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MORTALITY AND RISKS RELATED TO HEALTHCARE-ASSOCIATED INFECTION

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ABSTRACT: Healthcare-associated infections are a major cause of morbidity-mortality among hospitalized patients. The aim of this epidemiological study was to determine mortality and risks related to death in adult patients with healthcare-associated infections admitted to a teaching hospital in one year. Patient data were collected from infection medical reports. The mortality rate associated with infections was 38.4%, and it was classified as a contributing factor to deaths in 87.1% of death cases. The correlation between healthcare-associated infection and death was statistically significant among clinical patients (41.3%) presenting comorbidities related to the diagnosis (55.8%), cardiovascular infection (62.2%), pneumonia (48.9%), developing sepsis (69.0%), as well as patients who had been colonized (45.2%) and infected (44.7%) by multidrug resistance microorganisms.

DESCRIPTORS: Cross infection. Epidemiology. Mortality. Risk factors.

MORTALIDADE E RISCOS ASSOCIADOS A INFECÇÃO RELACIONADA À ASSISTÊNCIA À SAÚDE

RESUMO: A infecção relacionada à assistência à saúde é uma das principais causas de morbimortalidade entre pacientes hospitalizados. O objetivo deste estudo epidemiológico foi determinar a mortalidade e os riscos associados ao óbito de pacientes adultos com infecção relacionada à assistência à saúde, internados em um hospital-escola no período de um ano. Dados dos pacientes foram coletados das fichas de notificação de infecções. A taxa de mortalidade associada a essas infecções foi de 38,4%, classificadas como fator contribuinte em 87,1% dos óbitos. A associação das infecções relacionadas à assistência à saúde com o óbito foi estatisticamente significativa entre pacientes clínicos (41,3%), que apresentavam comorbidades associadas ao diagnóstico (55,8%), com infecção cardiovascular (62,2%), pneumonia (48,9%), que evoluíram com sepse (69,0%), colonizados (45,2%) ou infectados (44,7%) por microrganismos multirresistentes. Concluiu-se que as infecções contribuíram para o óbito da maioria dos pacientes.

DESCRITORES: Infecção hospitalar. Epidemiologia. Mortalidade. Fatores de risco.

MORTALIDAD Y RIESGOS ASOCIADOS A LA INFECCIÓN RELACIONADA CON LA ASISTENCIA A LA SALUD

RESUMEN: La infección relacionada con la atención sanitaria es una de las principales causas de morbimortalidad entre los pacientes hospitalizados. El objetivo de este estudio epidemiológico fue determinar la mortalidad y los riesgos asociados con el fallecimiento de pacientes adultos con la infección relacionada con la atención sanitaria ingresados en un hospital universitario en el periodo de un año. Los datos de los pacientes se obtuvieron de registros de notificación de infecciones. La tasa de mortalidad asociada con las infecciones fue del 38,4%, y fueron clasificados como un factor que contribuye en el 87,1% de las muertes. La asociación de la infección relacionada con la atención sanitaria con el fallecimiento fue estadísticamente significativa entre pacientes clínicos (41,3%), que presentaron comorbilidad asociadas a el diagnóstico (55,8%), con infección cardiovascular (62,2%), neumonía (48,9%), que desarrollaron sepsis (69,0%), colonizados (45,2%) o infectados (44,7%) por microorganismos multirresistentes. Se concluyó que las infecciones contribuyeron a la muerte de la mayoría de los pacientes

DESCRIPTORES: Infección hospitalaria. Epidemiología. Mortalidad. Factores de riesgo.

