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Réf : .....

Dissertation

To obtain the diploma

Master's degree

Characterization of the resistance mechanisms of Acinetobacter baumannii isolated at the CHU of ORAN

Presented by :
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In front of a jury composed of :

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Dedicace

I dedicate this work to my very dear parents that they find here

All my gratitude for their support throughout my studies

There are no words to describe how much my parent has meant to me all my life.

They have given me so much, thanks for your faith in me,

My lovely sisters Narimene , Maissa and Lydia

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For those which gave me everything without anything in return

And finally all those who contributed to the realization of this work

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With the help of Almighty God, I was able to produce this work, which I dedicate to you:

To my very dear Father, I would like to pay tribute to you on this memorable day for me,dear Dad,Iwould have liked you to be there but Iknow that you are proud of me where you are,and your love I will carry forever, I owe you my humble and profound thanks for all your sacrifices,

May God welcome you in to his vast paradise,Daddy dearest...

To my dearest Mother, So many sentences and expressions cannot express my gratitude and appreciation. You are my source of willpower, dear Mum, I owe you my deepest thanks for the sense of perseverance you taught me throughout my studies, your sacrifice, your advice and your encouragement, may God keep you in very good health for me.

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Sommary

AmK: Amikacine.

CA-SFM : Comité de l'Antibiogramme de la Société Française de Microbiologie

CAZ : Cetazidime

CIP:Ciprofloxacine

CS : Colistine

CHDLs:Carbapenem-hydrolyzingclassDbeta-lactamases

CSF: Cerebrospinalfluid

Dox :Doxycycline

ESBL:Extended-spectrumβ-lactamase

GeN: Gentiamicine

***gyr*A**:DNAgyrase gene

IMP: Imipeneme

IMA:MedicineInterneA

IPD:InfectionsandParasiticDiseases

Lvx: Levofloxacine

LPS: Lipopolysaccharide

mat:Maternity

MDR:Multidrugresistanc

NDM:NewDelhimetallo-β-lactamase

NFC:Nouarfadelaclinic

OXA : Oxacilline / oxacillinase .

OMPA:Outer Membrane Proteins

OMA : Outer membrane

PIP:Piperacilline

***par*C**:GenecodingfortheCsubunitoftopoisomeraseIV

PIP: Pipéracilline

Pp:Pneumologyandphthisology

Pavillon 5 : Gastroentrology

Pavillon 7 : Dermatology

PBPs:Penicillin-bindingproteins

QRDR:Quinoloneresistance-determiningregion

SIM: Seoul Imipenemase

SXT:Triméthoprimesulfametoxazole

Sca:surgicalclinicsA

TCC:Ticarcilline+clavulanic acid

TIC:Ticarcilline

TOB: Tobramycine

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Introduction

Introduction

The origin of the term "antibiotic" can be traced back to the word "antibiose" first used by Paul Vuillemin in 1890 in his publication as an antonym to "symbiose" to describe the antagonistic action between different microorganisms. It was not until 1928 that penicillin was discovered, and subsequently, several classes of antibiotics were developed with mechanisms of action that include inhibition of cell wall synthesis, depolarization of the cell membrane, inhibition of protein synthesis, inhibition of nucleic acid synthesis, and inhibition of metabolic pathways in bacteria. The discovery of antibiotics revolutionized modern medicine until the 1950s, after which resistant strains started to emerge **(Kyriacos C Nicolaou and Stephan Rigol,2017 ; Wanda C Reygaert, 2018 ; Matt Hutchings 1 and *al* ., 2019)**.

Antimicrobial resistance mechanisms fall into four main categories: limit in guptake of a drug; modifying a drug target; inactivating a drug; active drug efflux. Intrinsic resistance may make use of limiting uptake, drug inactivation, and drug efflux; acquired resistance mechanisms used may be drug target modification, drug inactivation, and drug efflux., (**Mahon CR, Lehman DC, Manuselis G, 2014**).

The emergence and spreate of this bacteria resistance caused by many factors include: increased consumption of antimicrobial drugs, both by humans and animals; and improper prescribing of antimicrobial therapy **(Wanda C Reygaert, 2018)**.

The ESKAPE pathogen group has gained clinical importance due to their high and increasing resistance, as well as their ability to evade antibiotic treatment and exhibit novel concepts of transmission, pathogenesis, and resistance, as named by the Infectious Diseases Society of America (IDSA). This group includes *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter* species **(VishvanathTiwari , 2018)**.

Nosocomial infections with *Acinetobacter baumannii* are responsible for an increase in mortality, longer hospital stays and higher hospital costs **(Naijaand *al.*,2009)**, with clinical manifestations such as : ventilator-associated pneumonia, blood stream infections, urinary tract infections and meningitis (**Hing Jian Meaand *al*,.2021).**

In Algeria, numerous studies have focused on the resistance mechanisms of *A.baumannii*. Therefore, our objective was to investigate the prevalence of *A.baumannii* infections at the Oran University Hospital (CHU d' Oran) and determine the antibiotic resistance profiles of its strains.

Bibliography

Currently, the genus *Acinetobacter* comprises 74 species (**Jeong Ho Jeon and *al.*,2022).** The history of the *Acinetobacter* genus dates back to the beginning of the 20th century when a Dutch bacteriologist in 1911 described an organism called *Micrococcus calcoaceticus*, which was isolated for the first time on a minimal medium enriched with calcium acetate (**Dijkshoorn, 2008; Doughari and *al.*, 2011).** During the following decades, similar microorganisms were described and attributed to at least 15 different genera and species. It was only in 1954 that Brisou and Prevot suggested the genus *Acinetobacter* (from the Greek "akinetos"; nonmotile), based on two characteristics: inability to move and non-pigmented **(Brisou and Prevot, 1954; Jung and Park, 2015)**.In 1968, Baumann et *al.* placed all such isolates in one genus, Acinetobacter, which was accepted by the committee on the taxonomy of *Moraxella* and Allied Bacteria four years later. Using DNA/DNA hybridization techniques, *Bouvet and Grimont* succeeded in distinguishing 12 genomic species **(Peleg and *al.*, 2008).** There has been a lot of confusion about the taxonomy of the genus *Acinetobacter*, which is finally taxonomically classifiedas follows: Bacteria; *Proteobacteria; Gammaproteobacteria*; *Pseudomonadales*; *Moraxellaceae*, Genus: *Acinetobacter* **(Jung J, Park W, 2015)**.

