**Risk factors for septic shock from healthcare-associated infections in the intensive care unit of Algiers: “About a cohort study”**

**T. Ait Mouheb**, O. Benrabah L. Ait mokhtar, M. Slimani, Z.Amine, M. Benouanes, F. Labaci

Introduction: Healthcare-associated infections are a public health problem worldwide. Increasingly serious in poor countries where indicators of quality of life remain poor. The consequences on morbidity and mortality are linked to lack of human and material resources, poor organization due to the absence of regulations and the lack of representative surveillance data. The prognosis of these patients is conditioned by regular monitoring of the bacterial ecosystem, the proper use of antibiotics and the emergence of increasingly resistant strains in particular, Acinetobacter baumanii.

Materials and methods: After approval of the ethics committee and consents obtained from patients admitted to the intensive care unit. We carried out a descriptive analytical cohort study spread over a period of two years from December 1, 2019 until January 31, 2021, including all patients over 18 years old, hospitalized in the UMC department in which we collected all infections linked to healthcare. Furthermore, we carried out a multivariate study by logistic regression with the following variable as dependents variables: Occurrence of septic shock with or without high lactate levels (>02 mmol/l). We included the following variables in the model (Age, hypertension, diabetes, stroke, heart disease, hypoximiant pneumonia, VAP, COPD, head trauma, polytrauma, acute pancreatitis, acute endocarditis, Guillain-barré syndrome, nosocomial infections (Acinetobacter baumanii, Klebsiella pneumoniae, central line sepsis, urine sepsis, lactate level >02 mmol/l and length of hospital stay. the initial model includes all the variables at 0.2 of degree of significance and the variables described in the literature as being risk factors for septic shock, in order to eliminate the confounding factors in the logit equation of logistic regression

Results: The specific incidence of Acinetobacter baumanii infections was 26%.

54 samples were positive among those taken from patients with signs of sepsis and (QSofa and Sofa more than 02 points). Acinetobacter baumanii was the most identified germ with a relative frequency of 40% and was respectively resistant to carbapenems in 90%, ceftazidime in 93% of cases, and ciprofloxacin in 49% of cases. Strains tested for sensitivity to colistin were consistently susceptible except in a single case. From the initial model, after having introduced all the independents variables of the study, to explain the occurrence of septic shock (dependent variable) (tab….). in the final model of the multivariate, Klebsiella pneumoniae infection; p = 0.001 - 95% CI- ORa = 9.92 (2.7-36.7) and antibiotic resistance against Acinetobacter baumannii p=0.022 ORa=6.14(1.3-28.9), are significantly linked to septic shock.

Discussion: In our study, the resistance of Acinetobacter baumanii to carbapenems and other antibiotics, as observed in our study.compared to what has been reported in other studies, as an independent risk factor for infection with acinetobacter baumani (OR: 4.11 [1.58–10.73]) and essentially the use of carbapenems (OR: 5.22 [1.99–13.67])

**Introduction:**

Healthcare-associated infections constitute a real public health problem. This increases the cost of caring for patients admitted to the intensive care unit, but also their mortality [1,2]. Around 60% of deaths [3]. Healthcare-associated pneumonia is responsible for the increase in frequency of 10 and 40%, it is 1.9 to 18 per 1000 hours of mechanical ventilation [4,5,6] . Infections on central intravascular catheters represent the second cause [7,8]. followed by urinary infections more than 40% of all associated infections [9].

Poor prognosis factors are mainly linked to the presence of comorbidities and the resistance of bacteria to antibiotics [10,11]. The World Health Organization has identified the problem of antibiotic resistance as a real threat to public health [11]. The rapid emergence of increasingly resistant bacteria compromises the efficacy of antibiotics [11,12]. Antibiotic resistance of bacteria is classified into BMR (multi-resistant bacteria), BHR (highly resistant bacteria) and BPR (pan-resistant bacteria). The U.S. Centers for Disease Control and Prevention (CDC) estimates that more than 2 million people in the United States are infected with BMRs each year and at least 23,000 die from these infections [ 13].

