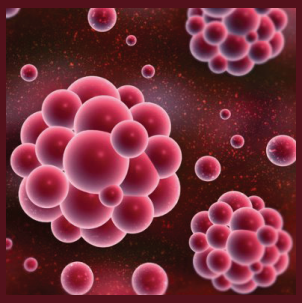
ISSN: 2766-838X

RAS MICROBIOLOGY AND INFECTIOUS DISEASES

Research Article: Major risk factors and outcomes of the extensively drug-resistant *Acinetobacter baumannii* acquisition in a Moroccan surgical intensive care unit



Issue Type: Volume 3 Issue 1

Author Name:
Adel Hilmi[a, b,*], Loubna Aitsaid[a], Ahmed Tadlaoui Ouafi[c], Kawtar Zahlane[a]

[a] Laboratory of Medical Analysis, IbnTofail Hospital, University Hospital Center-Mohammed VI, Marrakesh, Morocco.
[b] Laboratory of Microbial Biotechnologies, Agrosciences and Environment, CNRST Labeled Research Unit N°4, Faculty of Sciences Semlalia, Cadi Ayyad University, Marrakesh, Morocco.
[c] Center of Agro-Biotechnology and Bioengineering,CNRST Labeled Research Unit N°5, Faculty of Science and Technics -Gueliz, Cadi Ayyad University, Marrakesh, Morocco.

Corresponding Author:
Dr Adel HILMI, PhD.

Citation: Dr Adel HILMI, PhD., Major risk factors and outcomes of the extensively drug-resistant *Acinetobacter baumannii* acquisition in a Moroccan surgical intensive care unit

Received Date: 25th April 2023

Published Date: 9th May 2023

Copyrights: Dr Adel HILMI, PhD., This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract:

Purpose: *Acinetobacter baumannii* has emerged as an important nosocomial pathogen causing worldwide hospital outbreaks. The aim of this study was to determine the antibiotic resitance profile, the risk factors and outcomes related to the acquisition of extensively drug-resistant *A. baumannii.*

Methods: A case control study was conducted from April 2017 to April 2018 in a 10-bed tertiary intensive care unit (ICU) of IbnTofail University Hospital Mohammed VI in Marrakesh-Morocco. All adult patients with a first clinical episode of infection were included. The level of antibiotic resistance has been studied by the agar diffusion method, the choice of antibiotic susceptibility testing and interpretation criteria were made as recommended by the Antibiogram Committee of the French Microbiology Society (2017).

Results: Among 305 isolated bacteria from patients in the IUC, 85 were represented by extensively drug-resistant *A. baumannii*. The high and alarming antibiotic resistance levels were obtained for ciprofloxacin, gentamicin, tobramycin, and amikacin (95%,94 %, 93%, and 75 % respectively). Regarding the studied risk factors, this damageable bacteria was mainly associated to pneumonia, catheter-related bloodstream, and blood stream infections (56%, 30%, and 24 % respectively). Moreover, out of the 35 hospitalized patients and infected with *A. baumanni*; 31 were deceased due to this infection.

Conclusions: In this study, the decrease of infection control measures and the abusive prescriptions and use of antibiotics has contributed to the increase rate of this *A. baumanni* acquired infections.

Keywords: Risk factor, Antibiotic resistance, *Acinetobacterbaumannii*, Intensive care unit.

Introduction

The opportunistic pathogen *Acinetobacter baumannii* is an aerobic Gram-negative rod-shaped, pleomorphic and non-motile bacteria. Around the world, infections due to *A. baumannii* are emerging scourges in intensive care units (ICU) [1,2]. During the three last decades, it has been transformed from a simple opportunistic bacteria to one of the most damageable, virulent, multidrug-resistant and pathogenic organism. In addition, it tolerates external conditions like desiccation, survives longer, and persists on hospital environments and surfaces [3, 4].

This microorganism has also become a matter of great concern due to its extraordinary capability to cause nosocomial infections and to acquire resistance to commonly used antibiotics. Many international studies have shown that infections caused by *Acinetobacter* spp. represent 7.9 % of ventilator-associated pneumonia and 5.7 to 15.7 % of bloodstream infections in the ICUs [6, 7]. In addition, polymyxins represent the last therapeutic options for this highly resistant bacteria. However, the emergence of colistin-resistant *A. baumannii* strains has been worldwide reported [5, 8, 9]. Regarding the risk factors associated with the acquisition of *A. baumannii* it was found that the most ones influenced the infection with MDR strains , include the previous colonization, the prior antimicrobial treatment, the period of hospital stay, the urinary catheterization, and the surgery [8,10,12].

The emergence of multi-resistant *A.baumannii* strains, mainly in ICUs, threatens the possibilities of antibiotic treatment options and lead to serious and high mortality rates [13,14]. These infections were related to high levels of mortality ranging from 28.3% to 84.3% in the ICU [11, 14].

In Moroccan ICUs, the antibiotic resistance of *A. baumannii* increased for piperacillin / tazobactam, third generation cephalosporins, carbapenems, and for amikacin [10,11]. For this reason, we conducted this study to analyze the antibiotic resistance related to the risk factors and the outcomes of extensively drug-resistant *A. baumannii* acquisition in a Moroccan surgical ICU.

