	~	100	42.9	63.6
TOTAL				100	91.7	71.4	87.5	71.4	86.9
IV~Biosintesis de folatos	Sulfonamids		Trimetroprima/ Sulfametoxazol	100	91.7	71.4	100	100	94
GRAN TOTAL				81.8	79.2	64.3	78.7	82.9	78.8

appeared in 2016 and 2017. Only until 2017, four emergent bacteria were detected for the first time: *Serratia* plymuthica (pneumonia), *Kocuria* rhizophila (peritonitis), *Alcaligenes xylosoxidans* (Achromobacter xylosoxidans) and *Aeromonas veronii* biovar sobria (both from surgery wounds). *Acinetobacter iwoffi* was found up to four cases yearly and caused a brief epidemic broke out in the ICU in 2016; but there were not cases at 2015 and only one case in 2017. The rest of the bacterial species appeared every year, although with a changing frequency and etiology.

Regarding to the ESKAPE group, our Hospital had different data than other sources. *Escherichia coli* continues to be a main infective agent and *Enterobacter* cloacae (2% and 11th place in 2017) and, even more, *Enterococcus faecium* (0.2% and 23rd place) are less unfrequented; being a bigger concern about nosocomial infections *Enterococcus faecalis* (3.9% and 7th place) and *Staphylococcus epidermidis* (3.7% and 8th place).

The top 5 germens identified (57.2% of the positive cultures from 2012 to 2017) were *E. coli*, which prevailed in the first place from 2012 to 2015 (18.1%); being surpassed by *S. aureus* in 2016 and 2017 to the first place and 20%. *P. aeruginosa* was the third most frequent pathogen until 2016, to fall down to the 4th place and 9.2% in 2017. Except in 2015, *Acinetobacter baumannii* was more frequent than surpassed K. pneumoniae and occupied the third place, overtaken even *P. aeruginosa* in 2017 (Figure 1).

Acinetobacter baumannii kept an increasing tendency in the period of the study, with the successive percentages from positive cultures: 6.5%, 7.4%, 7.9%, 5.7%, 7.9%, and 13.7%. From 2012 to 2017, the percentage increased 2.1 fold. In addition to an increased detection, *A. baumannii* showed a two-fold increase in the infection rate from 2012 to 2017: 0.45 to 0.92 nosocomial infections per 100 hospital releases (Figure 2). To measure the correlation between detection frequency and its impact in the annual rates of nosocomial infections, we calculated the r Pearson value, obtaining a result of 0.995, showing a positive correlation.

The types of nosocomial infections caused by *A. baumannii* are shown in Table 1. While keeping its predominance as a cause of pneumonia (59%, associated to mechanical ventilation), and there were not variations in the catheter infections and decubitus ulcers; in 2017, *A. baumannii* diversified its etiology causing bacteremias and respiratory tract infections. There was a relative decrease in the cases of surgery site and urinary tract infections. Noteworthy, besides its independent infections, *A. baumannii* caused nosocomial co-infections with *E. coli* (surgery site and decubitus ulcer), *S. aureus* (insertion tunnel for venous central catheter), and Enterobacter cloacae (surgery site). *Acinetobacter baumannii* general resistance to 20 antibiotics was of 61.9% in 2012, it increased to 72.5% in 2015

and went up to 78.8% in 2017. Therefore, it increased 16.9% in the six years of the analysis (Table 2). For *A. baumannii*, all individual antibiotic resistances increased from 2012 to 2017. With the exception of tetracyclines, since 2012 *A. baumannii* showed high resistances to antibiotics. The increase was higher in resistance to antibiotics that target cell wall synthesis (β lactams); followed by folate and protein synthesis inhibitors; and in lesser amount, nucleic acid synthesis inhibitors. The increase in resistance was higher for Cefalosporins and Meropenem (+34.9 and +22.9% of β lactams resistances); and medium for Trimetroprim-Sulfamethoxazole (+17.6%) and Tetracyclins (+12.1%). Increased resistances for Fluoroquinolones, Aminoglycosides and Penicillins were of +8.7%, +7.7%, and +3.1%, respectively. With lesser resistance, were surgical site infections (79.2%), bacteremia (78.7%), and central venous catheter infections (64.3%).

