The Risk of Death among Patients with Healthcare-Associated Infections and Cardiovascular Diseases Admitted in Intensive Care Unit in Romania

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Article

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Abstract: Nowadays, healthcare-associated infections (HAIs) represent a major global public health problem and the burden of these infections is high. In order to reduce the incidence of HAIs and to prevent the spread antibiotics resistant organisms is mandatory to develop surveillance systems. We undertook a retrospective case-control study of all patients presenting HAIs admitted in Intensive Care Unit (ICU) in order to assess risk factors associated with death among patients with HAIs. Patients admitted to Intensive Care Unit who died were more likely to present an infection with a multidrug resistant bacteria, an infection with *Acinetobacter baumannii*, and to suffer from acute myocardial infarction. Among the patients enrolled in the study, a higher probability of death was also observed in association with certain gram-negative pathogens: *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. The longer the patient remains admitted in ICU, the higher the risk of getting an infection that can often become fatal. Acquiring a nosocomial infection also increases the length of hospitalization which will lead to increased financial damage.

Keywords: healthcare-associated infections; intensive care unit; cardiovascular diseases; multidrug resistant bacteria

1. Introduction

In 2016, the European Centre for Disease Prevention and Control (ECDC) estimated that the burden of healthcare-associated pneumonia, surgical site infection, Clostridium difficile infection, neonatal sepsis, urinary tract infection, and primary bloodstream infection, the six main types of healthcare-associated infection (HAI), was higher than the burden of 31 other infectious diseases combined evaluated by ECDC [1,2]. Moreover, the majority of these infections are caused by multidrug resistant organisms. Is well known that factors as old water systems, inadequate, irrational and prolonged usage of antibiotics, poor adherence to regulations regarding hand hygiene, disinfection and sterilization processes are correlated to a higher incidence of HAIs, therefore surveillance systems were created in order to reduce mortality and morbidity associated with these type of infections [3–6]. There is a continuous fight against HAIs given the fact that the burden of these infections is high and they represent a global public health issue [1,7–9].

An important problem that needs to be highlighted is that low and lower-middle income countries, with limited medical resources, have a higher incidence of HAIs, resulting in a higher rate

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percentage of patients with disabilities and consequently increasing costs for their healthcare system. However, information regarding HAIs and the burden of death caused by this type of infections are not as clear and complete as it is in high income countries. This problem, aside from the variation caused by objective factors, makes it impossible to apply well known characteristics regarding HAIs to other countries, regions and hospitals from data that was already provided [10–12].

Patients admitted to Intensive Care Unit (ICU) often undergo invasive procedures such as insertion of urinary catheter, intravascular catheter, mechanical ventilation, presenting, in addition other risk factors, making them susceptible to develop HAIs [1,2]. This complication among patients in ICU translates into a prolonged hospitalization with negative impact in both the patients and the healthcare system, more frequent readmissions, as well as being correlated with an increase in morbidity and mortality [3,4].

In order to reduce the incidence of HAIs and to prevent the spread antibiotics resistant organisms, a number of organizations recognized that is mandatory to develop action plans that must be implemented in hospitals all around the world [1]. Giving the fact that type of infection, the spectrum of microorganisms causing these infections, their antimicrobial resistance patterns vary according to country and hospital, in order to establish and implement action plans is mandatory to describe all these characteristics for each hospital [1].

Nowadays, antibiotic resistance is known to be not a unidimensional problem, but a problem that we need to addresses in more than one way. Developing new generations of antibiotics and conducting molecular epidemiological investigations represent necessary parts of a puzzle aside from improving hygiene systems, safe disposal of medical waste, following rigorous procedures for hand hygiene and sterilization processes, in order to reduce the rates of HAIs [13–18].

The aim of this study is to evaluate the risk of death among patients with HAIs admitted in ICU, hospitalized for cardiovascular diseases, compared to those with similar pathologies, without infections.

2. Materials and Methods

2.1. Study design

We undertook a retrospective case-control study of all patients presenting HAIs admitted in Intensive Care Unit from a public hospital from 1st of January, 2018, to December 31, 2021. From the total number of patients enrolled in this study, 131 were patients with cardiovascular diseases and infections with bacteria resistant to antibiotics and the rest of 131 were patients admitted in the same department, with cardiovascular diseases, but with no sighs of infection. Underage patients were excluded from this study. All data collected were based on routinely collected hospital admissions data, there was no interaction with patients and information regarding laboratory finding were extracted from the informatics system used by healthcare providers in this hospital.

This study included a descriptive analysis of the patients' characteristics, causative bacteria and outcomes of severe infection and a case-control analysis in order to assess risk factors associated with death among patients with HAIs.