Material and methods

Patients and study design

This is a case control study conducted in a 10-bed clinical-surgical ICU for adults, which lasted 12 months, (from April 1st, 2017 through April 1st, 2018) in order to evaluate the major risk factors and outcomes of extensively drug-resistant *A. baumannii* acquisition in a Moroccan surgical intensive care unit. Active epidemiological and microbiological screening for patients infected with extensively drug-resistant *A. baumannii* was conducted in this unit. During the period of our study, out of 478 patients transferred to the intensive care unit (ICU) of Marrakech UHC; 299 (62%) were from emergency unit of the hospital.

Laboratory Methods

The medical analyses were performed in the medical microbiology laboratory of the hospital and adult patients with a first clinical episode of infection with Healthcare acquired Infections (HAI) were included in the study. The strains were isolated from urine, bronchial aspirations, blood, pus and cerebrospinal fluid samples, which were sent to the laboratory for diagnostic purposes. The pathological samples taken from patients in the intensive care unit were plated on ordinary culture media (Columbia, Mueller-Hinton agar), for the development of the majority of bacteria and on selective media (MacConkey agar). Bacterial identification was made by the API 20 NE gallery (Biomerieux API). The study of antibiotic resistance level has been performed by the agar diffusion method in Muller Hinton agar (MH). For some antibiotics, this method was supported by the evaluation of the minimum inhibitory concentration (MIC) in liquid media as recommended by the AC-FMS and EUCAST, 2015.We excluded of all doubling *A. baumannii* isolates from the same samples and all *A. baumannii* strains were preserved at -20ºC in Brain Heart Infusion (BHI), containing 20% of glycerol solution.

Data Collection

Data on demographic characteristics, host and therapeutic factors, laboratory and bacteriology results, antibiotic therapy, and outcomes were collected using medical and laboratory records. This collection was done mainly through the use of an epidemiological monitoring questionnaire. Thus we prospected several variables and factors, starting with patients demographic characteristics such as age, sex, nature of pathological sampling, medical history of hospitalization, underlying disease at admission, patients nutritional state, unit of hospitalization, invasive procedures, biological and clinical signs of infection, date, site of the infection and the isolation of patients carrying *A. baumannii*. In addition, we studied antibiotic therapy, the patterns of resistance of *A. baumannii*, the period of stay in the unit, the outcomes of patients after the stay in the ICU and the rate of dead patients caused by infections with this pathogen.

Statistical Analysis

The data of our study were analyzed using the statistical package for social sciences (SPSS v 23, Chicago, USA). The Chi-square or Fisher's exact test were used to compare discrete variables. Fisher's exact test was used instead of the Chi-square test when one or more expected values were equal or less than five. All p-value <0.05 was considered statistically significant.

Factors with a p value < 0.05 were analyzed using multivariate regression model. The dependent variable we used in this model, is extensively drug-resistant *A. baumannii*. All variables with $p<0.05$ in univariate analysis were included in the multivariate model as independent variables to identify independent predictors of multi-resistance, and calculated the odd's ratio to prove the strength of the association between the important factors.

Ethics statement

This study did not require ethical approval and informed consent, but we applied and received a study permit from the hospital institutional administration. The full name of the ethics committee that approved our study are Prof. Kawtar ZAHLANE and Prof. Hicham NEJMI.

Results and Discussion

Clinical and epidemiological characteristics of patients

A. baumannii is the most current ongoing troublesome and causing infections mainly in sensitive patients in ICUs. The number of studies about *A. baumannii* incidence is limited, and it is usually considered a healthcare-associated pathogen.As shown in table 1, Almost 59 (12.34%) developed infections with MDR *A. baumannii* Fig 1 (D), 45 (76%) of these patients were males Fig 1 (A).

Regarding the age distribution, 34 (58%) were between 20 and 40 years Fig 1 (C). The most common diagnosis at the admission of the ICU was polytrauma 29 (45%), followed by severe trauma-cranial 10 (17%). The average overall length of the ICU was 15 days. In this study, the incidence rate of multi-resistant *A. baumannii* infections is 12.34 %, which was different than the incidence reported in a Moroccan, Indian and in Mexican studies (8.5%, 10 % and 4,6 %) respectively [16,17,18]. In Spain, the overall incidence of *A. baumannii* infection was ranging from 2.34 % to 9.06 % [19]. Commonly, the incidence of *A. baumannii* nosocomial outbreaks is increasing worldwide [15]. As well as in our studies, the high prevalence of *A. baumannii* infections in ICUs can be explained by a lack of good isolation precautions, insufficient staff numbers and the increasing numbers of patients in short periods.

Bacteriological and antibiotic resistance profile findings:

During the period of this study, the results showed that among 305 isolated bacterial strains, the prevalence of *A. baumannii* isolates among all bacterial isolates is 85 (28%) (Fig 2). Our study revealed a multidrug resistant *A. baumannii* rate of 70% among all isolated MDR resistant bacteria from the ICU and the different other MDR bacteria represented 30%.

Regarding antibiotic use and prescription in the ICU, Fig 3 showed that amoxicillin/clavulanic acid was prescribed as the first antibioterapeutic cure (13.5%), followed by the third generation of cephalosporins (ceftriaxon), quinolons (moxifloxacin), and colistin (11%, 9% and 7.5% respectively).

