International Journal of Sciences & Applied Research

www.ijsar.in

CURRENT INCIDENCE OF CARBAPENEM RESISTANCE AND THERAPEUTIC CONSEQUENCES

Anass Sakhi[1-2]*, LeilaEl Omari[1-2], TahaEl Meghraoui[1-2], Mouhcine Miloudi[1-2], Youssef El Kamouni[1-2], Said Zouhair[1-2], Lamiae Arsalane[1-2]

[1]Department of Microbiology-Virology and Molecular Biology. Avicenne military hospital, Marrakesh, Morocco
[2] Faculty of medicine and pharmacy of Marrakesh, Cadi Ayyad University, Marrakesh, Morocco
***Corresponding author:** SAKHIANASS@GMAIL.COM

ABSTRACT

Bacterial multi-resistance is currently a major problem in our hospitals, because of the morbidity and mortality it generates mainly in intensive care and intensive care settings, and also a current medical problem. The objective of this study was to describe the epidemiological profile, frequency, and resistance status of bacteria resistant to Carbapenems at the Avicenne military hospital in Marrakech, over a period of 7 years from 2015 to 2021.

This is a retrospective descriptive study of all the highly resistant bacteria identified from the database of the microbiology department at the HMA in Marrakech. The results show that the general prevalence of these HRBs was 7.54%, with a clear predominance of Carbapenem-resistant *Acinetobacter baumannii* (53.4%), followed by Carbapenem-resistant *Klebsiella pneumoniae* (20.68%), then Carbapenem-resistant *Enterobacter cloacae* (9.57%), and finally Carbapenem-resistant *Pseudomonas aeruginosa* (6.17%).

The general evolution of isolated HRBs was marked by the gradual and continuous increase in the prevalence of these bacteria during the study period, with a peak in 2020, when the prevalence reached 13.98%.

High co-resistance has been found to several antibiotic molecules, which can be administered as an alternative.

The rationalization of the prescription of antibiotics and the rigorous application of hygiene and prevention rules will make it possible to limit the emergence of these multi and highly resistant bacteria in our care structures.

Knowledge of the bacteriological profiles and rates of resistance to antibiotics of this type of bacteria will allow treatment more adapted to each hospital context, and better targeted.

Keywords: Carbapenem resistance, Highly resistant bacteria, Multi resistant bacteria, Co-resistance.

INTRODUCTION

With the worsening of the bacterial resistance crisis, the resistance of gram-negative bacteria to carbapenems poses a real clinical challenge, as these molecules have long been considered the most effective against multi-resistant gram-negative bacteria. Indeed, in the global priority list of antibiotic-resistant bacteria published by the WHO in 2017, 3 of the 4 pathogenic species designated as critical priority for the development and research of new antibiotic molecules, includes carbapenem-resistant *Enterobacteriaceae*, carbapenem-resistant *Pseudomonas aeruginosa* and carbapenem-resistant *Acinetobacter baumannii* [1]. The main elements that define the risk of carbapenem resistance include the increasing incidence of these pathogens worldwide [2], the lack of effective and tolerated molecules once the efficacy of carbapenems is lost [3] and the high mortality rate due to carbapenem-resistant GNB infections [4].

This situation has required a renewed interest in the development of new molecules effective against these pathogens. These efforts have led to the discovery of new molecules that fight carbapenem-resistant GNB, such as Cefiderocol, which could find their place in clinical practice [5].

The aim of this study is to determine the current frequency of carbapenem resistance and to clarify its therapeutic consequences.

MATERIALS AND METHODS

This is a retrospective descriptive study, based on data from the microbiology laboratory of the Avicenne military hospital of Marrakech (AMH). This study was conducted on all diagnostic samples from inpatients or outpatients, received between 01 January 2015 and 19 August 2021.
Isolation of bacterial strains was performed on enriched and selective agar media incubated at 37°C for 24 to 48 hours.

Bacterial identification was based on the study of morphological, cultural and biochemical characteristics (API 20E and NH galleries), completed by an automated identification by the Phoenix® M50 automated system.

After isolation and identification of the bacterial strain, an antibiotic susceptibility test is performed by an automated method using micro-dilutions in liquid medium with the Phoenix® automated system, which determines MICs, as well as the measurement of inhibition diameters by the diffusion method of antibiotic discs in Mueller-Hinton (MH) agar medium on Petri dishes incubated at 37°C for 24 hours.