2.2. Research Ethics Committee Approval

The study received approval from the hospital committee (No 9920/14.12.2021).

2.3. Statistical analyses

Statistical analysis was performed using the Statistical Package for Social (SPSS, version 23, Chicago, IL, USA). Data not found in charts or the informatics system were labelled as missing. Mean, median and percentages were reported. Risk factors that could be associated with death were analyzed using logistic regression and the multivariable model was created using a p value <0.05, adjusting for all variables found significant in the univariable analysis and factors considered "a priori", reporting crude Odds Ratio (OR), adjusted Odds Ratio (aOR), confidence intervals (95%) and p values.

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3. Results

3.1. Characteristics of the study groups

A total of 262 patients were included in this study during the study period, with a mean age of 62.61 years for our case group and 64.6 years for control. More than two third of patients were men (64.9% case and 71% control).

When evaluating length of hospitalization in ICU there was a significant difference between the two groups (p-0.0001; 11 days in the case group vs. 2 days in the control group).

The most frequent bacteria identified was *Klebsiella pneumoniae* (33.8%), followed by *Acinetobacter baumannii* (20.6%) and *Staphylococcus aureus* (13.7%), in 60.3% of cases infection was caused by a multidrug resistant organism. 60.3% of patients in the case group died, compared to 16.8% in the control group (p-0.0001).

Of the patients who died, 75.9% of cases the infection was caused by a multidrug resistant bacteria, with a higher length of hospitalization in ICU, compared to those who survived (p-0.0001; 11 days vs. 2 days) *Klebsiella pneumoniae* was again the most frequent organism identified among patients that died during hospitalization in ICU with a percentage of 40.5% and the second most frequent was in this case *Acinetobacter baumannii* (30.4%). The most common cardiovascular pathology among deceased patients was valvulopathy (34.2%), followed by chronic heart failure (30.4%) and acute myocardial infarction (30.4%). Often patients suffer from more than one cardiovascular disease.

3.2. Uni and multivariable analyses of risk factors associated with death

Patients enrolled in the control group that died are more likely to suffer of valvulopathy (OR: 1.21; 95%CI 1.08-2.23), acute myocardial infarction (OR: 10.08; 95%CI 3.21-31.66) and cardio-respiratory arrest (OR: 7.8; 95%CI 2.12-28.57), and after creating the multivariable model valvulopathy are more likely to be associated to death among these patients (aOR: 1.12; 95%CI 1.01-2.002). (Table 1)

When evaluating risk factors associated to death among patients with infections admitted to ICU acute myocardial infarction (OR: 2.4; 95%CI 1.98-5.86) and acute pulmonary edema (OR: 4.04; 95%CI 1.85-10.05) were factors found significant, and these patients are more likely to present an infection with *Klebsiella pneumoniae* (OR: 2.26; 95%CI 1.03-4.98) and *Acinetobacter baumannii* (OR: 7.12; 95%CI 2.02-25.13). (Table 2)

Acute myocardial infarction (OR: 4.72; 95%CI 2.4-9.27), cardio-respiratory arrest (OR: 3.66; 95%CI 1.73-7.74), acute pulmonary edema (OR: 4.79; 95%CI 1.48-15.50), infections with multidrug resistant bacteria (OR: 10.93; 95%CI 5.87-20.37), *Klebsiella pneumoniae* (OR: 5.75; 95%CI 1.65-16.89), *Acinetobacter baumannii* (OR:16.41; 95%CI 4.79-56.2), *Pseudomonas aeruginosa* (OR: 5.29; 95%CI 1.65-16.89) were found statistically significant when evaluating risk factors associated with death among all patients included in the study (Table 3). After adjusting for all variables found significant in the univariable analysis and prolonged hospitalization, factor considered "a priori", patients who died are more likely to present an infection with a multidrug resistant bacteria (aOR:3.43; 95%CI 1.31-8.95), and *Acinetobacter baumannii* (aOR:8.99; 95%CI 2.21-36.45) as a causative organism for infection, and to present an acute myocardial infarction (aOR: 4.50; 95% CI 1.92-10.51). (Table 3)

Table 1. Uni and multivariable analysis of risk factors associated with death among patients enrolled in the control group.