The main multi-resistant bacteria (MDR) responsible for severe infections are represented by methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), multi-drug resistant Pseudomonas aeruginosa (MDR), Acinetobacter baumannii resistant to imipenem, Escherichia coli and Klebsiella pneumoniae resistant to third generation cephalosporins. Extended-spectrum β-lactamase (ESBL)-producing pathogens and MRSA are rampant. Carbapenems are the last bastion of defense against non-Enterobacteriaceae pathogens such as A. baumannii and P. aeruginosa. Increasing resistance to carbapenems or fluoroquinolones will constitute a major threat in the future [14,15]. The link between the emergence of antibiotic resistance in healthcare units and antibiotic consumption has been well demonstrated by several studies [16,17].

Risk factors for BMR infection in intensive care units are variable and differ depending on the populations studied and the different bacterial ecosystems. Factors related to patient comorbidities, use of medical devices and factors related to the hospital environment. This allowed the identification of certain so-called “modifiable” risk factors [18,19]. The incidence and severity of BMR infections could decrease in intensive care units provided that prevention and treatment are optimized based on knowledge and documentation of modifiable risk factors [20,21].

**Materials and methods:** After approval of the ethics committee and consents obtained from patients admitted to the intensive care unit. We carried out a descriptive analytical cohort study spread over a period of two years from December 1, 2019 until January 31, 2021, including all patients over 18 years old, hospitalized in the UMC department in which we collected all infections linked to healthcare. Furthermore, we carried out a multivariate study by logistic regression with the following variable as dependents variables: Occurrence of septic shock with or without high lactate levels (>02 mmol/l). We included the following variables in the model (Age, hypertension, diabetes, stroke, heart disease, hypoximiant pneumonia, VAP, COPD, head trauma, polytrauma, acute pancreatitis, acute endocarditis, Guillain-barré syndrome, nosocomial infections (Acinetobacter baumanii, Klebsiella pneumoniae, central line sepsis, urine sepsis, lactate level >02 mmol/l and length of hospital stay. the initial model includes all the variables at 0.2 of degree of significance and the variables described in the literature as being risk factors for septic shock, in order to eliminate the confounding factors in the logit equation of logistic regression. (Tab 01)

**Results:** The specific incidence of Acinetobacter baumanii infections was 26%.

54 samples were positive among those taken from patients with signs of sepsis and (QSofa and Sofa more than 02 points). Acinetobacter baumanii was the most identified germ with a relative frequency of 40% and was respectively resistant to carbapenems in 90%, ceftazidime in 93% of cases, and ciprofloxacin in 49% of cases. Strains tested for sensitivity to colistin were consistently susceptible except in a single case. From the initial model, after having introduced all the independents variables of the study, to explain the occurrence of septic shock (dependent variable) (tab 01). The final model of the multivariate analysis by step-by-step descending logistic regression showed that the following explanatory variables remained statistically significant (P 0.05): Klebsiella pneumoniae infection; p = 0.001 - 95% CI, ORa = 9.92 (2.7-36.7); urinary sepsis p = 0.007 95% CI, ORa = 5.53 (1.6-19.16); Hyperlactatemia p=0.0001 95% CI ORa=19 (5.13-69.5) and antibiotic resistance against Acinetobacter baumannii p=0.022 ORa=6.14(1.3-28.9). (Tab 02).

In conclusion in our study: Klebsiella pneumoniae infection increases the risk of occurrence of septic shock by 9.9 times - ORa = 9.92 (2.7-36.7); by 5.5 times for urinary sepsis -ORa= 5.53 (1.6-19.16); by 19 times for hyperlactatemia ORa=19 (5.13-69.5) and by 6 times for antibiotic resistance for acinetobacter baumannii ORa=6.14(1.3-28.9)

**Discussion:** A.Baumannii were reported >50% of all isolates were resistant to carbapenems, quinolones and aminoglycosides, Much lower than our results at 90%.[22].The resistance of Acinetobacter baumanii to carbapenems and other antibiotics, as observed in our study (Tab 03).