Among *Acinetobacter* species, *Acinetobacter baumannii* is the most important member associated with hospital-acquired infections worldwide. It is a short bacilli or coccili, often in diploid or short chain formation , with a cell structure of Gram negative bacteria. For exam microscopic, it is ashort, plump, typically 1.0 to 1.5 µm by 1.5 to 2.5 µminsize(**JungandPark,2015),**catalase positive,oxidase negative,citrate positive ,urease positive, hemolyyse negative, asporulated, many strains are unable to reduce nitrates to nitrites and the optimum temperature is 33–35°C, however , A.*baumannii* has the particularity of being able to grow between 41°C and 44°C (**Fariba and *al* .,2019 ; Doughari and *al*., 2011)**, non motile and non fermenting coccbacilli, DNA G+C contentof 39% to 47% (**Almasaudi, 2018)**.

A.baumannii has emerged as the foremost *nosocomial* pathogen with significant implications for human health, owing to its escalating incidence and the emergence of multidrug-resistant (MDR) strains **(Nowak & Paluchowska, 2016)**. Hospital-acquired infections caused by*A. baumannii* are most commonly encountered in intensive care units, particularly among critically ill patients **(Nowak & Paluchowska, 2016**). The primary

modes of transmission in volve contact with contaminated hospital equipment or direct Exposure to health care personnel who have previously countered the microorganism **(Nowak&Paluchowska, 2016)**.

Acinetobacter baumannii is responsible for a diverse array of nosocomial infections, including hospital-acquired and community-acquired pneumonia, bacteremia, endocarditis, skin and soft tissue infections, surgical site infections, catheter-associated urinary tract infections, and meningitis, among others **(Nowak & Paluchowska, 2016**). In most cases, the acquisition of *A. baumannii* infections is attributed to exposure from persistently contaminated hospital equipment or contact with healthcare workers (**Maragakis and *al.*, 2004 ; Dijkshoorn and *al.*, 2007)**.

A previous comprehensive systematic review and meta-analysis, encompassing numerous studies, identified several risk factors associated with *A.baumannii* infections, including inadequate antimicrobial therapy, prolonged stay in intensive care units, mechanical ventilation, advanced age, comorbidities such as renal failure, malignancies, cancer, AIDS, immunosuppression, and leukemia **(Nimer, 2022)**.

Immunocompromised individuals, especially those with prolonged hospitalization, constitute a high-risk population for acquiring infections caused by this bacterium **(Zhou and *al.*, 2019**). Furthermore, other factors such as therapeutic procedures, endoscopic interventions, prolonged hospital stays, recent surgical interventions, prior exposure to antimicrobial agents, use of central venous catheters, previous hospitalization, nursing homeresidence,andlocalcolonizationpressureonvulnerablepatientshavebeenidentified as significant risk factors for the development of nosocomial *A. baumannii* infections **(Zhou and *al.*, 2019)**.

For a long time, the antibiotic therapy used against *A. baumannii* infections included beta-lactams (penicillins, cephalosporins, carbapenems, monobactams, and beta- lactamase inhibitors) **(Ioannis Kyriakidis.,2021),** aminoglycosides, quinolones and carbepnems.**(Nukaga and *al,* 2003).** The excessive use of broad-spectrum antibiotics such asthird-generation cephalosporins, aminoglycosides exert a selection pressure that plays a very important role in the emergence of multi-resistant strains **(ALLAL Hassiba HADBI**

Manel, 2018) and additonnaly the presence of genes linked to antimicrobial drug resistance was detected in both the core and accessory genomes of the species. Within the accessory genome, antimicrobial resistance genes were identified with in foreign genomic regions referred to as "alien islands," frequently surrounded by integrases, transposases, orinsertionsequences.This observation implies a potential acquisition of these genesthrough horizontal gene transfer, This has led to the emergence of drug-resistant *A. baumannii*strains since 1970s **(kayman Nasr, 2019)**.

A. baumannii exhibits inherent resistance to aminopenicillins, first and second-generation cephalosporins, ertapenem, fosfomycin, trimethoprim, aztreonam, and furans **(CA-SFM, 2013)**. Furthermore, *A. baumannii* naturally produces a chromosomal oxacillinase known as OXA-51 or OXA-69-like **(Nevgun and *al.*,2009)**. Additionally,non-enzymatic resistance mechanisms involving efflux pumps, membrane permeability, and alterations in the sequence of penicillin-binding proteins (PBPs) have been observed. Moreover, various enzymatic mechanisms, including the production of different β-lactamases, have been reported **(Kumar, S and *al.*, 2020).**

The mechanisms of resistance of *A. baumannii* to β-lactams include both enzymatic resistance and non enzymatic resistance **(Kyriakidis Ioannis and *al* ., 2021).**

For enzymatic resistance, it involves the production of class A, B, C and D beta-lactamases The classe A beta-lactamases (penicillinases) that confer resistance topenicillin, cephalosporins, monobactam , and carbapenems. Narrow-spectrum lactamase activity, especially against penicillins, inhibited by clavulanic acid extended-spectrum β- lactamase (ESBL) can hydrolyze extended-spectrum cephalosporins such as ceftazidime, ceftriaxone,cefotaxime,andaztreonam.Thegenesthatconferthisresistanceare: *bla*TEM- 92, *bla*SHV, *bla*GES-11, *bla*GES-14, *bla*PER-1, *bla*PER-7, *bla*VEB-and*bla*-CTX-M. **(Poirel, L. and*al.*, 2007)**.

Class B beta-lactamases, also known as metallo-beta-lactamases (MBLs), possess the ability to hydrolyze all beta-lactam antibiotics, including carbapenems. MBLs differ from carbapenemases due to the presence of a heavy metal ion, typically zinc, in their active site, which participates in the catalytic activityof these enzymes. Theyare classified into three subclasses: B1, B2, and B3. Several types of MBLs have been described, including IMP,

NDM, and SIM **(Cornaglia and*al.*, 2011)**. Class C beta-lactamases, on the other hand, confer resistance to cephamycins, penicillins, cephalosporins, and beta-lactamase inhibitors but are not inhibited by beta- lactamase inhibitors such as clavulanic acid. Acinetobacter baumannii, for example, possesses *Amp*C cephalosporinase (**Jeon and *al.*, 2015**).