MICs and inhibition diameters are thus compared to EUCAST references in order to determine the sensitivity profile of bacterial strains.

RESULTS

1- Overall prevalence

The number of carbapenem-resistant bacteria was 324, out of a total number of isolated bacteria of 4293, i.e. a prevalence of 7.54%. *Acinetobacter baumannii* was the most common strain isolated, followed by *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterobacter aerogenes* and finally *Proteus mirabilis*, out of all the bacteria isolated during the study period (Figure1).

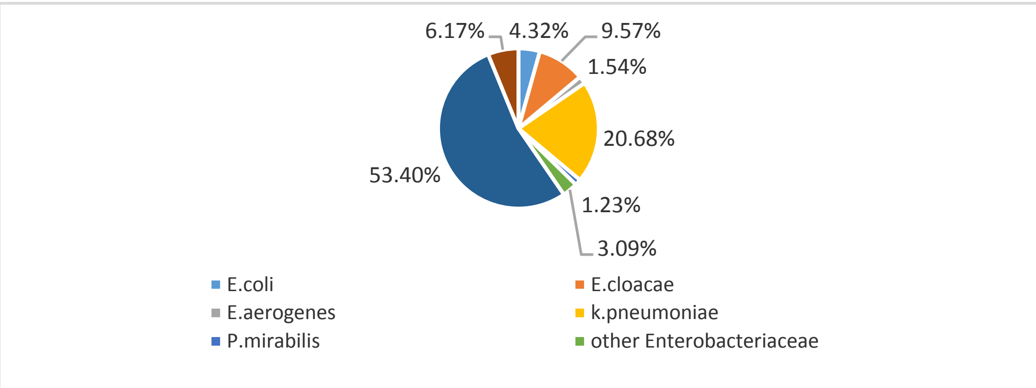

Figure-1: Distribution of carbapenem-resistant bacteria

2- Gender distribution

Males represent the majority of patients infected with carbapenem-resistant germs with a M/F sex ratio of 3.28.

3- Distribution according to the nature of the samples

The distribution of carbapenem-resistant bacteria revealed a predominance of PSB with 23.09%, followed by pus samples with 20.20%, then UCBE with 19.16%, BAL fluids with 14.43%, blood cultures with 11.81%, sputum with 3.67%, central venous catheters and biopsies with 2.62% each, peripheral venous catheters with 0.78%, pleural fluids with 0. 52% and lastly lumbar punctures, urinary catheters and as cites fluids.

- CREB was found mainly in urine and pus.
- CRAB was isolated mainly from PSB, BAL, and blood cultures.
- CRPA was isolated largely from PSB and pus specimens.

PSBs were the main site of isolation of carbapenem-resistant bacteria of all species, but dominated by CRAB. Therefore, ventilator-associated pneumonia in the resuscitation setting was caused primarily by CRAB. Urinary tract infections and suppurative infections were dominated by CREB. Bacteremia and systemic infections were dominated by CRAB but also by CREB.

4- Distribution according to hospital services:

The largest number of isolates of carbapenem-resistant bacteria was in the intensive care units with a percentage of 59.58%, followed by surgical units with a percentage of 16.79%, medical units constitute 6.82% of isolates while the rest came from outpatients (14.69%) and patients consulting in the emergency departments of the AMH (2.09%) (Figure No.2).