compared to what has been reported in other studies, as an independent risk factor for infection with acinetobacter baumani (OR: 4.11 [1.58–10.73]) [23], and essentially the use of carbapenems (OR: 5.22 [1.99–13.67]) [24]. Carbapenem resistance was 52.6% and colistin resistance was 17.9% in K. pneumoniae isolates and both increased over 3 years. When carbapenem-resistant K. pneumoniae infections were compared with carbapenem-sensitive K. pneumoniae infections, the independent risk factors associated with carbapenem resistance were found to be carbapenem use (p=0.008, OR: 8.45, 95% CI: 1.76-40.64), prior NI developing with different microorganism (p=0.005, OR: 8.70, 95% CI: 1.91-39.65) and total parenteral nutrition (TPN) use (p=0.04, OR: 4.2, 95% CI: 1.06-16.67) [25].n this study the risk is multiplied by 9 times. Almost identical result observed in study, ORa = 9.92 (2.7-36.7) p = 0.001- 95% CI. The prescription of inappropriate probabilistic antibiotic therapy is of the order of 25.8% [26]. This high frequency is at the origin of excess mortality (42.0%) when compared to that of infected patients receiving adequate antibiotic treatment (17.7%) with a statistically significant difference (RR: 2.37 [95% CI, 1.83 to 3.08] p < 0.001) [27]. In our study, this variable was not statistically significant in the multivariate study. Urinary catheterization has been reported as a risk factor linked to the use of urinary catheterization responsible for sepsis, in a statistically significant manner (OR: 21.04 [3.67 - 120.57] P<0.0001) [24]. It would multiply this risk by 21, compared with what we observed in our study. Risk multiplied by 5, (ORa = 5.53 (1.6-19.16), P=0.007 95% CI).

In a cohort study, Age > 65 years was reported to be a risk factor for the development of multi-resistant Acetobacter baumani infection, relative risk (RR) of 1.46 (CI 1.14–1.88) and (RR) of 4.23 (IC 1.11–16.04). An almost identical result was observed in a multicenter prospective cohort study of 147 Spanish intensive care units with a sample size of 16,950 patients. age > 65 years (RR 1.25 [CI 1.02-1.52]) [28]. In our study, age was not statistically significant, which can be explained by a small number of our study population in this age group.

Tab 01: multivariate analysis of the mortality by logistic regression

Initial logistic regression model: Variables in the equation

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | A | E.S. | Wald | ddl | Sig. | Exp(B) | CI Exp (B) 95% | |
| Inferior | Superior |
| Step 1a | Cardiaopathy | 3.858 | 13382.9 | .000 | 1 | 1.00 | 47.390 | .000 | . |
| A.stroke | -19.546 | 12950.5 | .000 | 1 | .999 | .000 | .000 | . |
| hypoximiant pneumonia | 6.034 | 2.48 | 5.91 | 1 | .015 | 417.229 | 3.22 | 54070.1 |
| PAVM | -15.10 | 3374.11 | .000 | 1 | .996 | .000 | .000 | . |
| T\_cran | -1.062 | 2.31 | .21 | 1 | .645 | .346 | .004 | 31.9 |
| P\_traum | 3.44 | 3.10 | 1.23 | 1 | .267 | 31.306 | .071 | 13711.4 |
| P\_aigue | 3.78 | 2.25 | 2.84 | 1 | .092 | 43.963 | .54 | 3593.21 |
| E\_aigue | -18.27 | 3374.12 | .000 | 1 | .996 | .000 | .000 | . |
| A\_souches | 1.57 | 1.43 | 1.21 | 1 | .271 | 4.817 | .29 | 79 |
| K.pneumonae | 2.71 | 1.37 | 3.92 | 1 | .048 | 15.012 | 1.03 | 219.6 |
| Urinary sepsis | 4.94 | 2.38 | 4.30 | 1 | .038 | 139.683 | 1.31 | 14856.4 |
| Hyperlactatemia | 20.9 | 3374.11 | .000 | 1 | .995 | 12265.02 | .000 | . |
| S\_Ktc | .76 | 1.57 | .233 | 1 | .629 | 2.13 | .099 | 45.96 |
| R\_atb | 2.83 | 2.37 | 1.43 | 1 | .231 | 17.03 | .16 | 1764.87 |
| A.Baumannii resistance | 1.04 | 1.21 | .74 | 1 | .389 | 2.82 | .27 | 29.93 |
| Constante | -29.50 | 3374.12 | .000 | 1 | .993 | .000 |  |  |