INTRODUCTION

Healthcare-associated infections (HAI) stand out as one of the major causes of morbidity-mortality concerning patients who undergo clinical procedures. These infections are deemed to be a relevant healthcare challenge generating high rates of health complications, extension of hospital stay, direct enhancement of healthcare costs. Additionally, HAI favor the selection and dissemination of multidrug resistance microorganisms.[1-2]

The Centers for Disease Control and Prevention (CDC) define HAI as a localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent acquired after the patient's admission to the healthcare service.[3] In Brazil, Ordinance 2,616 from the Ministry of Health considers HAI as a significant risk to the health of patients in the services, and defines them as any infection acquired after the admission of the patient to the healthcare service manifested either 48 hours following hospitalization or prior to such period whenever it is correlated with invasive procedures. Healthcare-associated infections may also manifest after the patient's discharge whenever it is associated with surgeries or invasive procedures carried out at healthcare services.[4]

The high mortality risk associated with HAI is intrinsically connected with factors such as the performance of diagnostic and therapeutic invasive procedures,[5] the severity of the patient's base disease,[6] the location of the infection,[7] the inadequacy of the therapy, and the sensitivity of microorganisms to antimicrobials.[8]

A North American multicentric study showed that nearly 1.7 million annual cases of HAI are observed in the US, and approximately 99,000 yearly deaths are associated with the occurrence of these infections in the country.[9] An European study concluded that HAI affect one out of 10 hospitalized patients and cause nearly 5,000 annual deaths in the continent.[10]

In Brazil, data related to HAI are still poorly documented due to the reduced consolidation of information on the part of several hospitals, thus making it very difficult for healthcare professionals to come up with a set of knowledge on the extension of the problem in the country. The Ministry of Health assessed the magnitude of hospital infections in 99 outsourced hospitals covered by the Unified Health System (SUS), and located in Brazilian capitals, identifying a HAI rate of 13.0% among hospitalized patients.[11]

Bearing in mind the complexity and severity of HAI, demonstrated by the high mortality rates found, the need for a deeper approach regarding the prevention and control of infections as a patient's safety promotion strategy[12] and the direct contribution of the nursing practice to the control of this type of infection, the aim of the present study was to determine mortality rates and risks associated to the death of adult patients with HAI admitted to a teaching hospital.

METHOD

This descriptive, retrospective epidemiologic study, whose sample was comprised of all medical condition notification forms and medical reports of adult patients (aged 18+) diagnosed with HAI, was carried out between December 2009 and January 2011, in compliance with the criteria established by the Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN)[3] and the admission criteria of the University Hospital (UH). The University Hospital of Londrina stands out as a supplementary organ of the State University of Londrina (UEL), a reference center for the SUS in the Northern region of the state of Paraná, Brazil. The hospital counts on 316 beds

distributed among hospitalization units, emergency unit and intensive care unit (ICU). The wards addressed by this study were as follows: emergency unit, nursing departments (male, female, tuberculosis and transmissible diseases), maternity, burn care center (BCC), bone marrow transplant center and adult intensive care unit (ICU 1 – post-surgery patients; ICU 2 – chronic patients).

Data were gathered from the patients' medical reports and medical condition notification forms regarding HAI, and formulated in compliance with the criteria established by the North American infection surveillance system, the National Nosocomial Infection Surveillance (NNIS),[13] filled out and analyzed by the multiprofessional team of the Hospital Infection Control Commission (CCIH) of the UH-UEL in all cases of HAI.

The gathered variables included outcome (discharge and death), gender, age, ward and length of stay, treatment classification (clinical and surgical), presence of comorbidities (Charlson Comorbidity Index - CCI),[14] major location of the infection, development of sepsis, invasive procedures carried out, microorganisms isolated in cultures, and sensitivity profile against antimicrobials.

The correlation between death and HAI was classified as: 1) death related to HAI; 2) death not related to HAI; or 3) undefined correlation between death and HAI. This classification standard was determined by medical criteria and grounded on preset concepts advocated by the CDC, which take into account the patient's whole clinical context. As for the development of sepsis, such complication was classified as sepsis, severe sepsis, and septic shock, in compliance with the criteria set forth by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM).[15]