ClassDbeta-lactamases(oxacillinases)constituteaheterogeneousgroupcapableof hydrolyzing oxacillin, cloxacillin, and benzylpenicillin. These enzymes are not inhibitedbyclavulanicacid orotherinhibitors **(Poirel, L and *al* ., 2010).** However, certain enzymes within this class have been shown to be susceptible to inhibition by clavulanic acid, sulbactam, and tazobactam. Some enzymes in this class also exhibit carbapenemaseactivity and are referred to as carbapenem-hydrolyzing class D beta-lactamases (CHDLs). There are several blaOXA genes associated with class D beta-lactamases, including *bla*OXA-51, *bla*OXA-23, *bla*OXA-24, *bla*OXA-58, *bla*OXA-143, and *bla*OXA-235 **(Wong and *al.*, 2019)**.

Regarding non-enzymatic resistance to beta-lactams,it iscausedby mechanisms such as: increases efflux, reduces influx and protects Antibiotic target.
Carbapenem resistance in *A.baumannii* is mediated by multiple mechanisms, including the production of various types of carbapenemases. Ambler class A beta-lactamases, such as*bla*KPC-2and*bla*GES-14,aswellasmetallo-beta-lactamases,including*bla*IMP-like, *bla*VIM-like,*bla*SIM-1,and*bla*NDM-1,have been implicated in carbapenem resistance **(Bakour and *al.*, 2015).** Additionally, the presence of OXA-type beta-lactamases, such as *bla*OXA-23-like,*bla*OXA-24-like,and*bla*OXA-58-likegenes,isassociatedwith increased carbapenem resistance. The expression of these genes is often influenced by the insertion sequence ISAba1 in their promoter region (**M. Nguyen and S.G. Joshi, 2021)**, Other mechanisms contributing to carbapenem resistance involve alterations in penicillin-binding proteins(PBPs),leading to reduced drug affinity due to down regulation(**Almasaudi, 2018)**. Loss or mutation of outer membrane porins, which are responsible for thein
Fluxo fantimicrobial agentsintothecell,canal so contribute to resistance (**Manchandaand*al.*,2010;D'Souzaand*al.*,2019)**.Moreover,theoverexpressionof efflux pumps,which actively remove antimicrobial agents from the cell,has been observed in carbapenem-resistant strains **(Wong and *al.*, 2019)**.

Quinolone resistance is mainly mediated by mutations in the quinolone resistance-determiningregion(QRDR)oftheDNAgyrasegene(gyrA)and/ortopoisomerase IV gene (parC), These changes decrease the affinity of the quinolones binding to the enzyme-DNA complex. (**David and *al* .2015).**

Anathor mecanism of resistanc to the quinolon is caused by Drug influx and efflux system encoded by chromosomal DNA mediates reduced expression of OMPs involved in drug influx and increased expression of efflux proteins resulting in active drug expulsion; these are also responsible for quinolone resistance. Inaddition Plasmid-encoded quinolone resistance determinants qnrA, qnrB, and qnrS have also been identified in Acinetobacter . baumannii that protect DNA by inhibiting binding of quinolones to DNA gyrase and topoisomerase. (**Muhammad Asifand*al*., 2018)**.

A.baumannii resistance to aminoglycosides primarily results from the inactivation of the antibiotic by certain modifying enzymes, including acetyltransferases, adenyltransferases, and phosphotransferases . More recently, methylations of the 16SrRNA by methyltransferases, known as 16S rRNA methylases (ArmA and RmtA), have been described in A. baumannii strains isolated worldwide. Additionally, resistance to aminoglycosides is also associated with active efflux mechanisms (**Decré, 2012)**. *A. baumannii* infections are generally defined by resistance to three or more representatives from quinolones, cephalosporins, β-lactams, aminoglycosides and carbapenems family of antibiotics, and the appropriate treatment was colistin, tigecycline, and sulbactam. However, PANDR (Pan Drug-Resistant) phenotypes, which are resistant to all classes of antibiotics, have emerged. The resistance to colistin in CRPA is du to two mecanisme. The first mecanism isphospho ethanolamine addition to the lipid A moiety of lipopolysaccharide (LPS) resulting from mutations in the genes encoding the two component signaling proteins PmrA and PmrBand secondcomplete loss of LPS production due to mutations in the lpxA, lpxC, and lpxD genes **(Muhammad Asif1 and *al*., 2018)**. Many studies has been shown that mutations in the PmrAB TCS induce the overexpression of pmrC, leading to the modification of lipid A with PetN and colistin resistance **(Vincent Trebosc and *al* .,2019)**.

Recently, a plasmide –mediated colistin resistance gene , specially gene mcr-1 , has been identified in Echerichia Coli , but not in A.*baumannii* .(**Muhammad Asif and *al* , 2018).** The mcr gene reported so far and mcr -1is the predominantmcr type ,The mcr -1 which was discaverd in more than twentycountries.

The mecanisem of this gene is about phosphoethanolamine transferase enzymes that bind a phosphoethanolamine (PEtN) units on lipid A of outer membrane bacteria Gram negative, which causing arecession ofits net negative chargeand confersresistance to colistine **(NadheemaHammoodHussein and *al*.,2020)**. Tigecycline is a glycylcycline antibiotic with antimicrobial activity to ribosomal A site of the 30S subunit.

However, tigecycline mecanisme of resistance from the constitutive expression of resistance-nodulation-division (RND) efflux pumps.,the most extensively studied RND efflux system in the adeABCsystem.(**Xiaoting Hua and *al* ., 2021)**.

A.Baumannii is considred one of the most critical pathogene for his ability to survive in variaty of environments and his capacity to produce wide range of virulence factors (**Marta Martínez-Guitián and al ., 2019)**.

A. baumannii has developed many factors of virulence such as, phospholipasesWho are lipolytic enzymes responsible for cleaving phospholipids. These enzymes contribute to the pathogenesis of Gram-negative bacteria by catalyzing the cleavage of phospholipids present in cell membranes and mucosal barriers to facilitate cell lysis and bacterial invasion.

Two phospholipase C (PLC) and three phospholipase D (PLD) enzymes were identified in *A. baumannii*, all with substrate specificity toward the eukaryotic membrane component, phosphatidylcholin (**Michael J and *al* .,2012)** , It consists of two PLCs, namelyA1S-0043andA1S-2055.InactivationoftheA1S-0043generesultsincytotoxicity of epithelial cells (**Sinosh Skariyachanand *al* . , 2019)**

In addition, the three phospholipase D genes are associated with serum resistance, epithelial cell invasion, and in vivo pathogenic (**McConnell MJ and*al*.,2013)**.