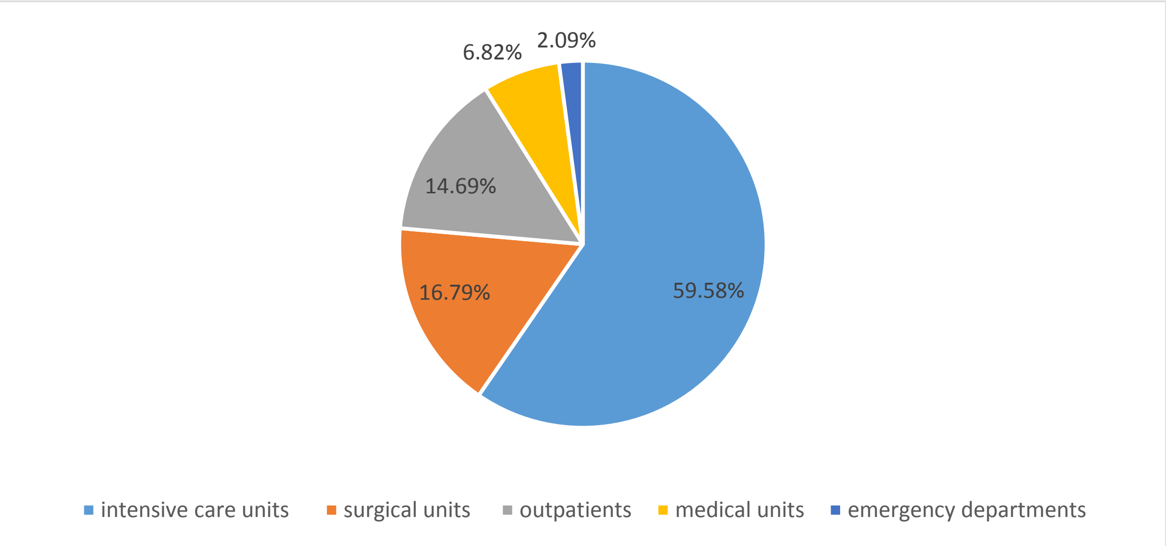

Figure-2: Distribution of carbapenem-resistant bacterial isolates by hospital department

5- Evolution of the prevalence according to the years

The evolution of the rate of HRB isolated in the microbiology laboratory of the AMH, was marked by an increase in 2016 from 5.09% to 8.80%, then a stagnation around 8% between 2016 and 2019, followed by a significant rise in 2020 with a percentage reaching 13.98%, as well as a decrease in 2021.

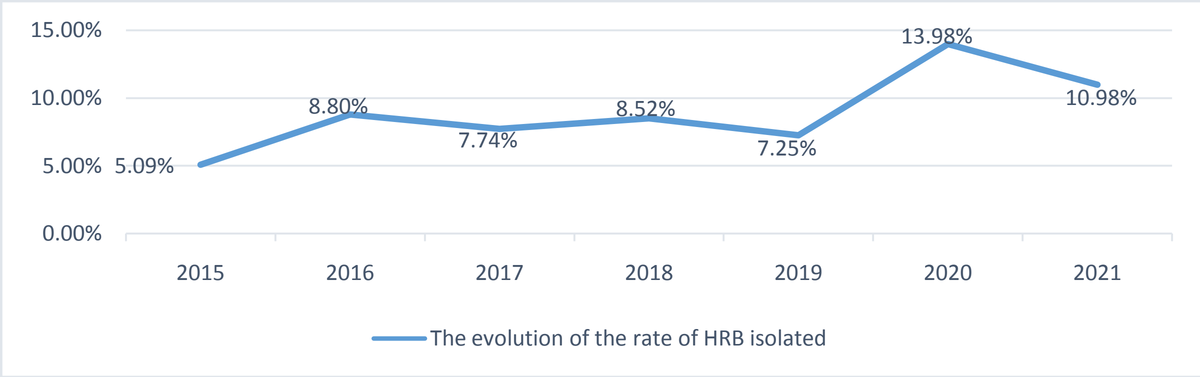

Figure-3 : Evolution of the prevalence of HRB isolated in our study

6- Co-resistance associated with carbapenems

The interest of studying the frequency of carbapenem resistance lies in its therapeutic consequences. Indeed, they lead to therapeutic failures and impasses, thus increasing the length of hospitalization and the mortality rate. Figures 4, 5 and 6 show the antibiotic resistance profile of the different bacterial species isolated.