Regarding the etiological agent, data were extracted from lab reports provided by the institution's computer system. Lab identification and the sensitivity profile of microorganisms against antimicrobials complied with the criteria established by the Clinical and Laboratory Standard Institute (CLSI).[16] The classification of such microorganisms concerning colonization or infection processes complied with the criteria established by the CDC/NHSN.[3] As for the classification of the multidrug resistance to antimicrobials, the criteria set forth by the CDC were complied with.[17]

Multidrug resistant microorganisms were classified as follows: *Acinetobacter baumannii* and *Pseudomonas* sp, resistant to carbapenemics; *Klebsiella pneumonial* and *Escherichia coli*, resistant to either carbapenems or cephalosporines (third or fourth generation) or monobactamics; coagulase-negative *Staphylococcus* and *Staphylococcus aureus* resistant to oxacilin; *Enterobacter* sp, other enterobacteria and *Serratia* sp, resistant to carbapenem or cephalosporine (fourth generation); *Enterococcus* sp, resistant to vancomycin and *Streptococcus* sp, resistant to penicilin, cefotaxime, levofloxacine, meropenem, glycopeptide and macrolides; *Burkholderia cepacia*, *Stenotrophomonas* sp and *Moraxella* sp were grouped as non-fermenting and all of them were considered as multidrug resistant microorganisms as a result of their intrinsic resistance to various antibiotics.[17]

Data tabulation and analysis were carried out using the Statistical Package for the Social Sciences (SPSS) software, version 19. Categorical variables were assessed as simple and relative frequencies and shown in tables. For continuous variables, the study applied the central and dispersion tendency measurements (mean, median and standard deviation). In order to assess the correlation of the variables with the hospital infection, the authors employed a bivariate analysis by means of Pearson's Chi-Square Test (X^2) or Fisher's exact Test. Relative risk and confidence intervals of 95% (CI 95%) were used as force measurements for the correlations. The adopted level of significance was 5% ($p \leq 0.05$).

The research proposal was approved by the Human Research Ethics Committee of the State University of Londrina, receiving the Ethics Appreciation Certificate (CAAE) under protocol number 0015.0.268.000-11.

RESULTS AND DISCUSSION

Throughout the period of the study, 11,177 adult patients were hospitalized at the UH-UEL. From these, 889 (8.0%) were diagnosed with at least one episode of HAI, from which 341 evolved to death, thus reflecting a mortality rate of 38.4%. Other studies found lower rates, namely 11.0%,[18] 12.8%,[19] and 16.8%.[7]

In the present study, the majority of deaths (87.1%) among the patients that showed HAI was related to these infections, thus generating a significant statistical association ($p<0.001$). A study carried out for one year in a French university hospital indicated that the infections were considered the major cause of deaths in 4.4% of patients with HAI. Concurrently, the infection was deemed to be a contributing factor toward death in 37.8% of patients.[18] Table 1 depicts the characteristics of the patients with HAI who evolved to death.

Table 1 - Relative death frequency, percentage and risk among patients with HAI (n=889) who evolved to death (n=341) according to sociodemographic and clinical variables. Londrina, Paraná, 2012

Variables	Total	Death		p value	RR*	CI 95%†	
		n	%				
Sex							
Male	601	247	41.1	0.015	1.26	1.04	1.53
Female	288	94	32.6				
Group age							
18-34	156	27	17.3	<0.001			
35-49	177	63	35.6				
50-64	203	83	40.9				
65-79	226	89	39.4				
≥ 80	127	79	62.2				
Length of stay							
Up to 15 days	299	112	37.5	0.908			
From 16 to 30 days	334	133	39.8				
From 31 to 45 days	129	49	38.0				
From 46 to 60 days	73	27	37.0				
> 60 days	54	20	37.0				
Type of patient							
Clinical	766	316	41.3	<0.001	2.03	1.42	2.91
Surgical	123	25	20.3				
Comorbidities							
Yes	387	216	55.8	<0.001	2,24	1,88	2,67
No	502	125	24.9				
Site of infection							
Cardiovascular	45	28	62.2	<0.001	1.68	1.31	2.14
Pneumonia	619	303	48.9	<0.001	3.48	2.56	4.72
Blood stream	31	13	41.9	0.677	1.10	0.72	1.67
Urinary tract	276	108	39.1	0.751	1.03	0.86	1.23
Skin and subcutaneous	43	10	23.3	0.037	0.59	0.34	1.03
Operation room	115	20	17.4	<0.001	0.42	0.28	0.63
Others	12	4	33.3	1.000	0.87	0.39	1.94
Sepsis							
Yes	413	285	69.0	<0.001	5.87	4.55	7.56
No	476	56	11.8				
Invasive procedures							
Tracheotomy	14	11	78.6	0.002	2.08	1.56	2.77
Orotracheal tube	386	261	67.6	<0.001	4.25	3.44	5.26
Central venous catheter	117	65	55.6	<0.001	1.55	1.29	1.87
Vesical probe	356	188	52.8	<0.001	1.84	1.56	1.17
Drains	40	13	32.5	0.436	0.84	0.53	1.33