The capsule is considered a virulence factor due to its significant role in protecting bacteria from the host's innate immune response. Numerous studies, including Weber BS, Harding have demonstrated the essentialityof the capsule for the survival of Acinetobacter

baumannii during infection and growth in serum **(CM, and Feldman MF 2016),**

Protein secretion systems in Gram-negative bacteria exhibit extensive diversity in terms of function and composition, playing a crucial role as important mediators of virulence. Recentresearch,asdiscussedby(**Weber BS, Harding CM, and Feldman MF (2016)** has elucidated multiple mechanisms by which Acinetobacter species secrete proteins and their involvement in the pathogenesis of these bacteria.

In *A.baumannii,* the type two-secretion system, including the genes lipA and lipH, has attracted attention **(Weber BS, Harding CM, Feldman MF, 2016).** This type of secretion system operates through two mechanisms, depending on the Sec/Tat system for substrate translocation to the periplasm **(Eijkelkamp and *al*., 2014).**

Outer membrane vesicles (OMV) are spherical nano vesicles pheric nanovesicles identified in Gram-negative bacteria. They are composed of LPS, outer membraneproteins, periplasmic proteins cytoplasmic, proteins, lipids, DNA and RNA..**(McConnell MJ, Actis L, Pachón J, 2013).***A. baumannii* secretes OMVs during infections which are also capable of transferring resistance genes, as shown for the blaOXA has been shown for the blaOXA-24-like gene, suggesting a role for these vesicles in spreading in the spread of antibiotic resistance **(Rumbo C and *al.*,2011)**.

Quorum sensing is a ability to sense, respond, and to communicate binding to neighboring cells is critical to the success of the population bacteria detected and respond to hormone. In addition, Quorum sensing contributes to Acinetobacter pathogenicity by controlling gene expression , promoting biofilm formation and, consequently, survival and resistance to antibiotics. **(Roca Subirà and *al* .,2012)**.

Micronutrients are vital for the survival and growth of bacteria. *A.baumannii* has developed various metal systems to scavenge essential nutrients such as zinc, iron, and manganese. In order to acquire these ions. *A.baumannii* produces and secretessiderophores, which are low molecular weight iron scavengers capable of chelating iron with high affinity within the cellular environment (**Sheldon, J.R.; Skaar, E.P, 2020)**. Additionally, *A. baumannii* can obtain iron through siderophores. Examples of A. baumannii iron chelators include fimsbactins A-F and baumannoferrin A and B, with acinetobactin being the most

characteristic siderophore (**Gaddy JA and*al*., 2012)**.

Outer membrane proteins of Gram-negative bacteria are investigated for their association with antimicrobial resistance, pathogenesis, and variation in the adherence of the host cell.

OmpA of *A. baumannii* is a major surface-bound protein, which facilitates the attachment process and host cell invasion and helps in the commencement of apoptosis at the onset of infection. (**Guo, Y.; Xun, M.; Han, J. A bovine, 2018).**The OmpA adds to the initiation of cell apoptosis, the invasion of epithelial cells, and serum resistance, and others Gram-negative bacteria generally produce outer membrane vesicles.

Another factor of *A. baumannii* is its ability to adhere to both biotic and abiotic surfaces, leading to the formation of biofilms. This process serves as a virulence factor contributing to the pathogenicity of *A. baumannii*. The regulation of biofilm formation involves a wide range of bacterial factors, including pili, outer membrane proteins(OmpA), exopolysaccharide production,andthetwo-component regulatorysystemBfmRs. Additionally, cellular and environmental factors such as quorum sensing signaling molecules, temperature, light, and iron availability play a role in this process **(Michael J. McConnell and *al*., 2013).**

A.baumannii exhibits resistance to certain quaternary ammonium-based disinfectants and can proliferate in disinfectant bottles. Furthermore, it possesses theunique ability to survive for extended periods, exceeding eight days, in a dry environment **(Howard and *al.*, 2012).**

Methodology, Results and Discussion

I. Bacterial strains:

A collection of *A. baumannii* strains was compiled between September 2020and January 2022. These strains were obtained from various samples and isolated by the bacteriology laboratory at the University Hospital of Oran. Subsequently, they were stored and dispatched to the microbiology laboratory at A/MIRA University in Bejaia.

II. Isolation and identification of *A.baumannii*:

A. baumannii, as adistinctive characteristic, has the ability to grow at a temperature of 44°C and does not ferment citrate. To confirm the identification of our strains, we followed the following steps: firstly, we streaked the strains onto Trypticase Soy Agar and incubated them at 44°C for 24 hours. Subsequently, all the colonies that grew were subcultured onto Simons citrate agar and incubated at 37°C for 24 hours.

III. Antibiotics susceptibility studies(antibiograms):

The susceptibility of *A. baumannii* strains to antibiotics is determined by antibiograms. This is carried out on Mueller Hinton agar according ofthe recommendations of the French Society of Microbiology's(French Antibiogram Commite).**(CA-SFM 2018).**

Agar plates were inoculated by flooding with a germ suspension Antibiotic .Discs were applied to the agar surface using sterile forceps. u. Plates were incubated for 18 to 24 hours at 37°C. Using a ruler graduated in mm, the different diameters of the zones of inhibition obtained around the antibiotic discs were measured twice, then interpreted as Sensitive (S) Intermediate (I) or Resistant.

Table1: The antibiotics tested are listed in TableN°1(CA-SFM 2018).

Antibiotic	**Abbreviations**	**Disc load in(□g)**	**Critical diameter(mm)**	
			S	**R**
Amikacine	Amk	30	≥19	<19
Ceftazidime	Caz	30	≥18	<15
Ciprofloxacine	CIP	5	≥50	<21
Doxycycline	DOX	30	≥13	<13
Gentamicine	Gen	10	≥17	<17
imipenem	Imp	10	≥24	<21
Levofloxacine	Lvx	5	≥23	<20
Piperacilline	PIP	100	≥21	<18
Triméthoprime sulfametoxazole	SXT	1.25-23.75	≥14	<11
Ticarcilline + clavulanic acid	TCC	75-10	≥20	<15
Ticarcilline	TIC	75	≥20	<15
Tobramycine	TOB	10	≥17	<17

S:sensible **R:**resistant

Result:

Atotal of 61 of *A.baumannii* were isolated from different clinicals samples.