In addition, this study demonstrated the high level of bacterial isolates resistance to the most tested β-lactams antibiotics used in clinical therapeutic, such as penicillins, β-lactamase inhibitors, cephalosporins, monobactams, and carbapenems. All the studied *A. baumannii* isolates showed resistance to carbapenem, particularly to the imipenem. The Fig 4 presents different co-resistance levels to the other antibiotic classes. ABRI has a very high level of co-resistance to the other antibiotics, mainly to gentamicin 94%, tobramycin 93% and to ciprofloxacin 94%. While, all the *A. baumannii* resistant isolates to imipenem (ABRI) were sensitive to colistin antibiotic. This molecule is the only available antibiotic treatment option to be used single or in association with other antibiotic molecules. In the last two decades, resistance rate to carbapenems, quinolones and aminoglycosides, which are commonly used in the treatment of *A. baumannii* infections, have worldwide increased [6, 7]. The abusive use of carbapenems is responsible for the alarming increase in the number of *A. baumannii* in the ICUs. In a northern Indian ICU, researches have documented the high rate of *A. baumannii* resistant to imipenem 75.9 % and aminoglycosides 80.6 %. While13 % of *A. baumannii* were resistant to colistin [21]. In the same context, other authors demonstrated that *A. baumannii* was the most isolated MDR bacteria in ICU and showed its low level of sensibility to colistin [23,24]. Scientists from Turkey, have conducted a survey in various ICUs and showed an average rate of resistance to carbapenem and to imipenemin *A. baumannii*, which was between 55% and 63% [19]. In the other hand, an epidemiological survey conducted in France showed low percentages of resistance to imipenem, which was estimated between 0% and 5.9%. Recently, this incidence increased to 11% [22]. It has also been demonstrated in South Korea, a lowest carbapenem resistant *A. baumannii* incidence (6 %) [26]. The most explanation for this increase may be the increased overuse of antibiotics, particularly carbapenems and the lack of infection control measures.

Pathological samples and invasive devices distributed among ICU infected patients

The ICU is the epicenter of the high rate of invasive devices uses. This study analyzed and showed the rate of invasive acts performed on patients during their hospitalization with high levels of urinary and venous catherizations (Fig 5). Considering the overall pathological samples and as shown in Fig 6, the high levels were obtained for bronchial aspirations, catheters and blood samples (47%, 29%, and 18% respectively). While the lowest rates were unregistered for pus, cerebrospinal fluid and urine samples which corroborated with other studies [27, 28, 29]. However, a study carried out by Sileem et al. [30] demonstrated a rate of 3.8%, which was lower than our results.

In addition, *A. baumannii* strains were also isolated from blood and catheter samples, each with the same rate (15.79%). Concerning catheters colonized by *A. baumannii*, they represented a low rate of 3.85% by Uwingabiyeet al. [29].

Prevalence of resistant *A. baumannii's* Healthcare Acquired Infections (HAI)

Among the suspected cases of HAI and after the analysis of *A. baumannii* distribution in pathological samples, this work proved that 206 episodes of *A. baumannii* infections were acquired in ICU which dominated by healthcare acquired pneumonia and bacteremia, 39% and 29% respectively (Fig 7). In fact, some studies proved that the respiratory tract infections were the most frequent infections caused by *A. baumannii*, followed by bloodstream infections [19,31,32]. Moreover, Wong et al. [32] noticed that in one well-publicized case, a health care worker developed fulminant pneumonia after inhalation of *A. baumannii* aerosolized during endotracheal suctioning of a ventilated patient. However, other researchers found that pneumonia and bacteremia related to resistant *A. baumannii* were represented with the lowest rates of infection among ICU patients [26, 33].

Risk factors of acquiring MDR *A. baumannii*

This work could be considered as a pilot study in Moroccoto find possible answers to significant risk factors and variables responsible for acquiring infections with the most virulent and damageable MDR *A. baumannii*. According to univariate logistic regression analysis with ($P \leq 0.05$) as shown in table 1, the major significant risk factors for acquiring *A. baumannii* were represented by probabilistic curative antibiotherapy ($P < 10\text{-}3$), directed curative antibiotic therapy ($P < 10\text{-}3$), stay period in ICU ($P < 10\text{-}3$), nasogastric intubation ($P = 0.001$), artificial patients feeding ($P=0.001$) and admission diagnosis with polytrauma ($P = 0.001$). In addition, the invasive devices, such as artificial mechanical ventilation ($P = 0.005$) and the age ($P = 0,031$) were significant clinical and epidemiological risk factors for acquiring MDR *A. baumanni*.

However, according to the multivariate analysis and based on binary logistic regression model and including the Wald test to measure and classify the most important factors related to the acquisition of resistant *A. baumannii* in ICU, only directed curative antibiotic therapy (OR:4.784 ; 95 % CI: 0.002-0.029 ; $P<10\text{-}3$) and probabilistic curative antibiotherapy (OR: 3.177; 95% CI: 0.012-0.150; $P <10\text{-}3$), and were the most dominant and significant clinical and epidemiological factors for acquiring infections with resistant *A. baumannii* related to this study. However, the most commonly reported risk factors in other Moroccan study, are the increased length of ICU stay, the use of invasive medical devices, and the previous use of drug therapy [16]. However, in many carried studies, the known risk factors for *A. baumannii* infections have been proved to be longer ICU stay period, the previous admission to another ward, prior use of antibiotics such as third-generation cephalosporins and immunocompromised patients. In addition neutropenia, malignancy, haemodialysis, and invasive procedures such as assisted mechanical ventilation, central venous catheter, urinary catheter and nasogastric catheter were confirmed to be independent risk factors for acquiring *A. baumannii* infections [14,19,21,25,26].