*RR: relative risk; †CI: confidence interval.

According to Table 1, there was a statistical association related to the HAI among men (41.1%). [A long list of factors contributes to the development of HAI. Among them, those specifically related to exposed patients, especially those in advanced age, stand out.[7] In the present study, the mean age of patients was 56.97 years (18-98 age range) and the major prevalence of infections was observed in individuals aged 50 years or over (62.5%). A similar finding was observed in relation to mortality rates, where 62.2% of deaths related to older individuals (p<0.001) stood out, according to table 1.

Another factor that collaborates to the occurrence of HAI is the prolonged hospital stay.[19] In the present study, the mean length of hospital stay of patients with HAI was 27.2 days and most of the individuals (66.4%) remained in the hospital for a period longer than 15 days. Among the deaths, the mean length of hospital stay varied from 37.0%, for periods higher than 60 days, to 39.8%, for 16-30

days, and did not show any significant statistical association. Accordingly, a retrospective study that identified 133 deaths associated with HAI in a Brazilian outsourced hospital in a period of one year showed a mean length of hospital stay of 35 days and a maximum of 236 days.[20]

As for the hospitalization departments, critical units presented higher HAI rates, namely the BCC (98.2%), ICU 2 (48.7%) and ICU 1 (24.8%) when compared with the nursing ward (7.9%) and the emergency unit (4.6%). Consequently, a higher mortality percentage among patients with HAI was also observed in these units, ICUs (93.8%) and BCC (77.8%). Studies highlight that the highest mortality rates among patients with HAI are correlated to the hospitalization in ICUs.[9,21] Taking into account that these wards handle the hospital's most severe cases, high mortality rates are quite comprehensible. Additionally, patients at these wards are more exposed to infections as a result of the severity and diversity of invasive procedures often carried out there.

A prevalence of clinical diagnoses among patients with HAI (86.2%) was observed in comparison with surgical diagnoses (13.8%). Mortality was twice as high among clinical patients ($p<0.001$) undergoing the risk of evolving to death in comparison with surgical cases (Table 1). Similarly, a North American study carried out for eight months in an ICU of an outsourced hospital identified that 60.3% of patients with HAI were hospitalized as a result of clinical diagnosis, whereas 39.7% were submitted to surgical procedures.[8] A study performed in ICUs in Greece for a period of 11 months revealed that among the 152 patients with HAI, 67.1% were clinical patients and 32.9% were surgical patients.[22]

Literature data highlight that the clinical conditions and the presence of comorbidities in the moment of admission to the hospital represent relevant risk factors for death among patients with HAI.[23-24] Another study indicates the occurrence of higher mortality rates associated with HAI and observes a special correlation between death rates and the presence of risk factors, such as chronic diseases, immunosuppression, and neoplasia.[24]

The analysis of pathologies associated with the HAI diagnosis in the present study allowed for the identification of a high frequency of comorbidities (43.5%) among patients with HAI, with cerebrovascular diseases (20.4%), congestive cardiac insufficiency (11.6%) and neoplasias (11.6%) being the most prevalent comorbidities. However, other comorbidities showed stronger impact in the mortality of patients with HAI. Among 13 patients with metastatic tumors associated with an infectious status, 84.6% evolved to death. When the infection was observed in patients with chronic liver disease (16), death reached 81.2% of cases. In patients with diabetes mellitus (25), 80% evolved to death. Mortality among patients with comorbidities was quite expressive (55.8%, $p<0.001$), with nearly twice as high risk of death when compared with patients who did not show any comorbidity (Table 1).