Risk factors	Patients who survived n = 109	Patients who died n = 22	Univariable analysis		Multivariable analysis	
			cOR* (CI** 95%)	p value	aOR*** (CI** 95%)	p value
Aortic dissection	8	3	1.93 (0.48-8.2)	0.33	-	-
Valvulopathy	46	1	1.21 (1.08-2.23)	**0.04**	1.12 (1.01-2.00)	**0.04**
Diabetes mellitus	8	2	1.26 (0.24-6.39)	0.77	-	-
Chronic hypertension	22	5	1.16 (0.38-3.49)	0.78	-	-
Ischemic cardiomyopathy	29	6	1.03 (0.36-2.89)	0.94	-	-

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Cardiac failure	21	5	1.23 (0.4-3.72)	0.71	-	-
Acute myocardial infarction	7	9	10.08 (3.21-31.66)	**0.001**	5.39 (1.14-17.99)	**0.045**
Cardio-respiratory arrest	5	6	7.8 (2.12-28.57)	**0.02**	3.89 (0.95-15.92)	0.059

* cOR-crude Odds Ratio. ** CI-confidence interval. *** aOR-adjusted Odds Ratio.

Table 2. Uni and multivariable analysis of risk factors associated with death among patients enrolled in the case group.

Risk factors	Patients who survived n = 52	Patients who died n = 79	Univariable analysis cOR* (CI** 95%)	p value	Multivariable analysis aOR*** (CI** 95%)	p value
Aortic dissection	7	8	0.72 (0.24-2.13)	0.55	-	-
Valvulopathy	17	27	1.06 (0.5-2.24)	0.86	-	-
Diabetes mellitus	2	6	2.05(0.39-10.59)	0.38	-	-
Chronic hypertension	16	20	0.76 (0.35-1.65)	0.49	-	-
Ischemic cardiomyopathy	4	18	3.54(1.12-11.15)	**0.03**	3.49 (1.97-12.54)	**0.04**
Cardiac failure	12	24	1.45 (0.65-3.24)	0.36	-	-
Endocarditis	3	4	0.87 (0.18-4.06)	0.86	-	-
Acute myocardial infarction	8	24	2.4 (1.98-5.86)	**0.04**	2.41 (0.83-6.97)	0.1
Acute pulmonary edema	2	11	4.04(1.85-19.05)	**0.03**	2.27 (0.41-12.43)	0.34
Cardio-respiratory arrest	7	17	1.76 (0.67-4.6)	0.24	-	-
Multidrug resistant organism	19	60	5.48(2.55-11.78)	**0.0001**	3.87 (1.53-9.18)	**0.004**
Klebsiella pneumoniae	12	32	2.26 (1.03- 4.98)	**0.041**	1.24 (0.46-3.36)	0.66
Acinetobacter baumannii	3	24	7.12(2.02-25.13)	**0.002**	5.97 (1.53-23.28)	**0.01**
Pseudomonas aeruginosa	4	11	1.94 (0.58-6.46)	0.280	-	-
Staphylococcus aureus	8	10	0.79 (0.29-2.17)	0.658	-	-
Higher length of admission in ICU	-	-	-	-	1.03 (0.99-1.078)	0.11

*cOR-crude Odds Ratio. **CI-confidence interval. *** aOR-adjusted Odds Ratio.

Table 3. Uni and multivariable analysis for risk factors associated with death among all patients enrolled in the study.

Risk factors	Patients who survived n = 161 (39%)	Patients who died n = 101 (61%)	Univariable analysis cOR* (CI** 95%)	p value	Multivariable analysis aOR*** (CI** 95%)	p value
Aortic dissection	15	11	1.19 (0.52-2.7)	0.67	-	-
Valvulopathy	63	28	1.59(1.34-2.02)	**0.04**	0.68 (0.33-1.37)	0.28
Diabetes mellitus	10	8	1.29 (0.49-3.4)	0.59	-	-
Chronic hypertension	38	25	1.06 (0.59-1.9)	0.83	-	-
Ischemic cardiomyopathy	33	24	1.2 (0.66-2.19)	0.53	-	-
Cardiac failure	33	29	1.56 (0.87-2.78)	0.12	-	-
Endocarditis	3	4	2.17 (0.47-9.91)	0.31	-	-
Acute myocardial infarction	15	33	4.72 (2.4-9.27)	**0.001**	4.50 (1.92-10.51)	**0.001**
Acute pulmonary edema	4	11	4.79 (1.48-15.50)	**0.009**	1.13 (0.27-4.70)	0.85
Cardio-respiratory arrest	12	23	3.66 (1.73-7.74)	**0.001**	1.64 (0.61-4.44)	0.32
Multidrug resistant organism	19	60	10.93 (5.87-20.37)	**0.001**	3.43 (1.31-8.95)	**0.012**
Klebsiella pneumoniae	12	32	5.75 (2.79-11.85)	**0.001**	2.01 (0.72-5.66)	0.18
Acinetobacter baumannii	3	24	16.41 (4.79-56.2)	**0.001**	8.99 (2.21-36.45)	**0.002**
Pseudomonas aeruginosa	4	12	5.29 (1.65-16.89)	**0.005**	3.63 (0.89-14.7)	0.07
Staphylococcus aureus	8	10	2.1 (0.8-5.51)	0.13	-	-
Being part of the case group	52	79	7.72 (4.22-13.39)	**0.001**	1.72 (0.07-3.97)	0.19

*cOR-crude Odds Ratio. **CI-confidence interval. *** aOR-adjusted Odds Ratio.

