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(RESEARCH ARTICLE)



Acinetobacter baumannii as a causative agent of health care associated infections

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Abstract

Acinetobacter baumannii is an opportunistic pathogen that seriously affects sick patients, causing Health Care Associated Infections (HCAI) such as pneumonia associated with mechanical ventilation, urinary tract infections and bacteremia, in recent years this bacterium has become a health problem worldwide, its isolation from infections present in hospitalized patients has been increasing, and it also has various mechanisms of resistance to antibiotics. The present documentary research aims to describe the mechanisms of pathogenicity and resistance to antibiotics used by *Acinetobacter baumannii* as a causal agent of HCAI. To carry out this work, a literature search was carried out in databases such as: Scielo, PubMed, NCBI, and Elsevier. The pathogenicity mechanisms that allow it to colonize and develop infections in hospitalized patients are: porins, biofilms, pili, lipopolysaccharides, phospholipases, outer membrane vesicles and the production of siderophores. It has enzymatic resistance mechanisms such as beta-lactamases and non-enzymatic mechanisms such as porin modification, efflux pumps, and modifications in DNA gyrase. There are extrinsic factors that favor the development of HCAI, such as the immunological and health condition of the patient, as well as the association with medical equipment. Studies carried out between the years 2005 to 2018 reveal that *A. baumannii* is one of the main causative agents of pneumonia associated with mechanical ventilation in patients admitted to the Intensive care unit.

Keywords: *Acinetobacter baumannii*; Health Care Associated Infections

1. Introduction

Acinetobacter baumannii is an opportunistic pathogen that affects severely ill patients [1]. It is widely distributed in nature, almost 100% of the samples from soil and water develop this bacterium, so any humid hospital environment can serve as an environmental reservoir [2]. Currently *A. baumannii* belongs to the group of non-fermenting bacilli, with Gram staining, this bacterium is observed in the form of cocci or coccobacilli, it is gram-negative, oxidase negative, strictly aerobic and immobile, in addition, it is one of the most frequent bacteria isolated in clinical laboratories and is characterized by resistance to penicillin [3].

The antibiotic resistance is the ability of some bacteria to survive in the presence of said antibiotic at different concentrations [4]. It is important to mention that antibiotics are one of the main therapeutic tools that the health sector has to face infectious diseases [5]. Likewise, the pathogenicity mechanisms that this bacterium possesses to be one of the main causes of Infections Associated with Health Care HCAI, formerly called nosocomial or hospital infections, are addressed, the World Health Organization (WHO) defines HCAI as "infections contracted by a patient during their

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treatment in a hospital or other health center and that said patient did not have, nor was it incubating at the time of admission” [6].

In recent years, *A. baumannii* has become a major health problem worldwide; It is attributed as the cause of various infections such as; bacteremia, urinary tract infections, but above all as a cause of nosocomial pneumonia, especially those associated with mechanical ventilation in patients admitted to the Intensive Care Unit (ICU) [7], being responsible for 2% to 10% of hospital infections caused by gram-negative bacteria [8].

The fact that this bacterium is one of the most frequent causes of outbreaks of hospital infections is due to that it has an enormous capacity for adherence and survival on surfaces such as biomedical equipment, personal protective equipment, curtains, ventilation ducts, and even in the mobile devices of healthcare workers, in addition to being resistant to most intermediate-grade disinfectants [9]. One of the things that stands out the most about *A. baumannii* is its ability to accumulate various resistance mechanisms [10]. Because *A. baumannii* is the causative agent of 10% of all infections in hospital patients (2016), this in relation to other gram-negative bacteria that cause them, in addition to being a bacterium with a considerable mortality rate in patients immunosuppressed, we consider it important to carry out a documentary research, which allows us to recognize the pathogenicity mechanisms used by *A. baumannii* to cause infections associated with health care, the extrinsic factors that favor their development, as well as to identify the mechanisms of resistance to antibiotics possessed by this bacterium in the treatment of the disease.