Similar data were observed in other studies. A study carried out in two university hospitals and involving 390 patients with HAI and sepsis identified a high mortality frequency among individuals presenting associated risk factors, such as metastatic disease (93.6%), chronic diseases (68.2%) and immunosuppression (55.2%).[24] Additionally, an European study demonstrated that the most frequent comorbidities among patients with HAI, which evolved to death, were diabetes mellitus (27.8%), neoplasias (27.8%) and the malignant hematological disease (22.2%).[25]

As for the data related to the location of the infection, 1,141 infection episodes were diagnosed among the 889 patients that participated in this study, being pneumonia (54.3%), infection in the urinary tract (24.2%) and infection at the operation room (10.1%) the most frequent diagnoses. Infection of the cardiovascular system (62.2%, $p<0.001$), pneumonia (48.9%, $p<0.001$) and infection at the operation room (17.4%, $p<0.001$) presented significant statistical association. Mortality rates among patients with pneumonia were three times higher than those observed in patients who did not display such infection (Table 1).

A three-month long study carried out in hospitals in Belgium and involving 754 patients with HAI also revealed higher mortality rates among patients with infections in the respiratory tract (23.7%). In the same study, infections in the blood stream responded for 15.0% of HAI that evolved to death; infections at the operation room reached 7.6%[19]. Both frequencies are relatively lower than those observed in the present research.

Sepsis, the main complication of infections, affected 46.5% of patients with HAI. Its correlation with deaths was significant (69.0%, $p<0.001$) and increased up to six times the death risk for patients with such complication (Table 1). Figure 1 shows the distribution of patients in accordance with the classification of the sepsis.

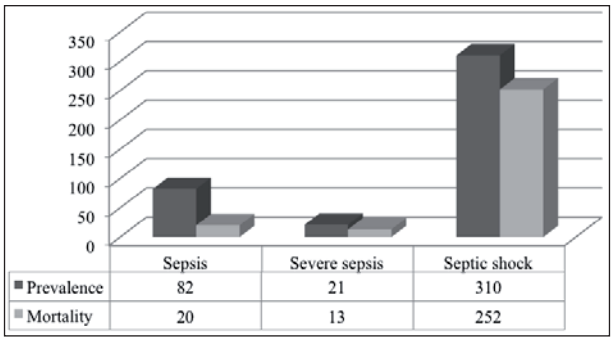

Figure 1 - Patients' prevalence and mortality rates, according to the sepsis classification. Londrina, Paraná, 2012

Among patients with sepsis, septic shock affected most of the individuals (n=310, 75.1%); data show that 81.3% of patients with septic shock, 61.9% of patients with severe sepsis, and 24.4% of those with sepsis died (Figure 1). [Unlike the above–mentioned data, a multicentric study involving 28 hospitals in Europe, Canada and Israel showed a lower frequency of sepsis among patients with HAI (28.0%); septic shock also presented the most frequent evolution (30.0%). The same study indicated that the mortality rate associated with sepsis varied from 44.8% to 67.9%, and the rates related to septic shock ranged from 47.2% to 63.8%; the highest percentages were observed in patients hospitalized in the ICUs of the healthcare centers involved in the study.[21]

The broad employment of invasive procedures in the hospital environment considerably enhances the risk level for HAI. Studies point out that, among infected patients, the performance of invasive procedures varied from 74.6%[26] to 93.0%.[7] These studies found lower percentages in comparison with those found in this study. The present study observed that invasive procedures were carried out in 57.9% (515) of patients with HAI, with some of them being submitted to more than one procedure. Over half of deaths (55.0%) occurred in patients who had undergone invasive procedures, mainly tracheotomy and intubation, with frequency of 78.6% and 67.6%, respectively. These procedures were significantly associated with death, thus enhancing in four and two times, respectively, the death risks for patients with HAI (Table 1).