Phenotype test:

In our study, all 61 strains that were inoculated on tryptic soy agar and incubated at 44 degrees Celsius successfully grew. However, not all strains demonstrated citrate fermentation. These results suggest that they may belong to the *A. baumannii* species. Nevertheless, confirmation of *A. baumannii* presence will require MALDI-TOF identification.

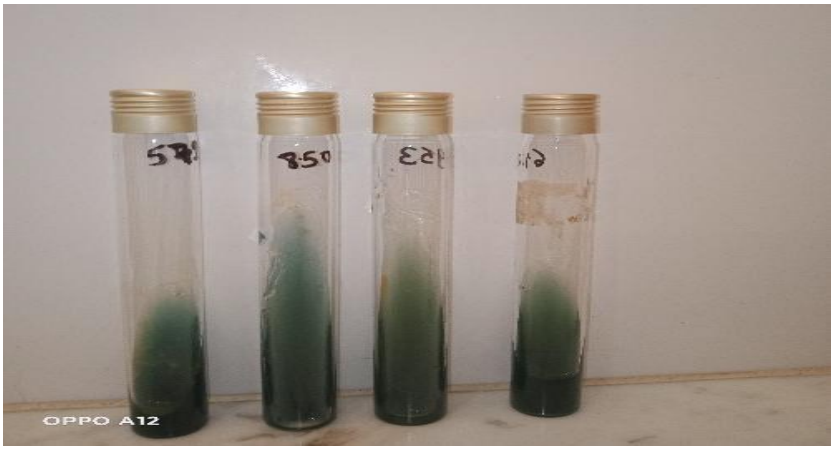

Figure1: citrate test-

Distribution of *A.baumannii* isolates by type of sample:

The figure 2showed that *A. baumannii* strains are more frequently isolated from PC, blood and pus samples, with rates of 32.75% (20 strains), 27.86% (17 strains) and 26.22% (16 strains) respectively.

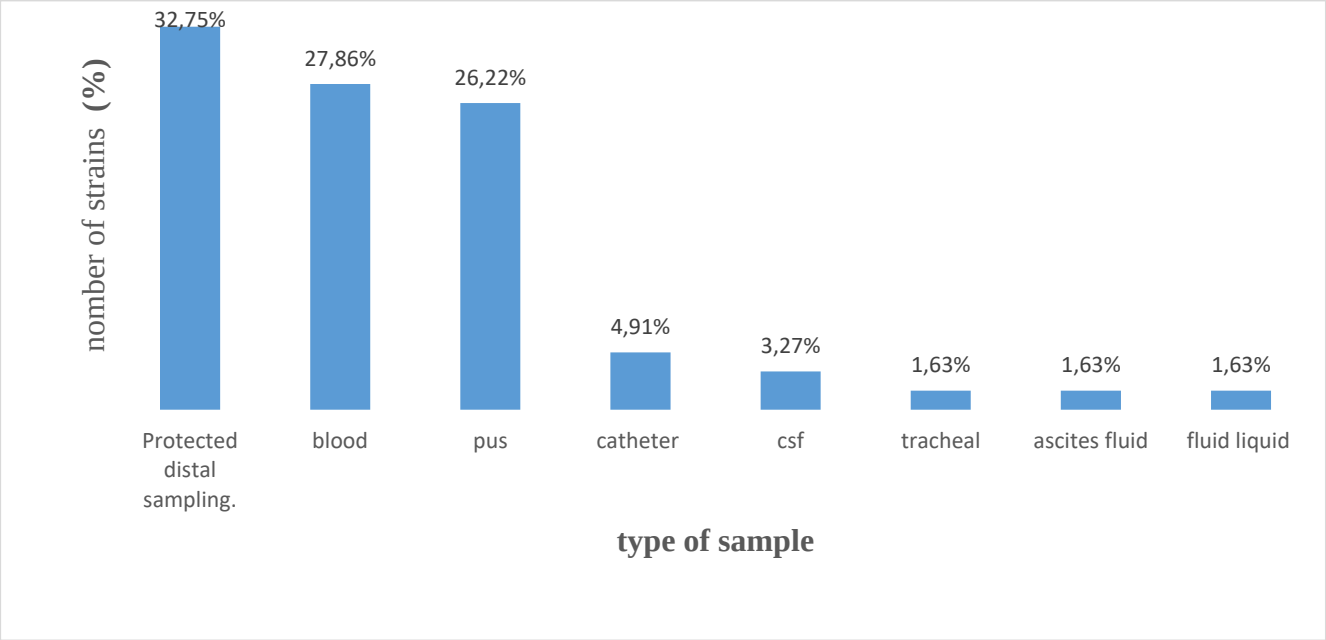

Figure2: Distribution of *A.baumannii* strains by type of sample

Distribution of *A.baumanii* strains by department:

During the study period, *A. baumannii* was detected in various departments of Oran Hospital. Figure 3 illustrates the distribution of *A. baumannii* strains by department. The intensive care unit exhibited the highest prevalence of *A. baumannii*, accounting for 44.26% (27 strains), followed by the reaumc unit with a rate of 14.75% (9 strains). However, a minimal presence of A. baumannii was observed in the followingdepartments: PP, Pav-5, IPD, NFC, UMC, , and NCH, with a rate of 1.63%.