2. Material and methods

The present work is a descriptive documentary investigation, for which a literature search related to the bacterium *Acinetobacter baumannii* was carried out, the collection of information was obtained from four bibliographic databases, Scielo, PubMed, NCBI and Elsevier. In this search, articles published between the years 2000 to 2020, in English and Spanish, were selected, using keywords such as: "*Acinetobacter*, resistance, pathogenicity", the website of the World Health Organization was also consulted, an article published in the UNAM Digital University Magazine, an annual report issued by the Secretary of Health through the General Directorate of Epidemiology in Mexico and an electronic book "Koneman's Color Atlas and Textbook of Diagnostic Microbiology".

3. Results and discussion

Pathogenicity is the ability of an infectious agent to colonize and cause infection in a host [11]. *Acinetobacter baumannii* has pathogenicity mechanisms which give it the ability to colonize humans and subsequently develop infections. Currently *A. baumannii* is one of the pathogens mostly isolated from hospitalized patients and medical staff, being one of the main causes of HCAI [12]. Table 1 shows the pathogenicity mechanisms of *A. baumannii*.

Acinetobacter baumannii has become a clinically important pathogen worldwide due to its great capacity to develop antimicrobial resistance [13]. The mechanisms used by this bacterium can be enzymatic mechanisms, such as the action of beta-lactamases and non-enzymatic mechanisms such as the loss of porins, and overexpression of expulsion pumps (Figure 1) [9]. The enzymatic mechanisms are presented in Table 2 and the non-enzymatic ones in Table 3.

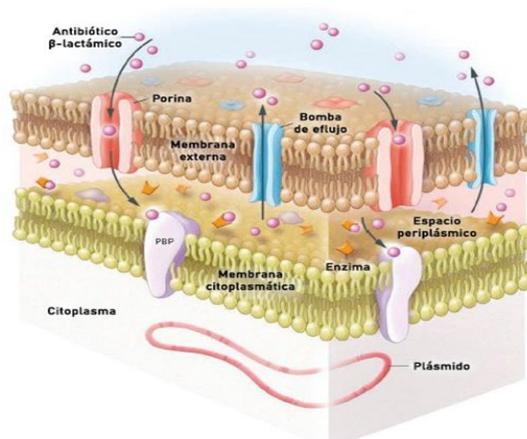


Figure 1 Mechanisms of resistance of *A. baumannii* [10]

Table 1 Pathogenicity mechanisms of *A. baumannii*

Mechanism	Function
Porins (OmpA)	It is the most abundant membrane protein of <i>A. baumannii</i> , it is known to bind to the epithelial cells and mitochondria of the host, causing edema, mitochondrial dysfunction and finally apoptosis of the cell; it also participates in the evasion of the complement system and in the formation of biofilms.
Biofilms	Populations of <i>A. baumannii</i> that are in skin and soft tissue infections form robust biofilms within the wound, as well as are capable of forming biofilms on abiotic surfaces in equipment associated with health care, which contributes to the development of infections associated with health care. These biofilms give protection to the bacteria.
Pili	They mediate the interaction between the bacteria and its environment. Most strains of <i>A. baumannii</i> encode and produce a pili system called Csu / pili, which are crucial for the formation and maintenance of biofilms on abiotic surfaces.
Lipopolysaccharide (LPS)	It is an immunostimulatory molecule that is important in bacterial resistance to external stress and human serum, it also allows adhesion to human epithelial cells.
Phospholipases	<i>Acinetobacter baumannii</i> possesses phospholipases C and D which allow the lysis of human cells by cleaving the phospholipids present in the cell membrane.
Outer membrane vesicles (OMV)	Allowing pathogens to interact with the host without close contact between the bacteria and the host, <i>A. baumannii</i> OMVs contain LPS, OmpA, proteases, and phospholipases.
Siderophores	Some strains produce siderophores because they synthesize outer membrane proteins that are dependent on iron, which allow it to live inside the human body.