Invasive procedures are more frequent in ICUs. A prospective study carried out in an ICU of a Brazilian outsourced hospital showed that all patients with HAI who evolved to death were submitted to at least one invasive procedure, being 100.0% submitted to delayed vesical catheterization, 93.3% employed central venous catheter, 80.0% were submitted to orotracheal intubation, and 46.6% were tracheotomized.[27]

As for the infections caused by invasive procedures, data show that mechanical ventilation was related to 30.7% of pneumonias; whereas urinary catheter was associated with 17.7% of the infections in the urinary tract. The study observed a statistical association for death risks in the pneumonia cases related to mechanical ventilation [PAV (68.5%, p<0.001)] and infection of the urinary tract associated with the vesical catheter [CAUTI (49.0%, p=0.002)].

A prospective study that investigated 1,731 cases of HAI in adults for three years pointed out the association between death and PAV (81.6%) and death and CAUTI (43.6%);[28] nonetheless, the highest death frequency was observed in PAV cases when compared with the current study. Data related to infection of the blood stream associated with a catheter were not assessed in this study.

Still with regard to the PAV, it should be highlighted that the implementation of a series of nursing cautions would be quite relevant toward preventing and reducing infection rates and consequently the death frequencies associated to such infection. A qualitative study carried out in a public hospital in the Brazilian state of Santa Catarina addressed the collective construction of a PAV prevention bundle, and came up with a set of four critical cautions: oral hygiene with 0.12% chlorhexidine; headboard elevated at 30-45º; cuff pressure of 20-30 cm H_2O; and special care with the aspiration of tracheal secretions. All of these measures generated strong proof regarding their effectiveness toward preventing the PAV, such as a high level of scientific evidence, application feasibility, and easy adherence.[29]

As for the microbiologic data, 2,784 microorganisms were separated from the positive cultures collected from the 889 patients with HAI. It was detected that 52.5% of these microorganisms were isolated from colonization processes; the remainder were isolated from infectious processes. In relation to the species of microorganisms, *Klebsiella pneumoniae* was the most prevalent microorganism both at the patient's discharge (19.0%) and death (21.2%) cases. The second most frequent microorganism in patients who evolved to death was *Acinetobacter baumannii* (18.5%). Among discharged patients, the most frequent microorganism was *Pseudomonas aeruginosa* (11.3%), according to Figure 2.