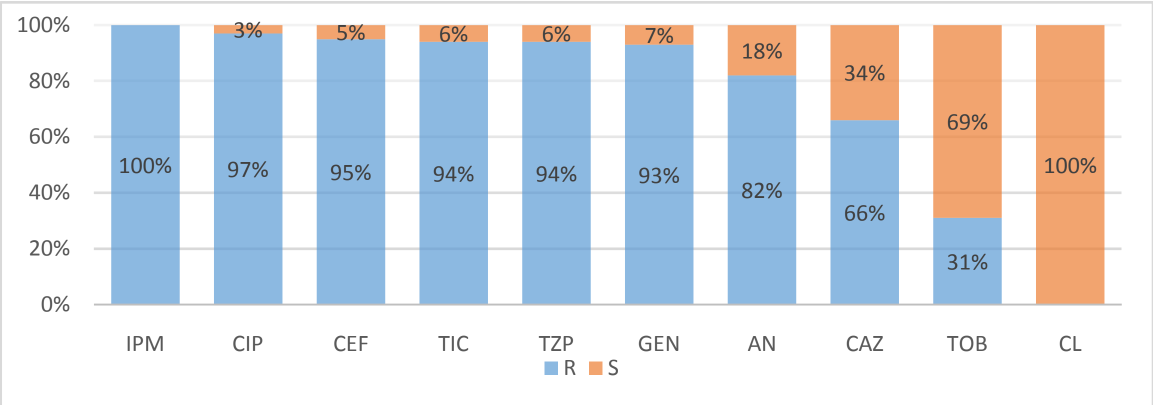

Figure-4: Antibiotic resistance profile of isolated CRAB strains.

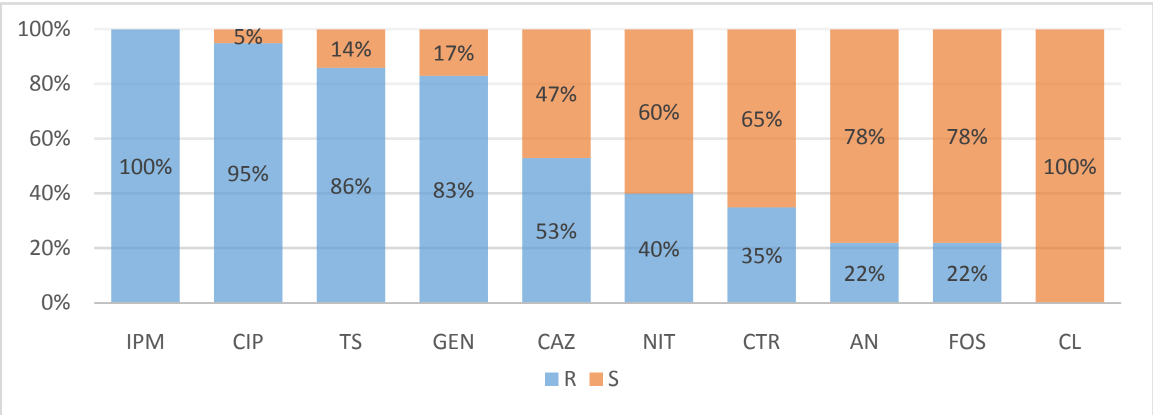

Figure-5: Antibiotic resistance profile of isolated carbapenem-resistant strains of *Klebsiella pneumoniae*.

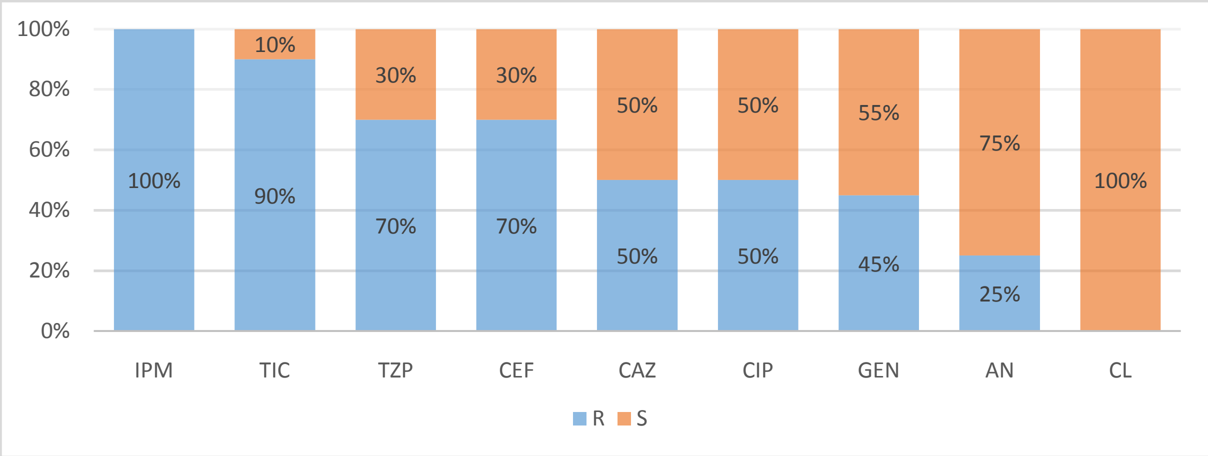

Figure-6: Antibiotic resistance profile of isolated CRPA strains.