[13, 8, 12, 14, 15, 16]

Table 2 Enzyme resistance mechanisms of *A. baumannii*

Enzymes	Function
Betalactamases	The mechanism of action of these enzymes consists of the breakdown of the amide bridge of the beta-lactam ring, which prevents these antibiotics from being able to bind to penicillin-binding proteins (PBPs) and thus allow the formation of the bacterial wall to continue. Through this mechanism, acid derivatives are produced which do not have bactericidal properties.
Class A betalactamases Broad spectrum (TEM-1, TEM-2, CARB-5) Spread spectrum (ESBL) VEB-1, PER-1, TEM-92	Resistance to penicillins.
Class B betalactamases • Metallo-beta-lactamases (MBL)	Resistance to carbapenems.
Class D betalactamases OXA type carbapenemases (OXA-23, OXA-24, OXA-40, OXA-51, OXA-58 and OXA-143)	Resistance to carbapenems.
Cephalosporinase • AmpC (ADC)	When ADC is expressed at a low level it confers resistance to penicillin. When ADC is expressed at a high level it provides resistance to cephalothin, piperacillin, cefotaxime, ceftazidime and aztreonam.
Inactivating enzymes such as: APH (3'5') I, AAD and APH (3') VI	Resistance to aminoglycosides.

[17, 9, 18, 13, 19]

Table 3 Non-enzymatic resistance mechanisms of *A. baumannii*

Mechanism	Function
Changes in outer membrane proteins. • Loss of porin CarO • Alteration of porin OmpA	Loss of porin CarO is associated with resistance to imipenem and meropenem. Because carbapenems use these channels to reach their target site, <i>A. baumannii</i> strains decrease the permeability of the antibiotic in the outer membrane through mutations that cause deficiencies in porins, either generating a decreased expression of porins or non-functional porins. Alteration of the ompA gene significantly lowers the minimal inhibitory concentrations (MICs) of several antibiotics such as chloramphenicol, aztreonam, and nalidixic acid.
Efflux pumps	Efflux pumps are a class of transporters that are involved in the uptake of essential nutrients and ions, as well as in the excretion of toxic substances and in communication between cells and the environment.
MFS superfamily pumps (major facilitator superfamily) 1. Tet (A) 2. Tet (B) 3. cmlA	They exert their function from the proton-motive force, the Tet (A) and Tet (B) systems expel tetracyclines by exchanging a proton for a tetracycline-Mg ⁺² complex. 1. Tetracycline resistance. 2. Resistance to tetracycline and minocycline. 3. Resistance to chloramphenicol.
MATE family pumps (multidrug and toxic compound extrusion) 1. AddeM	To exercise their function they use an electrochemical gradient provided by Na ⁺ or H ⁺ ions. 1. Resistance to norfloxacin, ofloxacin, ciprofloxacin, gentamicin, among others.
RND family pumps (resistance-nodulation-cell division). Of two types: 1. AdeABC 2. AdeIJK	They exert their function from the proton-motive force. 1. Resistance to tetracycline, erythromycin, chloramphenicol, cefotaxime, gentamicin, kanamycin, and tigecycline. 2. Resistance to beta-lactams, chloramphenicol, tetracycline, erythromycin and to a lesser degree to fluoroquinolones.
Mutations in DNA gyrase	Resistance to fluoroquinolones is also mediated by mutations in the <i>gyrA</i> gene and the <i>parC</i> gene, the combination of both mutations is reflected in the resistance that <i>A. baumannii</i> presents to these antibiotics.

[20, 15, 13, 21, 19]

3.1. Extrinsic factors that favor the development of HCAI

There are extrinsic factors that favor the development of HCAI caused by *A. baumannii*, studies reveal that people infected by this bacterium are commonly patients with prolonged hospitalization and those with great immunosuppression. These infections usually occur in debilitated patients, the majority are patients admitted to the ICU, as well as those who need mechanical ventilation, these being the highest risk groups. Other factors related to colonization and infection are patients with recent surgeries, vascular catheterization, tracheostomy, enteral feeding, and those receiving antimicrobial therapy with third-generation cephalosporins, fluoroquinolones, and carbapenems [22, 23].

Due to the fact that *A. baumannii* has been shown to be one of the pathogens that causes HCAI, mostly isolated together with other gram-negative bacteria, in the last 20 years there have been studies that seek to demonstrate the frequency with which this bacterium occurs in hospitalized patients. In Chile, between 2000 and 2003, a study was carried out by the national epidemiological surveillance system of the Ministry of Health (MINSAL), which indicated that *A. baumannii* was the leading cause of pneumonia associated with mechanical ventilators in adults, with 38.2% of the total also mentioned that it represented the third etiology in bloodstream infections in adults with 8.7% and the seventh cause in urinary tract infection (UTI) associated with a urinary catheter with 4.4% as can be seen in table 4 [24].