In relation to the metabolic targets, *A. baumannii* showed high resistance to the folate synthesis inhibitor Trimetroprim-Sulfamethoxazole (94%). Resistance to cell wall synthesis inhibitors was 87.4% (reaching 100% for Nitrofurantoin); and 86.9% resistance for Fluoroquinolones, nucleic acid synthesis inhibitors. The lesser resistance (44.7%) was registered for proteic synthesis inhibitors; mainly caused by *A. baumannii* susceptibility to Tigecycline.

Grouping the antibiotics in their families (Table 3), *A. baumani* was slightly more resistant to second generation Fluoroquinolones (86.9%) than to a β lactams (86%); due to its power against Ciprofloxacin (92%), and notwhithstanding its 100% resistance to Ampicillin, Ticarcillin/Clavulanic Acid, Cefazolin, Cefotaxime, Imipenem, and Aztreoman; 90% Ceftriaxone resistance, and 88% resistance to Piperacillin/Tazobactam; but lesser resistance towards Meropenem (84%), Cefepime (82%) and Ampicillin/Sulbactam (32%). *Acinetobacter baumannii* resistance was moderated against Aminoglycosides (64.9%), 72.7% to Amikacin and 62% to Gentamicin. Only for Tigecycline, sensibility was 100%, but only until February 2017, when the first cases of intermediate resistance occurred in pneumonia and central venous catheter tunnel infections. Even so, there was not a single register of complete Tigecycline resistance in the period studied in this project.

Discussion

In accordance with the global trend, recently, *A. baumannii* increased its relevance in the morbidity and mortality at the HGR1 [24,25]. As in other clinics, detection frequency of *A. baumanni* in hospital acquired infection has increased; particularly in diagnostic and therapeutic invasive procedures [26]. In addition to the pathogenic increase, *Acinetobacter* antibiotic multiresistance has also expanded [27-29].

Acinetobacter baumannii persistence in the clinical environment is an evidence of its adaptation. Developing abilities to colonize a biotic surfaces and humans; and to prevail in competition with other organisms, *A. baumannii* achieved its permanence. Our result (Figure 1) shows that at HGR1, *A. baumannii* surpassed *P. aeruginosa* and *K. pneumoniae* relative frequencies, even rivaling *S. aureus* and *E.coli*.

Similar to hospitals in other regions [27,29], *A. baumannii* frequency and diversity shows a marked ascending tendency, even if with fluctuations; i. e. the brief decline in 2015, and then increasing in 2016 and 2017 (Figure 2). During the studied period, *A. baumannii* both detection percentage in cultures and incidence in hospital acquired infections increased two-fold. According to R. Lenski [7], it is possible that constant increases are interrupted by sudden declines in mutation frequencies. In a previous work conducted in Spain [27], *A. baumannii* infections presented similar oscillations than those at HGR1: ICU infections were of 5.2% in 2004, 8.9% in 2007 and 5.5% in 2008. In pneumonia with mechanical ventilation, *A. baumanni* infections were 7.5% (2004), 12.8% (2006) and 9% (2008). In central venous catheter associate bacteremia, percentages were of 4.1% (2004), 6.9% and 2.5% (2008).

A wide array of infections caused by *A. baumannii* has been reported [15,27,29]: pneumonia, bacteremia, traumatic and surgery wounds, urinary tract infections, peritonitis, endocarditis, meningitis, conjunctivitis and keratitis. Predisposing conditions for those infections include immunocompromised elder patients, malignant diseases, trauma, intravascular lines, long term antibiotics intake, post-surgery processes, urinary catheters, kidney transplants, thoracentesis, parenteral nutrition, and extended hospitalizations [17]. In our study, pneumonia was the most frequent infection, also (Table 1). Pneumonia was remarkably linked (59%) to mechanic ventilation; which is the leading risk for bacteremia [17]. Even as we found diverse *A. baumannii* infections in our hospital, not all of the possible infections reported in previous works have appeared yet.