DISCUSSION

1- Overall prevalence

In a study done in the framework of a thesis work at the Hassan II University Hospital of Fez in 2012, about multi-resistant bacteria, the prevalence of MRB was 11.8%, that is to say 420 MRB out of a total number of isolated bacteria of 3559. [6]

In another Moroccan study, done in the Avicenne military hospital in Marrakech published in 2010, the prevalence of MRB was high reaching 20%, that is 84 MRB out of a total number of 414 bacteria isolated from the different samples emanating from the hospital's resuscitation department. [7]

Table-1: Comparison of HRB prevalence.

	Our study	**India 2014[8]**	**UHC Hassan II Fès 2012[6]**	**AMH Marrakech 2010 [7]**
HRB prevalence	7,54%	13,8%	11,8%	20%

The prevalence of HRB found in our study was distinctively the lowest compared to the literature data.

In the Indian study, the trend of the results was not in accordance with the data of our study, where broad spectrum B-lactamase producing *Enterobacteriaceae* and carbapenemase producing *Enterobacteriaceae* were the dominant ones, among the HRB isolated with a number of 53 or 41% (predominantly *K. pneumoniae* n=25 or 19%), followed by MRSA n=38 or 29%, then *Pseudomonas aeruginosa* n=29 or 22%, and finally *Acinetobacter baumannii* with a number of 8 or 6%. [8]

According to a prospective descriptive study, which was conducted at the level of the microbiology department of the UHC Tlemcen from October 15, 2016 to February 28, 2017 (a period of 4 months and a half) about the prevalence of MRB in the intensive care unit on sampling of materials. *Enterobacteria* occupied the 1st place with a percentage of 44%, followed by *Acinetobacter baumannii* 37%, then *Pseudomonas aeruginosa* 10%, and finally MRSA with a percentage of 9%. [9]

In a Moroccan study, done at the Hassan II University Hospital in Fez, the distribution was almost in line with the previous study, of which ESBL *Enterobacteriaceae* were the most frequently isolated MRB (n=199), followed by carbapenem-resistant *Acinetobacter baumannii* (n=163), and finally Ceftazidime-resistant *Pseudomonas aeruginosa* (n=38),. [6]

2- Gender distribution

According to the Algerian study, the distribution of isolates according to sex showed a male predominance with a sex ratio of 1.17 [9], which is in line with the results of our study.

In the same context, and in a Moroccan study, carried out at the Hassan II University Hospital in Fez, about MRB, the distribution of isolates according to sex, also showed a male predominance with a sex ratio of 1.61. [6]

3- Distribution according to the nature of the samples

The infectious profile in our study is different from that of the study of the Hassan II University Hospital of Fez, which was restricted to MRB, in which urinary tract infections were predominant, they represented 23.3%, followed closely by pneumonia (22.1%) and sepsis (21.4%), then suppurations (19.5%), catheter infections (6.1%) and ascites fluid infections (2.1%). [6]

4- Distribution according to hospital departments

In the Indian study, the results were not totally consistent with our own, where surgical wards accounted for the majority of isolated HRBs with a proportion of 28.1%, followed by intensive care units 17.8%, then medical wards 15%. [8]

In the Moroccan study of the Hassan II University Hospital of Fez, the intensive care unit also came first among the services at the origin of the MRBs with 45%, followed by the surgical services (19%), then the medical services (14%). [6]

5- Evolution of the prevalence according to the years

The results of our study were different from those found in a study done in the same laboratory, published in 2010, concerning the MRB, where the trend was a slight decrease throughout the 3 years of study since 33 MRB (7.97%) were isolated from October 2006 to September 2007, 26 (6.28%) MRB from October 2007 to September 2008, and 25 (6%) from October 2008 to September 2009 [7]