Outcomes related to *A. baumanni* infections

Were considered as outcomes, the mortality rate as well as the death cases related to acquisition of infections with resistant *A. baumannii*. The mortality rate among *A. baumanni* infected hospitalized patients was 88%. In addition, secondary outcome was defined as the total days stay in ICU and the antibiotic consumption and prescription to infected patients during the period of stay. During the period study, the acquired infection episodes caused longer periods of antibiotic consumption.We also found that more than 18 antibiotics from different classes were prescribed for the patients in this unit, (Fig 3). Another carried study within ICU patients in Rabat confirmed similar results [16]. Huang et al. [22] indicated that *A. baumannii* was involved in high morbidity and mortality among patients in several intensive care units.While, in a relevant European investigation (Spain, Belgium, Germany), a reviewed matched six case-control studies found that the mortality rate is ranged

from 7.8 % to 23% [20]. These results propose the requirement for the earlier retreat of invasive devices in order to prevent the *A. baumannii* colonization and/or infections.

Conclusion

The alarming high rate of incidence, antibiotic resistance of *A. baumannii* in ICU is responsible for a damageable and high level of morbidity and mortality. These outcomes are related to many significant independent risk factors. The increase of *A. baumannii* infections in ICU is explained by a lack of good isolation precautions, insufficient staff numbers and the increasing numbers of patients in short periods, the overuse of antibiotics, particularly the carbapenem antibiotics.

Compliance with Ethical Standards

All authors reported no potential conflicts relevant to this article.

Table 1: Clinical and epidemiological risk factors for extensively drug-resistant *A. baumannii* infections in ICU based on univariate analysis

Clinical and epidemiological factors	Case patients N= 59	Control patients N= 419	Total N=478	P value
Directed curative antibiotictherapy	34 (79,1%)	9 (20,9%)	43	<10-3
Probabilistic curative antibiotherapy	14 (51.9%)	13(48.1%)	27	<10-3
Stayperiod in ICU (≤ 15 days)	33 (7 %)	437 (93 %)	470	<10-3
Admission diagnosis with polytruma	43 (17.1%)	209 (82.9%)	462	0,001
Nasogastric intubation	39 (17.6%)	183 (82.4%)	222	0,001
Artificial patients feeding	81 (33.9%)	198 (66.1%)	239	0,001
Mechanical ventilation	41 (16.5%)	208 (83.5%)	249	0,005
Lack of patients isolation precautions	36 (16.3%)	185 (83.7%)	221	0,019
Age (20-60 years)	50 (12.3%)	419(87.7%)	478	0,031
Comorbidities	54 (16,7%)	408(7,5%)	462	0,079
Central venouscatheter	46 (13.8%)	287 (86,2%)	333	0.111
Preventiveantibiotic of prophylaxis	15 (14.4 %)	89 (85.6 %)	104	0,209
Peripheralvenouscatheter	57 (12.2%)	412 (87,8%)	469	0,247
Sex	45 (13.4%)	291 (69.6%)	478	0,283
Urinarycatheter	58 (12.3 %)	415 (87,7%)	473	0,44
Antibiotic treatment duration (From 8 to 15 days)	10 (12.5%)	70 (77.5%)	80	0,677

NOTE. MDR, multidrug resistant; ICU, intensive care unit.