Of all the natural selection factors that favor *A. baumannii* evolutionary adaptation of to the hospital environment, probably the most important is the development of antibiotic multiresistance. We found *A. baumanni* strains with a wide array to neutralize antibiotics attacks to folate, cell wall, nucleic acids, proteins and synthesis. Even if a current resistance to aminoglycosides and tigecycline is low and mild, there is the possibility of a future increase.

Differences in resistance percentages according to the infection type; being 64.3% in cases of central venous catheter and 82.9% to others (urinary infections, decubitus ulcers, and respiratory infections all together); could be related to differences in the *A. baumannii* strains (deduced by variations in sensibility and resistance patterns), pharmacokinetics, and pharmacodynamics or the combination of the three factors.

It will be important to define the genetic and genomic mechanisms of *A. baumannii* increasing multiresistance. This could be done by the analysis of inactivating enzymes, outer membrane proteins, efflux pumps, and DNA replication enzymes. In addition to resistance proteins, it will be valuable to analyze *A. baumannii* biofilm formation, which requires the bfmS gene [30].

Conclusion

Hospital acquired infections represent a complex socio-biologic process happening in the ecological niche of a social institution with areas and medical and assistance services (emergency, internal medicine, surgery, gynecology, pediatrics, intensive care, and so on) operating by a managed organization with systematical norms and hierarchy.

This study shows the significance of an evolutionary approach to the analysis of nosocomial infections, in order to comprehend them and to define proper strategies to attack them and cause their decrease. This approach requires to comprehend the intrinsic contradictions of the dynamic and developing process by an objective analysis (based on scientific evidence), encompassing it as a whole (as a socio-biological entity). Analysis of hospital acquired infections by *A. baumannii* at HGR1, from 2012 to 2017, shows that the reached relevance that this

pathogen is due to its efficient evolutionary process; adapting to this environment, evading the resources and activities of nosocomial

hygiene, overcoming the competition with other microorganisms, diversifying and increasing its virulence and pathogenicity, helped by the development of antibiotic multiresistance. All these events were possible by process of genetic variations. As in other cases, the increasing role in hospital acquired infections is related to an increase in the mutation rate (hipermutability), the lateral gene transfer, and compensatory evolution of the bacterial population [31].

The Centers for Disease Control and Prevention (CDC), and other American institution declared: Eradication of Carbapenem resistant *A. baumannii* strains in a hospital requires multiple, progressive and intense interventions during several years. General recommendations for control and prevention of antibiotic multiresistant microorganisms at hospitals include: management measures and supervision, education, rational use of antibiotics, epidemiologic surveillance, and standard precautions to prevent transmission, environmental measures, and decolonization [25,26].

About the specific antibiotic therapy against *A. baumannii*, in 2017 WHO recommended: Tetracyclines, Aminoglycosides, Carbapenems, and Polymixins; and perform sensitivity test for: Tigecycline or Minocycline, Gentamicin, Amikacin, Imipenem, Meropenem or Doripenem, and Colistin [32]. Even so, in our study, high sensitivity was found only towards Tigecycline; and there was a high resistance (between a global 64.9% and 86.9%) to the rest of the antibiotics. However, there are reports of several Tigecycline secondary reactions, even death [33-35].

Since gene encryption to antibiotic resistance was found, periodic cycling of antibiotics was proposed, in order to vary and reduce selective pressures and development of resistances. However, this rotation is not a long term solution, because resistant strains do not disappear from the population and when the antibiotics are reinserted, the strains are reselected rapidly [12].

A successful combat to nosocomial antibiotic resistance requires a multidisciplinary approach, clinical and epidemiological, institutional and management levels, including preventive policies, plans, and programs (environment and hand hygiene, use of barrier measures, adequate asepsis and antisepsis in every procedure, isolation, etcetera). These measures should be monitored, evaluated and have periodical feedback. It is required constant surveillance and methodical and systematic research for every detected case and is needed a comprehensive therapeutic, not limited to antibiotic drugs. Moreover, use of antibiotics should be regulated, supervised, and evaluated with periodical feedback, accordingly to its expected efficiency in each patient [36].

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