6- Co-resistance associated with carbapenems

In the same trend of our results, a Brazilian study made at the University Hospital of São Paulo, about the emergence and persistence of multi and highly resistant strains of *Acinetobacter baumannii* between 2008 and 2014, where the results objectified that the highly resistant strains (XDR) and resistant to Carbapenems, had an associated resistance to Ciprofloxacin and Piperacillin-tazobactam reaching 100%, a resistance to Cefepime of 98%, to Ceftazidime of 96%, and to Gentamycin of 76,6%. [10]

In comparison with a Canadian study on the antibiotic resistance profile of highly resistant strains of *Pseudomonas aeruginosa* strains, the results were almost consistent and comparable with regard to resistance associated with Ciprofloxacin and Ceftazidime with 47% and 41% of resistance respectively, but different with regard to resistance to Pipercillin-Tazobactam and Amikacin, where resistance was 30.9% and 12.4% respectively, while all the strains were totally sensitive to Colistin, exactly as our results show. [11]

In comparison with an American study, the resistance profile of CREB isolated in this study was almost comparable with our results, where they showed very high associated resistance to Ciprofloxacin and Cotrimoxazole, and very low resistance to colistin and Amikacin. [12]

CONCLUSION

Antibiotic resistance is one of the most serious threats to global health today. It is the cause of prolonged hospitalizations and leads to increased mortality and medical expenses. A better knowledge of the local bacterial ecology allows the establishment of guidelines based on objective data.

In addition to the research and development of new antibiotics, the basic measures of prevention and control of infections with multi or highly resistant bacteria, remain fundamental and essential to avoid their spread and emergence.

Since the spread of resistance is also closely correlated to the extent of selection pressure, the only hope is to try to delay this spread through the careful, targeted and reasoned use of antibiotics.

It is also essential to develop and update the various surveillance programs of bacterial resistance to antibiotics, at the local and national levels, in order to ensure a dynamic and targeted adaptation of the various therapeutic and prophylactic protocols with respect to this type of bacteria.

POTENTIAL CONFLICT OF INTEREST

None declared.

AUTHORS CONTRIBUTION

All authors have contributed to the conduct of this work. All authors also declare that they have read and approved the final version of the manuscript.

ETHICAL CONSIDERATION

All the data has been collected anonymously following patient confidentiality.

LIST OF ABBREVIATIONS

AMH: Avicenne military hospital
AN: Amikacin
BAL: Bronchoalveolar lavage
CAZ: Ceftazidime
CEF: Cefepime
CIP: Ciprofloxacin
CL: Colistin
CRAB: Carbapenem-resistant *Acinetobacter baumannii*
CREB: Carbapenem-Resistant *Enterobacteriaceae*
CRPA: Carbapenem-resistant *Pseudomonas aeruginosa*
CTR: Cetriaxone
ESBL: Extended-spectrum betalactamase
EUCAST: European committee on antimicrobial susceptibility testing
FOS: Fosfomycin
GEN: Gentamicin
HRB: Highly Resistant Bacteria
IMP: Imipenem
MIC: Minimum inhibitory concentration
MRB : Multi-resistant bacteria
MRSA: methicillin-resistant *Staphylococcus aureus*
PSB : Protected specimen brush
TIC : Ticarcillin
TOB : Tobramycin
TS : Trimethoprim- Sulfamethoxazole
TZP: Piperacillin - Tazobactam
UCBE : Urine cytobacteriological examination
UHC: University Hospital Center
WHO: World Health Organization
XDR : Extensively-drug-resistant

REFERENCES

[1] Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, Pulcini C, Kahlmeter G, Kluytmans J, Carmeli Y, Ouellette M, Outterson K, Patel J, Cavaleri M, Cox EM, Houchens CR, Grayson ML, Hansen P, Singh N, Theuretzbacher U, Magrini N; WHO Pathogens Priority List Working Group. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018 Mar;18(3):318-327. doi: 10.1016/S1473-3099(17)30753-3. Epub 2017 Dec 21. PMID: 29276051.

[2] van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence. 2017 May 19;8(4):460-469. doi: 10.1080/21505594.2016.1222343. Epub 2016 Aug 11. PMID: 27593176; PMCID: PMC5477705.