Fig 1 Clinical and epidemiological characteristics of patients

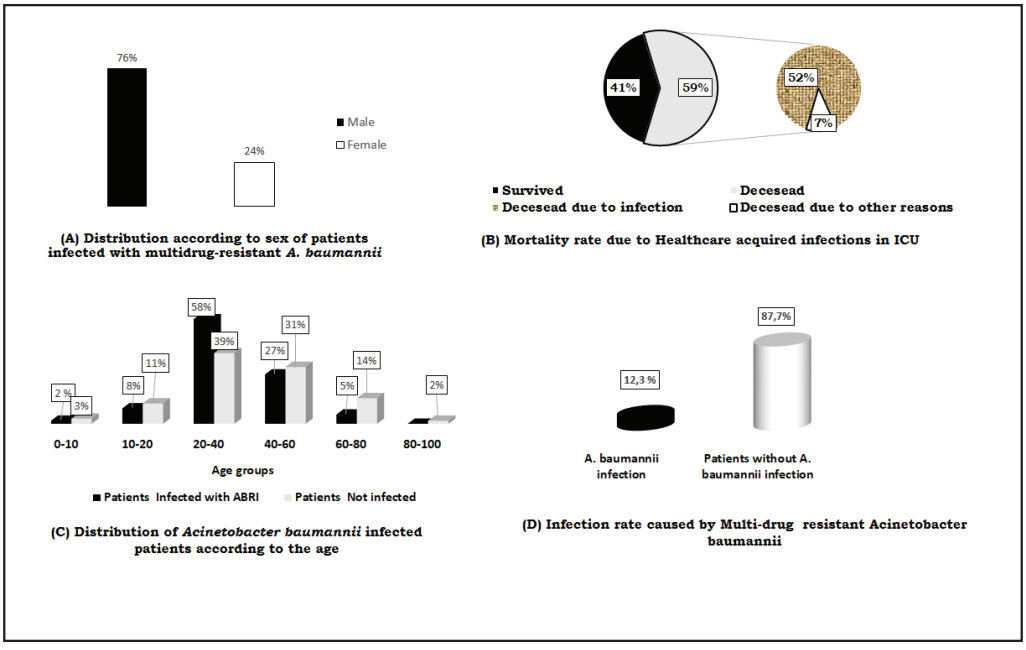


Fig 2 Distribution of bacterial strains isolated from intensive care unit

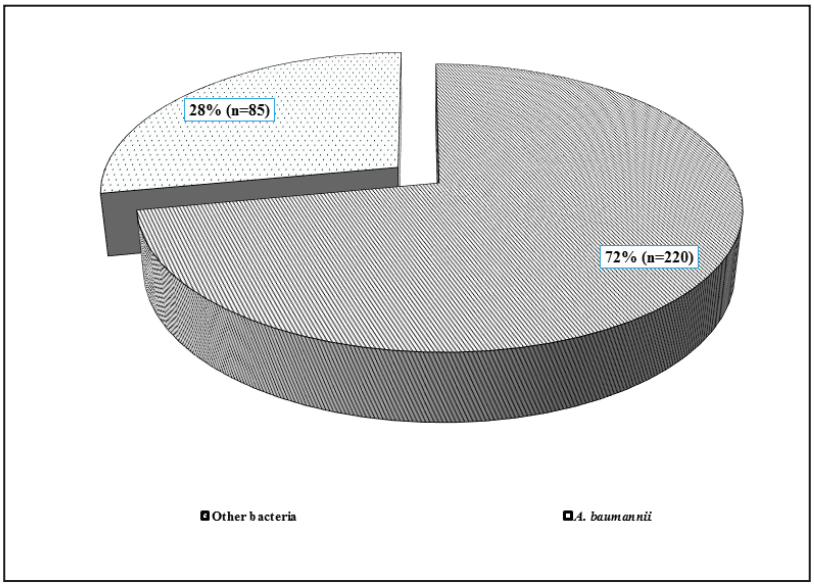


Fig 3 Antibiotic prescription of multi-drug resistant *A. baumannii* infected patients