Tab02: multivariate analysis of the mortality by logistic regression

Final logistic regression model: Variables in the equation

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | A | E.S. | Wald | ddl | Sig. | Exp(B) | IC pour Exp (B) 95% | |
| Inferior | Superior |
| Step 1a | K.pneumonae | 2.294 | .667 | 11.833 | 1 | **.001** | **9.92** | 2.684 | 36.66 |
| Urinary sepsis | 1.710 | .634 | 7.279 | 1 | **.007** | **5.53** | 1.596 | 19.15 |
| Hyperlactatemia | 2.938 | .665 | 19.523 | 1 | **.000** | **18.9** | 5.129 | 69.52 |
| A.Baumannii resistance | 1.815 | .790 | 5.277 | 1 | **.022** | **6.14** | 1.305 | 28.88 |
| Constant | -5.671 | .997 | 32.379 | 1 | .000 | .003 | 2.684 | 36.66 |

1. Variable(s) entered in step 1: K\_pn, S\_uri, H\_lact, B\_Resist

Tab 03: Antibiotic resistance: Resistant + intermediate strains

|  |  |  |  |
| --- | --- | --- | --- |
| Antibiotics | **Acinetobacter**  **baumanii(n=74)** | Antibiotics | **K . pneumoniae**  **(n=52)** |
| Ticarcilline | 65 | Ampicilline/amoxicilline | 24 |
| Ticarcilline+ Acide clavulanique | 68 | Amoxicilline+ Acide clavulanique | 28 |
| Ceftazidime | 69 | Céfazoline | 38 |
| imipenème | 68 | Céfotaxime | 36 |
| Gentamycine | 37 | Céfotaxime (BLSE confirmées) | 15 |
| Amikacine | 31 | Ciprofloxacine | 19 |
| Ciprofloxacine | 36 | Cotrimoxazole | 31 |
| Tobramycine | 34 | imipenème | 04 |
| Cotrimoxazole | 39 | Ertapénème | 06 |
| Colistine | No tested | Gentamycine | 18 |

Bibliographie :

[1] Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001; 29:1303–10.

[2] Vincent J-L, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. Jama 2009; 302:2323–9.

[3] Vincent J-L, Abraham E, Annane D, Bernard G, Rivers E, Van den Berghe G. Reducing mortality in sepsis: new directions. Crit Care 2002;6: S1.

[4] Andre C. Kalil, Management of Adults with Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society n.d.

[5] Koulenti D, Tsigou E, Rello J. Nosocomial pneumonia in 27 ICUs in Europe: perspectives from the EU-VAP/CAP study. Eur J Clin Microbiol Infect Dis 2017 ;36 :1999–2006. https://doi.org/10.1007/s10096-016-2703-z.

[6] Chastre J, Fagon J-Y. Ventilator-associated Pneumonia 2002 ;165 :37.

[7] Enquête nationale de prévalence des infections nosocomiales et des traitements anti-infectieux en établissements de santé, France, mai-juin 2012 n.d.

[8] Richards MJ, Edwards JR, Culver DH, Gaynes RP, National Nosocomial Infections Surveillance System. Nosocomial Infections in Combined Medical-Surgical Intensive Care Units in the United States. Infect Control Hosp Epidemiol 2000; 21:510–5. https://doi.org/10.1086/501795.

[9] Shuman EK, Chenoweth CE. Recognition and prevention of healthcare-associated urinary tract infections in the intensive care unit: Crit Care Med 2010;38: S373–9. https://doi.org/10.1097/CCM.0b013e3181e6ce8f.

[10] World Health Organization, editor. Antimicrobial resistance: global report on surveillance. Geneva, Switzerland: World Health Organization; 2014.

[11] Spellberg B, Gilbert DN. The Future of Antibiotics and Resistance: A Tribute to a Career of Leadership by John Bartlett n.d.:5.

[12] Hinsdale JG, Jaffe BM. Re-operation for Intra-abdominal Sepsis: Indications and Results in Modern Critical Care Setting. Ann Surg 1984; 199:31–6. https://doi.org/10.1097/00000658-198401000-00006.