[3] Morrill HJ, Pogue JM, Kaye KS, LaPlante KL. Treatment Options for Carbapenem Resistant Enterobacteriaceae Infections. Open Forum Infect Dis. 2015 May 5;2(2):ofv050. doi: 10.1093/ofid/ofv050. PMID: 26125030; PMCID: PMC4462593.

[4] Falagas ME, Tansarli GS, Karageorgopoulos DE, Vardakas KZ.Deaths attributable to carbapenem-resistant Enterobacteriaceae infections. Emerg Infect Dis. 2014 Jul;20(7):1170-5. doi: 10.3201/eid2007.121004. PMID: 24959688; PMCID: PMC4073868.

[5] Doi Y. Treatment Options for Carbapenem-resistant Gram-negative Bacterial Infections. Clin Infect Dis. 2019 Nov 13;69(Suppl 7):S565-S575. doi: 10.1093/cid/ciz830. PMID: 31724043; PMCID: PMC6853760.

[6] El brahmi R.PROFIL EPIDEMIOLOGIQUE ET DE RESISTANCE DES BACTERIES MULTI RESISTANTES AU CHU HASSAN II DE FÈS. http://www.chu-fes.ma/profil-epidemiologique-et-de-resistance-des-bacteries-multi-resistantes-au-chu-hassan-ii-de-fes/http://www.chu-fes.ma/profil-epidemiologique-et-de-resistance-des-bacteries-multi-resistantes-au-chu-hassan-ii-de-fes/

[7]L. Arsalane L, Qamouss Y, Chafik A, Boughalem M, Louzi L.
Epidémiologie des bactéries multi résistantes dans un service de réanimation polyvalente d 'un hôpital universitaire de Marrakech entre octobre 2006 et septembre 2009. LES TECHNOLOGIES DE LABORATOIRE - 2010, Volume 5, N°21

[8]Basak S, Singh P, Rajurkar M. Multidrug Resistant and Extensively Drug Resistant Bacteria: A Study. J Pathog. 2016;2016:4065603. doi: 10.1155/2016/4065603. Epub 2016 Jan 28. PMID: 26942013; PMCID: PMC4749793.

[9]Meriah S, Nabi I, Khatir S, Bousselham A."L'incidence des bacteries multi-resistantes ' bmr' en reanimation chu tlemcen : interet du portage digestif du 15 octobre 2016 au 28 fevrier 2017," 2017.https://www.theses-algerie.com/1963841946928939/memoire-de-fin-detude/universite-abou-bekr-belkaid-tlemcen/lincidence-des-bacteries-multiresistantes-bmr-en-reanimation-chu-tlemcen-interet-du-portage-digestif-du-15-octobre-2016-au-28-fevrier-2017?size=n_10_n

[10] Tavares LCB, de Vasconcellos FM, de Sousa WV, Rocchetti TT, Mondelli AL, Ferreira AM, Montelli AC, Sadatsune T, Tiba-Casas MR, Camargo CH.Emergence and Persistence of High-Risk Clones Among MDR and XDR *A. baumannii* at a Brazilian Teaching

Hospital. Front Microbiol. 2019 Jan 4;9:2898.doi:0.3389/fmicb.2018.02898. PMID: 30662431; PMCID: PMC6328482.

[11] McCracken MG, Adam HJ, Blondeau JM, Walkty AJ, Karlowsky JA, Hoban DJ, Zhanel GG, Mulvey MR; Canadian Antimicrobial Resistance Alliance (CARA) and CANWARD. Characterization of carbapenem-resistant and XDR Pseudomonas aeruginosa in Canada: results of the CANWARD 2007-16 study. J Antimicrob Chemother. 2019 Aug 1;74(Suppl 4):iv32-iv38. doi: 10.1093/jac/dkz285. PMID: 31505643.

[12] Little ML, Qin X, Zerr DM, Weissman SJ. Molecular diversity in mechanisms of carbapenem resistance in paediatric Enterobacteriaceae. Int J Antimicrob Agents. 2012 Jan;39(1):52-7.doi:0.1016/j.ijantimicag.2011.09.014. Epub 2011 Nov 3. PMID: 22055532; PMCID: PMC3237943.