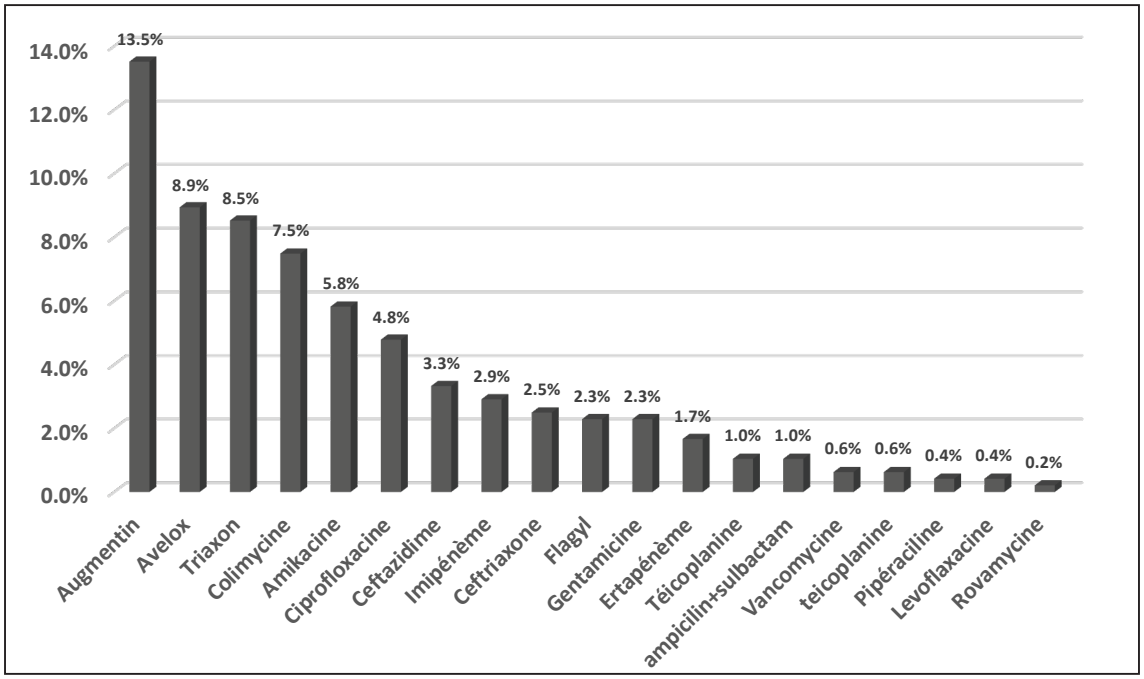


Fig 4 Co-resistance profile of the resistant *A. baumannii* to antibiotics

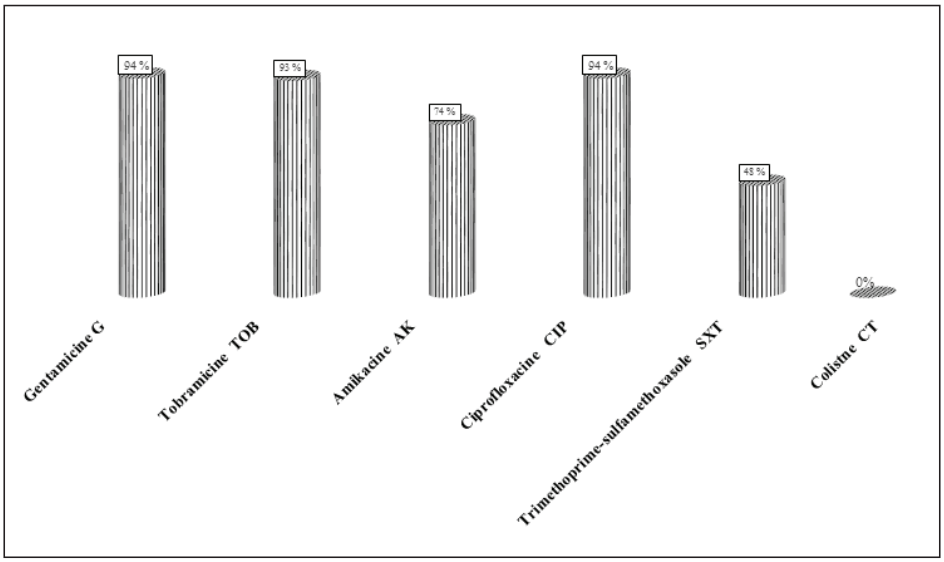


Fig 5 Distribution of *A. baumannii* strains according to the nature of pathological samples

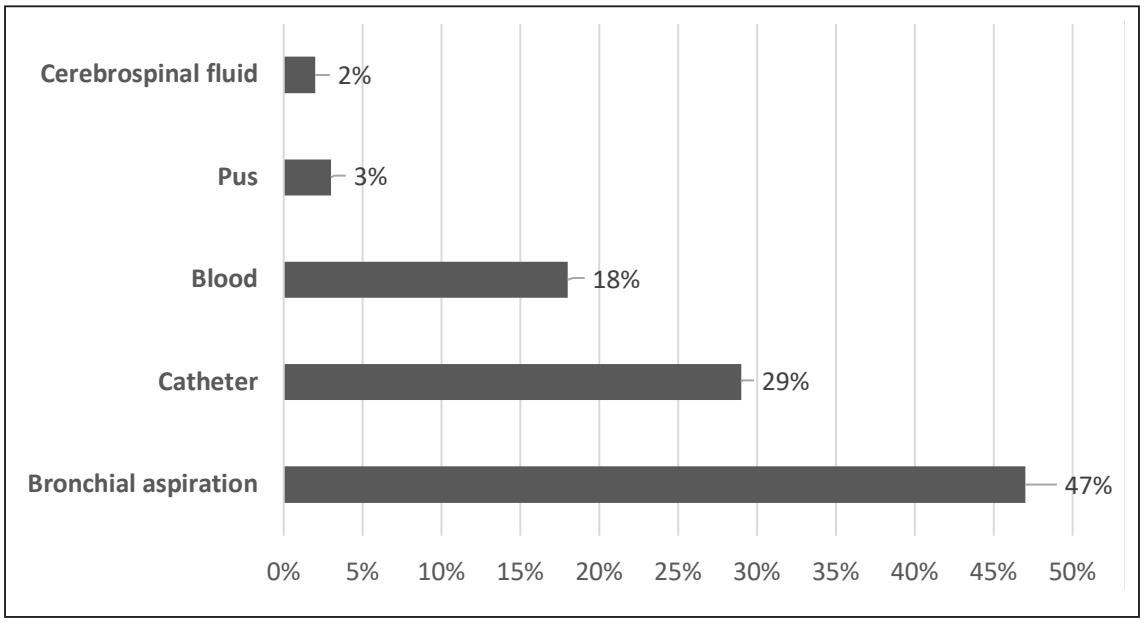


Fig 6 Rate of invasive devices performed on patients during their hospitalization