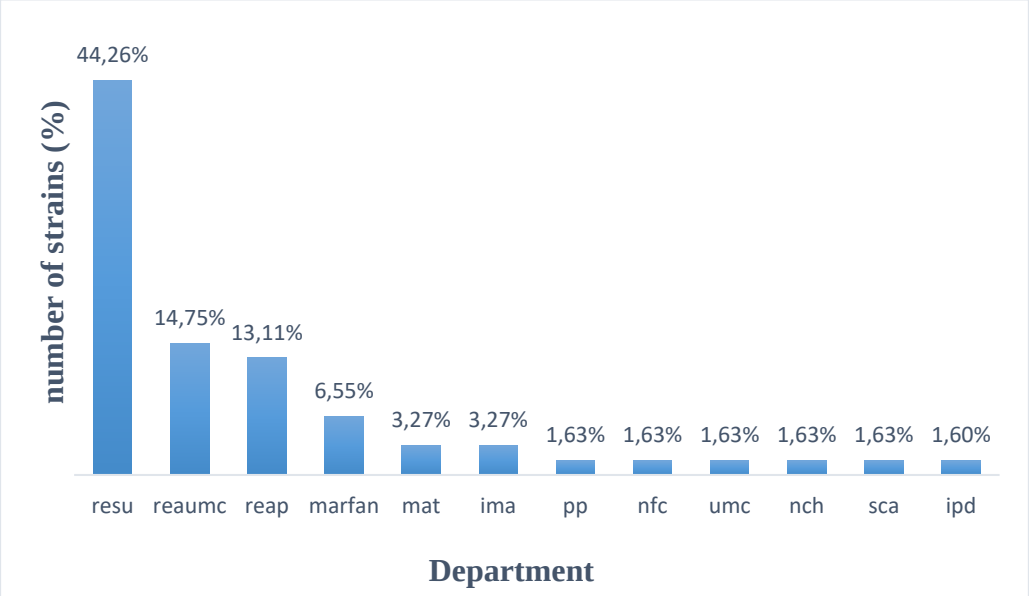

Figure3: Distribution of *A. baumanii* strains by department.

Rate of resistance of *A. baumanii* strains to the various antibiotics tested:

The figure 4 showed that ,the highest resistance rate was reported for piperacillin, with a rate of 93.44%, followed by ceftazidime at 91.8%. 86.88% of the strains were resistant to gentamicin, tobramycin, and ticarcillin. Resistance rates of 85.24% were reported for ticarcillin-clavulanic acid and levofloxacin. The resistance rate for imipenem was 83.60%. Lower resistance rates were reported for amikacin, tobramycin, and doxycycline.

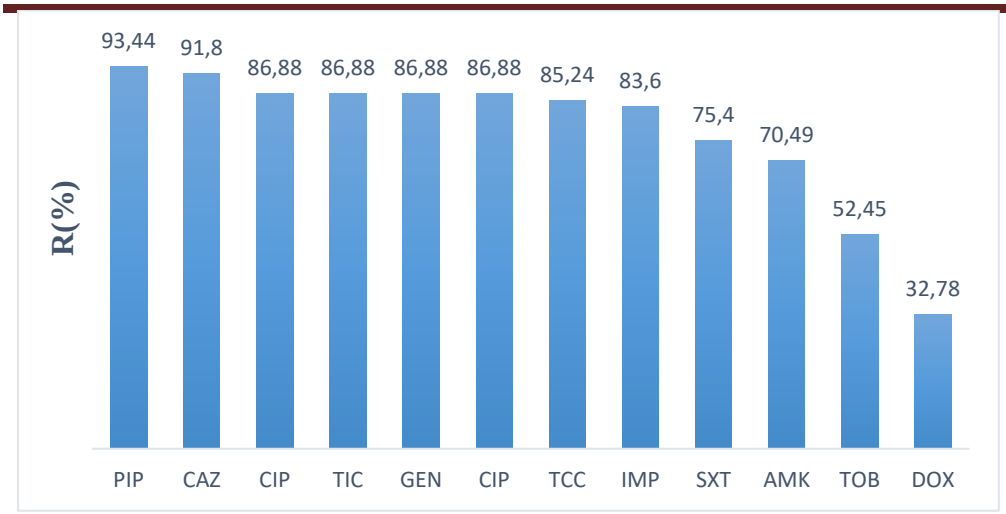

Figure4: Rate of resistance of *A.baumanii* strains to the various antibiotics tested.

Distribution of *Acinetobacter baumannii* by sex:

Figure 5 shows the distribution of *Acinetobacter baumannii* by sex: 54.09% in the female category with 33 strains, compared with 45.90% in the male category with 28 strains**.**

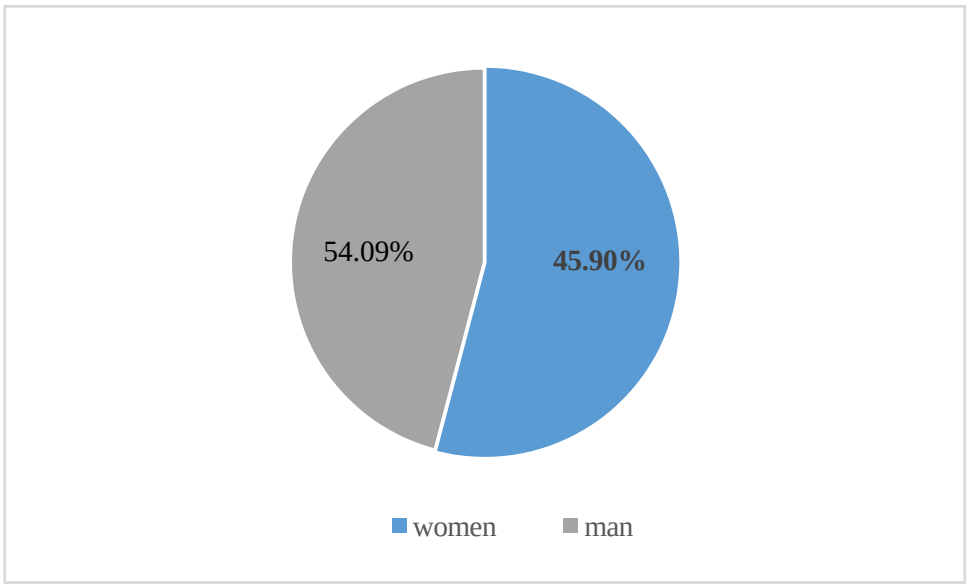

Figure5: Distribution of Acinetobacter baumannii by sex.

A. baumannii has been widely acknowledged as an opportunistic microorganism and has now emerged as a significant cause of hospital-acquired infections **(Giamarellou et al., 2008)**. According to the Algerian surveillance network, *A. baumannii* accounts for 61.67% of infections in Algeria **(Rahal, 2020)**. Our study detected the presence of *A. baumannii* in various departments, including infectious and parasitic diseases, internal medicine A, gastroenterology, dermatology, pneumo-phtisiology, surgical clinic A, and NouarFadela clinic (obesity clinic and gynecology).