Table 4 Relevance of *A. baumannii* as a causal agent of various hospital infections in the years 2000-2003.

Type of IHH * with known agent	Year of surveillance							
	2000		2001		2002		2003	
	N	%	n	%	n	%	n	%
Ventilator-associated pneumonia in adults	182	36.2	213	38.8	77	27.2	248	38.2
CVC ** associated bloodstream infection in adults	57	19.1	29	17.1	14	9.7	20	8.7
Urinary tract infection associated with urinary catheter	63	6.6	90	10.6	64	7.6	56	4.4

n = number of patients with *A. baumannii* as the etiologic agent. * IHH = nosocomial infections. ** CVC = central venous catheter [24].

In 2017, the Secretary of Health [25] presented a report made in Mexico through the Red Hospitalaria de Vigilancia Epidemiológica (RHOVE), which is in charge of the epidemiological surveillance of HCAI in Mexico, this report showed that from 2009 to 2015 *Acinetobacter baumannii* together with bacteria such as *Escherichia coli* and *Klebsiella pneumoniae* showed an upward trend as etiological agents of HCAI, in that year *A. baumannii* occupied 6.6% of the total etiological agents of HCAI, it was also one of the microorganisms with the highest frequency in the Intensive Care Units for Adults. Table 5 shows the resistance profile of *A. baumannii* and the rest of the isolated gram-negative bacteria.

Table 5 Resistance profile of gram-negatives isolated from RHOVE units.

Antimicrobial		Species					
		<i>E. coli</i> N=5,561	<i>K. pneumoniae</i> N=2,813	<i>E. cloacae</i> N=944	<i>A. baumannii</i> N=1,923	<i>P. aeruginosa</i> N=3,673	<i>S. marcescens</i> N=321
Ampicillin	n	2,092	1,299	167	576	862	55
	%	37.6	46.9	17.7	30.0	23.5	17.1
Amikacin	n	335	193	120	466	848	27
	%	6.0	6.9	12.7	24.2	23.1	8.4
Amp-Sulb*	n	1,162	636	136	191	502	55
	%	20.9	22.6	14.4	9.9	13.7	17.1
Piper-Tazob**	n	213	116	103	95	240	7
	%	3.8	4.1	10.9	4.9	6.5	2.2
Cefuroxime	n	339	169	53	40	86	22
	%	6.1	6.0	5.6	2.1	2.3	6.9
Cefepime	n	1,694	829	151	593	633	36
	%	30.5	29.5	16.0	30.8	17.2	11.2
Ceftazidime	n	540	240	120	268	423	21
	%	9.7	8.5	12.7	13.9	11.5	6.5
Ceftriaxone	n	1,712	857	250	729	1,406	38
	%	30.8	30.5	26.5	37.9	38.3	11.8
Cefotaxime	n	623	252	107	172	341	16
	%	11.2	9.0	11.3	8.9	9.3	5.0
Ertapenem	n	35	23	24	***U	***U	3
	%	0.6	0.8	2.5	***U	***U	0.9
Imipenem	n	85	41	17	162	387	5
	%	1.5	1.5	1.8	8.4	10.5	1.6
Meropenem	n	95	105	66	172	558	13
	%	1.7	3.7	7.0	8.9	15.2	4.0
Ciprofloxacin	n	1,895	521	132	689	667	27
	%	34.1	18.5	14.0	35.8	18.2	8.4

N = Number of isolates of that species. n = Number of strains resistant to that antimicrobial. *Ampicillin sulbactam. ** Piperacillin-tazobactam. ***Undetermined [25]

In 2017, according to an integrative review carried out by Oliveira, Marques and Prado [26], which aimed to analyze scientific evidence related to HCAI in Neonatal Intensive Care Units (NICU), 36 publications were analyzed that included since the 2000s to 2015, where 20% of the publications mentioned *Acinetobacter baumannii* as the cause of neonatal sepsis. This documentary research mentions that *A. baumannii* occupies 6.7% as the causal agent of HCAI.