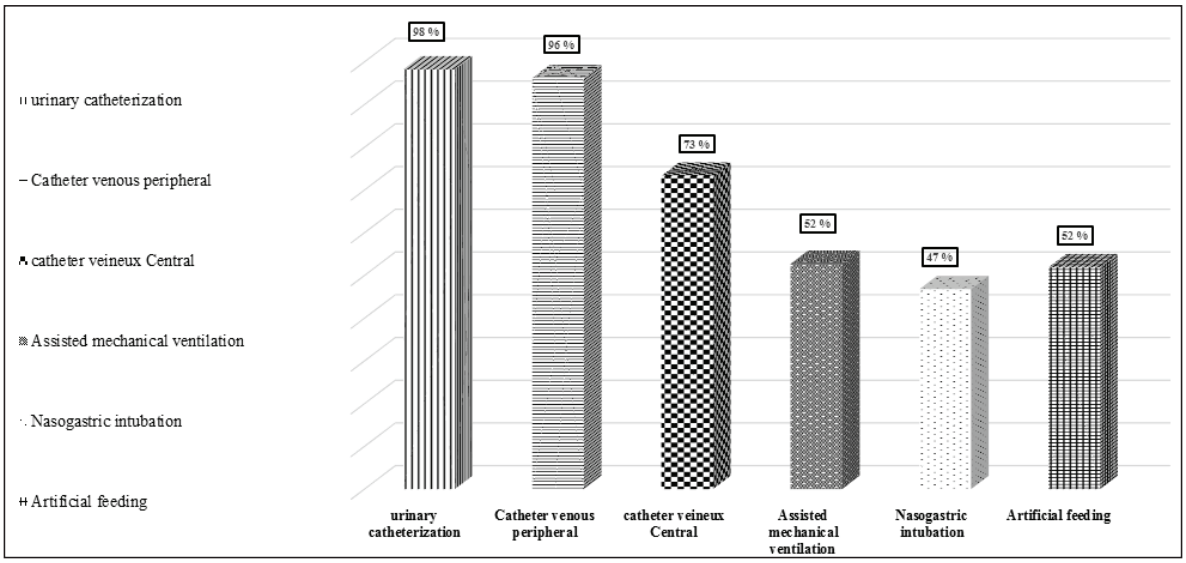
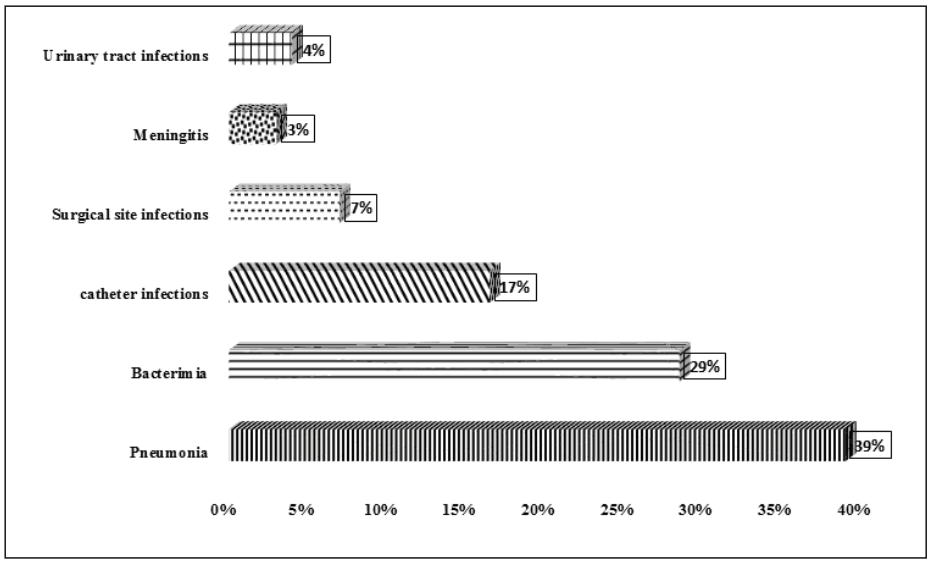


Fig 7 Distribution of healthcare acquired infections caused by resistant *A. baumannii*



References

1- Fournier, P.E.; Richet, H.: The epidemiology and control of *Acinetobacter baumannii* in health care facilities. Clin Infect Dis 42:692—9 (2006).

2- Dima, S.; Kritsotakis, E.I.; Roumbelaki, M.; Metalidis, S.; Karabinis, A.; Maguina, N.: Device-associated nosocomial infection rates in intensive care units in Greece. Infect Control HospEpidemiol 28:602—5 (2007).

3- Catalano, M.; Quelle, L.; Jeric, P.; Di, Martino, A.; Maimone, S.: Survival of *Acinetobacter baumannii* on bed rails during an outbreak and during sporadic cases. J Hosp Infect 42:27-35 (1999).

4- Wendt, C.; Dietze, B.; Dietz, E.; Ruden, H.: Survival of *Acinetobacter baumannii* on dry surfaces. J ClinMicrobiol 35:1394-7 (1997).

5- Suthat, R.; Charurat, S.; Termkiat, K.: Acinetobacter Infection in the Intensive Care Unit. J Infect Dis Antimicrob Agents 22:77-92 (2005).

6- Kalanurian A. A.; Ziai, W.; Mirski, M.: Ventilator-associated pneumonia in the ICU. Crit Care 18:208 (2014).

7- Timsit, J.F.; Soubirou, J.F.; Voiriot, G.: Treatment of bloodstream infections in ICUs. BMC Infect Dis 14:489 (2014).

8- Lin, M.F.; Lan, C.Y.: Antimicrobial resistance in *Acinetobacter baumannii*: From bench to bedside. World J Clin Cases 2:787-814 (2014).

9- Kim, U.J.; Kim, H.K.;An, J.H.; Cho, S.K.; Park, K.H.; Jang, H.C.: Update on the epidemiology, treatment, and outcomes of carbapenem-resistant *Acinetobacter* infections.Chonnam Med J 50:37-44 (2014).

10- Uwingabiye, J.; Frikh, M.; Lemnouer, A.: *Acinetobacter* infections prevalence and frequency of the antibiotics resistance: comparative study of intensive care units versus other hospital units. Pan Afr Med J 23:191 (2016).

11- Elouennass, M. ; Bajou, T. ;Lemnouer, A.H. ;Foissaud, V. ; Hervé, V. ; Baaj, A.J. :*Acinetobacter baumannii*: étude de la sensibilité des souches isolées à l'hôpital militaire d'instruction Mohammed V, Rabat, Maroc. Med Mal Infect 33:361-4 (2003).

12- Playford, E.G.; Craig, J.C.; Iredell, J.R.: Carbapenem-resistant *Acinetobacter baumannii* in intensive care unit patients: risk factors for acquisition, infection and their consequences. The Journal of hospital infection 65(3):204-211 (2007).

13- Maragakis, L.L.; Perl, T.M.:*Acinetobacterbaumannii*: epidemiology, antimicrobial resistance, and treatment options. ClinInfect Dis 46: 1254 – 63 (2008).

14- Baran, G.;Erbay, A.;Bodur, H.;Onguru, P.;Akinci, E.;Balaban, N.: Risk factors for nosocomial imipenem-resistant *Acinetobacter baumannii* infections. Int J Infect Dis 12:16 – 21 (2008).