Multiple studies have consistently reported the high prevalence of *A. baumannii* infections in intensivecare units(ICUs) **(Elouennassetal.,2003;Al-Agamy etal.,2014).** Our findings support the existing literature, indicating that ICUs remain the primary source of *A. baumannii* infections, although the rates may vary. In our study, *A. baumannii* strains were predominantly isolated from the ICU (44.26%). These results align with numerous studies, notably Lahsoune et al.'s (2007) study conducted in Morocco, which reported arate of 50.30%, and the study by Mina and Namigandain 2018 at Beni Messous Hospital in Blida,Algeria, which also reported a rate of 50%.(**Namiganda and Mina.,2018)**

The persistence of *A. baumannii* infections in ICUs can be attributed to various factors. Major predisposing factors for acquiring *A. baumannii* infection include prolonged hospital stays, mechanical ventilation, intravascular devices, advanced age, immunosuppression, previous broad-spectrum antimicrobial therapy, previous sepsis, ICU stays, and enteral feedings **(Dr. Shalini Singh and*al*., 2022).**

Regarding the types of samples from which *A. baumannii* strains were isolated in our study, the respiratory site was the primary site of infection, accounting for 32.75% of isolates from protected distal sampling. This was followed by 27.86% of isolates from bloodsamplesand4.91%from catheterization. Our find ingsalign with a study conducted

by R. Rada and *al* in 2022, which reported similar rates , 38% from the respiratory site and 4% from catheterization.(**R. Rada and *al*., 2022)** However, our results contradict those obtained in another study conducted by **(Abir Ramoul and al .,2016).**

In our study, *A. baumannii* strains were predominantly isolated from female patients, accounting for a high rate of 54.09%. In comparison, the male category had a slightlylowerrateof45.90%.Thesefindings align with there results reported by Shristi Raut and *al*. 2020, who observed rates of 43.50% and 56.50% for females and males, respectively **(ShristiRaut and *al*. 2020).**

It is important to note that these results may vary depending on the types of infection and hospital wards.The literature includes several etiological studies that suggest no significant difference between sexes in the acquisition of Acinetobacter spp. Infection(**Shristi Raut and *al*. 2020).**

The resistance rates of *A. baumannii* to different classes of antibiotics vary. In our study, we observed high rates of resistance to β-lactam antibiotics, with 93.44% resistance to piperacillin, 91.80% to ceftazidim, and 86.88% to ticarcillin. These findings closely align with the results obtained by Zaidi in 2014 who reported a resistance rate of 89.58% for the same compounds.(**Zaidi .FT ,2014)** Another study conducted by Benamrouche and *al*. in 2020 from various hospitals in Algeria also found similar resistance rates(**Benamrouche and *al*., 2020)**

Regarding aminoglycosides, we observed resistance rates of 86.88% for gentamicin, 52.45% for tobramycin, and 70.40% for amikacin in our study. These results are higher than those reported by Bakourand*al*2012. Resistance to aminoglycosides can be attributed to multiple mechanisms with the production of modifying enzymes and

Methylation of rRNA16S by armA being them most common resistance mechanisms

(Lambertetal.,2006)

The resistance of *A.baumannii* to carbapenems has significantly increased in recent decades, largely due to the overuse of this class of antibiotics in hospital settings (**Chabaniand*al*., 2004; Ling and*al*., 2005; Picazoand*al*., 2006).** Our study revealed a high level of resistance to imipenem, with a rate of 83.60%. This rate is higher than the 82% reported by Bentara and Abdelli 2015 (**Bentara and Abdelli 2015).** The elevated resistance to imipenem is concerning as it poses challenges to patients'treatment regimens, especially in intensive care units where imipenem is the preferred antibiotic for the treatment of nosocomial infections .((**Bakourand *al.*, 2012).**

The emergence of carbapenem resistance is mainly attributed to the production of carbapenemases, including class D carbapenem-hydrolyzing oxacillinases and, less frequently, class B metallo-β-lactamases. Class D oxacillinases in A. baumannii are predominantly represented by the blaOXA-23, blaOXA-24, and blaOXA-58 genes **(Peleg, 2008; Kempf, 2012).**

In our study, 86.88% of isolates showed resistance to fluoroquinolones. Ben Haj Khedher, 2010? reported a resistance rate of 92.3% to ciprofloxacin in Tunisian hospitals (**Ben Haj Khedher, 2010)**. According to the national network for monitoring resistant bacteria in Algeria in 2020, the resistance rate to ciprofloxacin was 89.58% in 20 laboratorie**(Rahal, 2020)**

Colistin is a highly effective antibiotic against strains of *A.baumannii*. However,the increasing use of colistin as monotherapy for the treatment of bacterial infections caused by multidrug-resistant *A.baumannii* strains

Heterogeneous resistance to this class of antibiotics **(BenHajKhalifaandKhedher,2010; Al-Sweith and *al.*, 2012).**

In Algeria, colistin resistance in *A. baumannii* was first detected in 2014 by Bakour and *al.* This resistance is associated with a mutation in the pmrB gene **(Bakour and *al.*, 2014).**

To maintain the effectiveness of colistin,studies suggest the combination of colistin with other antibiotics such as rifampicin **(Frasca and *al.*, 2008).** Furthermore, there is a need to develop and evaluate new strategies , such as the combination of colistin with tigecycline **(Giamarellou and *al.*, 2008).**

Conclusion

This research work focused on the mechanism of multi-resistant *A.baumannii* in the EHU of Oran.

Our resultas shows that *Acinetobacter baumannii* occupies an important place among opportunistic germs due to it sability to cause nosocomial infections, and that it is presented more specifically in intensive care units.

Currently in Algeria, resistances to the many antibiotics in term of morbidity, mortality due to the several facteures essentially increase multi of the duration of hospitalization.

In this is why epidemiological investigations in intensive care units are essential to control the emergence of this species.

The study we carried outenabled us to obtain the following results:

- 61 strains of acinetobacter baumannii were isolated at the Etablissement hospitalier d'Oran.
- The majority of strains come from pulmonary samples an dessentially from the reanimation department with a rate of 44.26 %.
- Ahugeincrease in resistance to beta-lactaman carbapenem antibiotics.

The results obtained in this study must be completed by a series of other tests, namely:

- Identification and characterisation of the genetic environment. (Insertion sequences, integrons and transposons,.) In order to determine the elements that mobility of genes resitance .
- Study of the genetic carriers (plasmid or chromosomal) responsible for possible dissemination of antibiotic resistance in*A.baumanni*.

In order to combat the emergence of these multi-resistant strains in our hospitales, were commend: ssetting up a system for monitoring the hospital environment and strictly hygiene measures , Equipping laboratories with tools for the rapid identification and detection of resistance to these bacteria , Making hospital visit or saware of the risks of direct contact with patients and the hospital environment.