4. Discussion

In our study we identified a high rate of HAIs caused by multiresistant germs, 60.3% compared to the 39.7% represented by bacteria sensitive to antibiotic treatment. The average age of patients in the case group 62.61 years old similar to data reported in the study conducted by Voidazan et al. [19], and 67.1% were men. Among the respective pathogens, gram-negative bacteria had the highest frequency: *Klebsiella pneumoniae* (33.6%) and *Acinetobacter baumnannii* (20.6%), similar results being obtained in a study conducted at a tertiary hospital in Jining, China regarding the analysis of

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multiresistant bacteria [20]. The number of deaths occurred in patients with multiresistant infections was considerably higher compared to infections sensitive to antibiotic therapy. 75.9% of patients with resistant pathogens died compared to a lower death rate of 22.4% among patients with susceptible infections. A higher probability of death was also observed in association with certain gram-negative pathogens: *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, an outcome also observed in a studies that dealt with mortality associated with infections with multi-resistant gram-negative germs and Staphylococcus aureus resistant to methicillin [21,22]. The probability of death was significantly higher in the case group showing that infections are a major factor in patient prognosis. The alarming situation observed not only in this study but also in numerous other studies should put us in a heightened state of awareness as we are at a critical moment in healthcare [23–26]. Infections have been and will remain one of the most important challenges, and the current situation exposes a flaw in the way they have been managed so far. The inertia acquired by the multi-resistance of bacteria to antibiotic treatments will not be easily stopped if a consensus is not implemented regarding their management, a management that must be strictly respected because joint effort is indispensable in solving this crisis. Intensive care units are the main frontline in the fight against infections because the vulnerability of patients is at its highest. Invasive monitoring devices, ventilators and immunosuppression are some of the causes favoring the emergence of infections. The biggest problem is represented by the limited treatment options in many cases. This is due to the ineffectiveness of providing antibiotic therapy caused by errors in prescribing the right antibiotic, dosage errors, low compliance in terms of doctor-patient collaboration, failure to observe the necessary time interval for treatment and many others.

Regarding the days of admission to the intensive care unit, a significantly higher probability of death associated with a longer period of hospitalization was observed, illustrating the unfavorable prognosis related to the time required for treatment. The longer the patient remains admitted in ICU, the higher the risk of getting an infection that can often become fatal. Acquiring a nosocomial infection also increases the length of hospitalization which will lead to increased financial damage. Cost-effectiveness also benefits when the infection is treated correctly, and even more so when the infection is prevented. The occurrence of organ failure was also a decisive factor for the occurrence of death in the exploratory analysis performed on the 29 patients, the strongest statistical association being cardiovascular failure and respiratory failure. Similar results were also observed in a study in which more days spent in the intensive care unit were associated with higher long-term mortality in both ventilated and non-ventilated patients [27], but another study resulted in a lack of association with risk of death in terms of intensive care unit hospital days [28].

The importance of this study is highlighted by the fact that nowadays HAIs represent a global public health problem. Organizations such as WHO (World Health Organization), CDC (Centers for Disease Control and Prevention), ECDC (European Center for Disease Prevention and Control) run continuously campaigns to train healthcare providers regarding prevention, early detection and prompt management of HAIs, as well as campaigns intended to inform the population regarding the misuse of antibiotics and the serious repercussions for not following the indications given by medical doctors. A limitation of our study incomplete data from medical charts, a disadvantage created by retrospective collection of data, as well as the lack of information listed in our informatics system. Prospective extension of the study would allow us to collect all data needed, and information's storage in our electronic system would facilitate data collection.

5. Conclusions

In conclusion, HAIs have a significant impact on risk of death, thus demonstrating the urgency of this problem. Prompt management is mandatory given the limited therapeutic resources caused by multidrug resistant organisms and finding new treatment approaches is necessary. But, by far, the most important aspect is prevention, information and education campaigns representing the key in reducing the prevalence of HAIs, as well as the burden of death caused by these infections.

Author Contributions: B.M.A. coordinated and monitored the study activities, analyzed the data developed and edited the manuscript. V.S. designed the study, prepared the material, statistically processed and analyzed the

data, interpreted the results. L.M. and K.J. reviewed the material used for the study and critically reviewed the manuscript. B.B.M. helped to collect and enter the data into the study database. All authors read and approved the final manuscript.

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