15- Maragakis, L.L.; Perl, T.M.:*Acinetobacter baumannii*: epidemiology, antimicrobial resistance, and treatment options. Clin Infect Dis 46(8):1254–63 (2008).

16- Jean, U.;Abdelhay, L.; Sabina, B.; Mohammed, F.; Jalal, K.:Intensive care unit-acquired *Acinetobacter baumannii* infections in a Moroccan teaching hospital: epidemiology, risk factors and outcome. GERMS 7(4):193 (2017).

17- Mathai, A.S.; Oberoi, A.; Madhavan, S.; Kaur, P.: *Acinetobacter* infections in a tertiary level intensive care unit in northern India: epidemiology, clinical profiles and outcomes. J Infect Public Health 5:145-52 (2012).

18- Ñamendys-Silva, S.A.; Correa-García, P.;García-Guillén, F.J.: Outcomes of critically ill cancer patients with *Acinetobacter baumannii* infection. World J Crit Care Med 4:258-64 (2015).

19- Murat, D.; OzlemGuzel, T.; Busra, E.; Kenan, H.: Nosocomial imipenem-resistant *Acinetobacter baumannii* infections: Epidemiology and risk factors, Scandinavian Journal of Infectious Diseases, 42:10,741-746 (2010).

20- Matthew, E.; Falagas, A., Bliziotis,; Ilias, I.: Attributable mortality of *Acinetobacter baumannii* infections in critically ill patients: a systematic review of matched cohort and case-control studies. Critical Care 10:R48 (2006).

21- Ashu, S.; Aroma, O.; Sheeba, M.; Parmdeep, K.:Acinetobacter infections in a tertiary level intensive care unit in northern India: Epidemiology, clinical profiles and outcomes. Journal of Infection and Public Health 5, 145—152 (2012).

22- Núñez-Núñez, M.: Navarro, M.D.; Palomo, V.; Rajendran, N.B.; del Toro, M.D.:The methodology of surveillance for antimicrobial resistance and healthcare-associated infections in Europe (SUSPIRE): a systematic review of publicly available information. Clin Microbiol Infect 24:171–174 (2018).

23- Chelazzi, C.; Pettini, E.; Villa, G.; De Gaudio, A.R.: Epidemiology, associated factors and outcomes of ICU-acquired infections caused by Gram-negative bacteria in critically ill patients: An observational, retrospective study. BMC Anesthesiol 15:125 (2015).

24- Ait el kadi, M. ; Aghrouch, M. ; Seffar, M. ; El harti, J. ; Bouklouze, A. : Prévalence des souches d'Acinetobacter baumannii et de Pseudomonas aeruginosa résistantes à l'imipénème par production de métallo-β-lactamases. Med Mal Infect 36:386–389 (2006).

25- Munoz-Price, L.S.; Weinstein, R.A.: *Acinetobacter* infection. N Engl J Med 358:1271—81(2008).

26- Joon Hwan An, M.D.; Yu-Hyoung Kim, R.N. Jung-Eun Moon, R.N.; Jong HaeJeong, R.N.; Su-Hyun Kim, M.D.: Active surveillance for carbapenem-resistant *Acinetobacter baumannii* in a medical intensive care unit: Can it predict and reduce subsequent infections and the use of colistin? American Journal of Infection Control 1; 45(6):667-672 (2017).

27- Namiganda, V.; Mina, Y.; Meklat, A.; Touati, D.; Bouras, N.; Barakate M.; Sabaou, N. : Antibiotic Resistance Pattern of *Acinetobacter baumannii* Strains Isolated from Different Clinical Specimens and Their Sensibility Against Bioactive Molecules Produced by Actinobacteria. Arab J Sci Eng (2019). https://doi.org/10.1007/s13369-019-03893-9.

28- Ben Haj Khalifa, A.; Khedher, M.: Profil de sensibilité aux antibiotiques des souches d'*Acinetobacter baumannii* isolées dans la région de Mahdia. Med. Mal. Infect. 40, 126–128 (2010).

29- Uwingabiye, J.; Frikh, M.; Lemnouer, A.; Bssaibis, F.; Belefquih, B.; Maleb, A.; Dahraoui, S.; Belyamani, L.; Bait, A.; Haimeur, C.; Louzi, L.; Ibrahimi, A.: *Acinetobacter* infections prevalence and frequency of the antibiotics resistance: comparative study of intensive care units versus other hospital units. PAMJ 23, 191–197 (2016).

30- Sileem, A.E.; Said, A.M.; Meleha, M.S.: *Acinetobacter baumannii* in ICU patients: A prospective study highlighting their incidence, antibiotic sensitivity pattern and impact on ICU stay and mortality. Egypt J. Chest Dis. Tuberc. 66, 693–698 (2017).

31- Delbos, V.: Manifestations cliniques et traitement des infections à *Acinetobacter baumannii*. RFL 441, 59–65 (2012).

32- Wong, D.; Nielsen, T.B.; Bonomo, R.A.; Pantapalangkoor, P.; Luna, B.; Spellberg, B.: Clinical and pathophysiological overview of *Acinetobacter* infections: a century of challenges. Clin. Microbiol. Rev. 30, 409–447 (2017).

33- Cisneros, M.J.; Rodríguez-Baño, J.: Nosocomial bacteremia due to *Acinetobacter baumannii*: epidemiology, clinical features and treatments. Clin. Microbiol. Infect. 8, 687–693 (2002).