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Composition of culture media(g/l).

Simmons citrate medium composition.

Citrate de sodium	**1.0g**
Bleu de bromothymol	0.08g
Chlorure de sodium	5.0g
Sulfate de magnésium	0.2g
Hydrogénophosphatede potassium	1.0g

Gélose trypticase soja composition

Digestion pancréatique de caséine	**1**
PeptonedeSoja	5g
Chlorure de soduim	5g
Gelose	5g

PH 7.3+0.2 à25 C

Gélose trypticasesoy broth composition

Tryptophane	17.0
Chloruredesodium	5.0 g

Phosphatedipotassique	2.5
Peptonedesoja	3.0 g
Glucose	2.5 g

PH7.3+-0.2à25 C

Equipment:

- Bunsenburner.
- Pasteur pipettes
- Petridishes.
- Platinum loop
- Oven
- Forceps.
- Antibioticdiscs.

TableN°II:Characteristics of the *A. baumannii* strains collected.

Code	Date	sex	Department	sampling
709	23/09/2020	F	ream	Protecteddistal
721	27/09/2020	M	reap	Pus
592	29/09/2020	F	ream	blood
737	01/10/2020	M	reaumc	Protecteddistal
699	17/11/2020	M	ream	Blood
720	25/11/2020	M	marfan	catheter
218	24/02/2021	M	ream	Protecteddistal
287	21/03/2021	M	reaumc	Pus
468	26/04/2 021	F	ream	Pus
483	29/04/21	F	ima	pus
736	23/06/21	M	nch	csf
740	27/06/21	M	sca	pus
1016	31/08/21	F	marfan	Ascritesfluid
600	14/09/21	M	marfan	blood
1128	11/02/20	F	reap	csf
907	27/11/2022	F	resu	Protecteddistal
770	16/12/22	F	resu	bood
978	20/12/20	F	resu	Protecteddistal
155	02/07/21	F	resu	Protecteddistal
211	23/02/21	M	resu	Protecteddistal
255	03/07/21	M	resu	Protecteddistal

109	04/01/21	M	reaumc	Protecteddistal
361	04/02/21	M	reaumc	Protecteddistal

419	13/4/2021	F	resu	pus
471	05/02/21	M	pp	Fluidliquid
601	31/05/21	M	reaumc	Protecteddistal
801	13/07/21	M	reaumc	pus
813	16/07/21	M	resu	Protecteddistal
506	18/07/21	F	mat	blood
823	22/07/21	F	reap	pus
525	27/07/21	M	marfan	Blood
850	29/07/21	F	reaumc	Protecteddistal
549	8/08/21	F	resu	blood
549	11/08/21	F	resu	Protecteddistal
549	18/08/21	F	resu	Protecteddistal
549	29/08/21	M	reap	tr
549	29/08/21	F	reaumc	blood
549	30/08/21	F	resu	Protecteddistal
549	30/08/21	F	resu	Protecteddistal
549	21/09/21	F	resu	blood
549	23/09/21	M	reap	pus
549	23/09/21	M	reap	pus
549	31/10/21	M	resu	blood
549	15/11/2021	M	pav.5	blood
549	17/11/21	F	resu	Protecteddistal
549	23/11/21	F	pav.7	Blood
549	28/11/21	F	pav.7	Pus
549	12/06/2021	F	resu	Protecteddistal
549	12/11/2021	F	resu	Protecteddistal
549	12/12/2021	M	ipd	Pus
549	13/12/2021	F	reap	Pus
549	15/12/2021	F	resu	Blood
549	20/12/2021	M	resu	Catheter
549	28/12/2021	F	ima	Pus
549	29/12/2021	M	nfc	Catheter
549	01/02/2022	F	reap	Blood
549	01/04/2022	F	Mat	Blood

549	01/11/2022	M	resu	Protecteddistal
549	23/01/2022	M	reaumc	Blood
549	26/01/2022	F	resu	Protecteddistal

M:male **F:**female**resu**;resuscitation

Résumé:

Les bactéries à gram négatif non fermentaire sont des pathogènes opportunistes due a leur capacité de provoquer des infections nosocomials.; elles ce manifeste a une résistance aux antibiotique, dont l'espèce *Acinetobacter Baumann*, qui pose un réel problème sur la santé humaine .

Objectif de ce travail est la caractérisation phénotypique et génotypique des mécanismes de résistances *d'Acinetobacter baumannii* aux différents antibiotiques, isolées dans différents services entre septembre 2020 et janvier 2022 au niveau l'EHU d'Oran.

L'étude de la résistance in vitro de ces germes vis-à-vis aux β -lactamines, aminosides, fluroquinolones, Aminoglycosides par la méthode des disques selon la société française de microbiologie (CA-SFM).

La résistance aux β-lactamines est due, soit à la production d'une BLSE, ou à la production des carbapénémases, dans point génétiques par la production des gènes de résistance tels que OXA-23 et NDM-1.

A fin de combattre cette émergence d'Acinetobacter baumannii multi résistantes qui pose un sérieux problèmes dans secteur thérapeutiques, d'où la nécessité de l'applications des règles d'hygiènes .

Mot clé: *Acinetobacter baumanni* Etablissement hospitalier universitaire d'Oran β – lactamines

Abstract

Non-fermentative gram-negative bacteria are opportunistic pathogens due to their ability to cause nosocomial infections; they manifest resistance to antibiotics, including the species *Acinetobacter baumannii*, which poses a real problem for human health.

The objectif of this work is to characterise the phenotypic and genotypic resistance mechanisms of Acinetobacter baumannii to different antibiotics, isolated in different departments between September 2020 and January 2022 at the EHU of Oran.

The study of in vitroresistance of these germsto β-lactams,aminoglycosides,fluroquinolones and aminoglycosides using the disc method according to the French Microbiology Society (CA-SFM).

Resistance to β-lactamsis due either to the production of an ESBL, or to the production of carbapenemases, in genetic points by the production of resistance genes such as *OXA-23* and *NDM-1*.

In order to combat this emergence of multi-resistant Acinetobacter baumannii, which posesserious problems in the therapeutic sector, it is essential to apply hygiene rules.

Keyswords: Establishing Hospital University of Oran, Acinetobacter baumannii, antibiotic, β-lactams, resistance phenotypes