[13] de Kraker MEA, Davey PG, Grundmann H, on behalf of the BURDEN study group. Mortality and Hospital Stay Associated with Resistant Staphylococcus aureus and Escherichia coli Bacteremia: Estimating the Burden of Antibiotic Resistance in Europe. PLoS Med 2011; 8: e1001104. https://doi.org/10.1371/journal.pmed.1001104.

[14] Meyer E, Schwab F, Schroeren-Boersch B, Gastmeier P. Dramatic increase of third-generation cephalosporin-resistant E. coli in German intensive care units: secular trends in antibiotic drug use and bacterial resistance, 2001 to 2008. Crit Care 2010;14: R113. https://doi.org/10.1186/cc9062.

[15] Poirel L, Nordmann P. Carbapenem resistance in Acinetobacter baumannii: mechanisms and epidemiology. Clin Microbiol Infect 2006; 12:826–36. https://doi.org/10.1111/j.1469-0691.2006.01456.x.

[16] Solomon SL, Oliver B. Antibiotic Resistance Threats in the United States: Stepping Back from the Brink 2014;89:6.

[17] Sievert DM, Ricks P, Edwards JR, Schneider A, Patel J, Srinivasan A, et al. Antimicrobial-Resistant Pathogens Associated with Healthcare-Associated Infections Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. Infect Control Hosp Epidemiol 2013; 34:1–14. https://doi.org/10.1086/668770.

[18] Laundy M, Gilchrist M, Whitney L, editors. Antimicrobial stewardship. First edition. Oxford: Oxford University Press; 2016.

[19] Kon KV, Rai M, editors. Antibiotic resistance: mechanisms and new antimicrobial approaches. Amsterdam: Elsevier, Academic Press; 2016.

[20] Arnold H, Micek S, Skrupky L, Kollef M. Antibiotic Stewardship in the Intensive Care Unit. Semin Respir Crit Care Med 2011; 32:215–27. https://doi.org/10.1055/s-0031-1275534.

[21] Luyt C-E, Bréchot N, Trouillet J-L, Chastre J. Antibiotic stewardship in the intensive care unit 2014:12.

[22] European Centre for Disease Prevention and Control (ECDC). Annual epidemiological report 2014. Antimicrobial resistance and healthcare-associated infections.2015. Available at [http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-annual epidemiological-report.pdf](http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-annual%20epidemiological-report.pdf)

[23] Huang H, Chen B, Liu G, Ran J, Lian X, Huang X, et al. A multi-center study on the risk factors of infection caused by multi-drug resistant Acinetobacter baumannii. BMC Infect Dis 2018 ;18. https://doi.org/10.1186/s12879-017-2932-5.

[24] Zheng Y, Wan Y, Zhou L, Ye M, Liu S, Xu C, et al. Risk factors and mortality of patients with nosocomial carbapenem-resistant Acinetobacter baumannii pneumonia. Am J Infect Control 2013;41: e59–63. <https://doi.org/10.1016/j.ajic.2013.01.006>.

[25] Yeşilbağ Z, Tekdöş-Şeker Y, Şenoğlu Ş, Hergünsel GO. [*Klebsiella pneumoniae*infections in intensive

care unit and risk factors for carbapenem resistance]. *Klimik Derg*. 2021; 34(1): 25-30.

DOI: 10.36519/kd.2021.05

[26] Zheng Y, Wan Y, Zhou L, Ye M, Liu S, Xu C, et al. Risk factors and mortality of patients with nosocomial carbapenem-resistant Acinetobacter baumannii pneumonia. Am J Infect Control 2013;41: e59–63. https://doi.org/10.1016/j.ajic.2013.01.006.

[27] Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate Antimicrobial Treatment of Infections. Chest 1999; 115:462–74. https://doi.org/10.1378/chest.115.2.462.

[28] El mekes A, Zahlane K, Ait said L, Tadlaoui Ouafi A, Barakate M. The clinical and epidemiological risk factors of infections due to multi-drug resistant bacteria in an adult intensive care unit of University Hospital Center in Marrakesh-Morocco. J Infect Public Health 2020;13:637–43. https://doi.org/10.1016/j.jiph.2019.08.012.