For the year 2018 Gómez, Buena and Vega [27] carried out a study in which the description of 1544 isolates of microorganisms from clinical samples of patients admitted to the Adult Intensive Care Unit (AICU), Medical Clinic, Pediatric Intensive Care Unit (PICU), Neonatology and pediatric wards of the National Hospital of Itauguá, Paraguay. The results of this study revealed that for samples of respiratory origin in the Medical Clinic room, out of a total of 185 isolates, in the first place, *A. baumannii* was obtained with 16%, these isolates presented 97% resistance to carbapenems. With respect to the Adult Intensive Care Unit, of 171 isolates, *A. baumannii* microorganisms occupies the first place with 30%. As can be seen in figure 2, this is the most isolated microorganism in samples of respiratory origin. The resistance profile of the same was also carried out, which is represented in table 6. And regarding the frequency of microorganisms isolated in urine samples from AICU, *A. baumannii* ranked third with 14%, only below *Klebsiella pneumoniae* with 18%, and *Escherichia coli* with 15%.

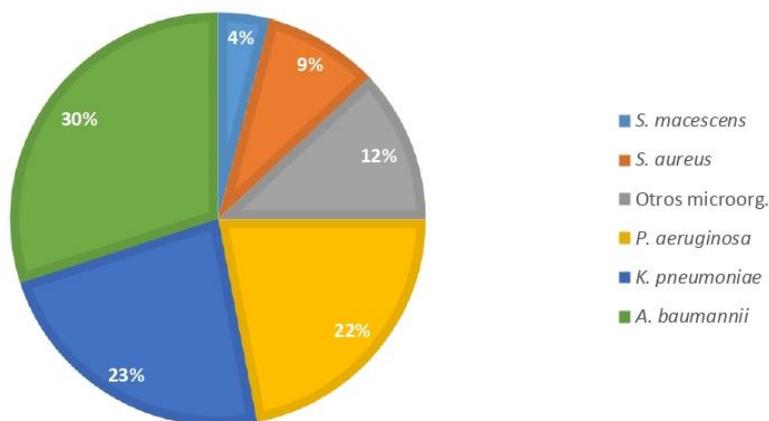


Figure 2 Percentage of isolated microorganisms from samples of respiratory origin [27]

Table 6 Resistance profile of *A. baumannii* strains from samples of respiratory origin [27]

Antibiotic	Resistance percentage
Ampicillin /sulbactam	90%
Piperacillin / Tazobactam	96%
Ceftazidime	87%
Imipenem	96%
Meropenem	96%
Cotrimoxazole	94%
Ciprofloxacin	96%
Gentamicin	48%
Tigecycline	0%
Colistin	0%

In 2018 Ortega *et al* [28] conducted a study that included 30 patients with a diagnosis of severe sepsis (SS) admitted to the ICU of the Pedro Kourí Tropical Medicine Institute hospital, the results showed that more than 60% of the cases revealed infections by gram-negative pathogens, where the most frequent microorganisms were *Pseudomonas aeruginosa* (34.8%), *Acinetobacter baumannii* (26.1%) and *Staphylococcus aureus* (13.1%), in addition the sensitivity of the microorganisms to the different antimicrobials showed an increase in resistance to carbapenems and colistin.

4. Conclusion

Acinetobacter baumannii is commonly the causative agent of pneumonia, urinary tract infections, and is frequently isolated in patients admitted to the Intensive Care Unit. Its pathogenicity mechanisms are porins, biofilms, pili, lipopolysaccharides, phospholipases, outer membrane vesicles and siderophores. These mechanisms together with extrinsic factors such as the immunological and health condition of the patient, and the association with a medical team favor the development of HCAI by *A. baumannii*. The antibiotic resistance mechanisms employed by *A. baumannii* can be enzymatic, such as the action of beta-lactamases, and non-enzymatic mechanisms, such as the modification of porins, the presence of efflux pumps, and mutations in DNA gyrase.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that they have no conflicts of interest.

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