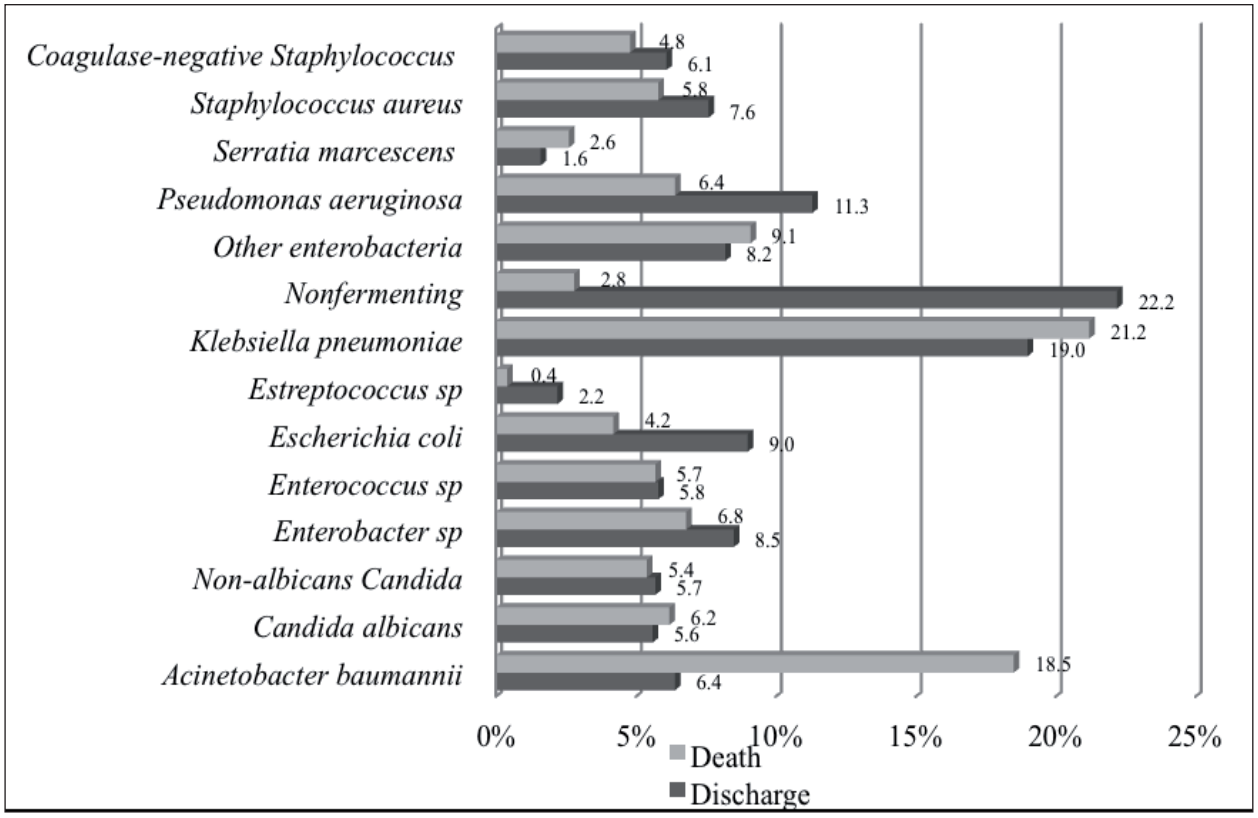

Figure 2 - Microorganisms according to the outcome of patients with healthcare-associated infections. Londrina, Paraná, 2012

In the present study, gram-negative bacteria stood out in the HAI epidemiology. Previous studies pointed out its remarkable relevance in mortality rates. Additionally, other studies show that the mortality rate caused by gram-negative bacteria is significantly higher in patients with HAI, ranging from 41.2%,[8] to 68.0%.[24]

The antimicrobial resistance profile showed slight differences among patients with distinct outcomes. Almost half of patients with infections (44.7%) or those colonized by multidrug resistant microorganisms (45.2%) evolved to death. Among those who did not present multidrug resistance, the mortality rate was lower (33.0% and 34.9%, respectively), thus indicating a significant correlation between the multidrug resistance and the mortality rate among patients with HAI (Table 2).

Table 2 - Relative frequency, percentage and risk of death among patients with HAI who evolved to death (n=341) according to the colonization and infection by multidrug resistant microorganisms. Londrina, Paraná, 2012

Multidrug resistant microorganism	Total	Death		p value	RR*	CI 95%†	
		n	%				
Colonizing							
Yes	392	177	45.2	<0.001	1.37	1.16	1.62
No	497	164	33.0				
Infecting							
Yes	318	142	44.7	0.004	1.28	1.09	1.51
No	571	199	34.9				

* RR: relative risk; †CI: confidence interval.

Infections caused by multidrug resistant bacteria represent a relevant public health challenge impacting several nations, and may become potential health and safety risks to patients. A North American study, based on NNIS and CDC data, associated multidrug resistant microorganisms with the elevation of death risks.[30]

A prospective study carried out in three ICUs in Greece between July 2009 and June 2010 showed a close correlation between multidrug resistant bacteria and deaths, indicating a mortality rate of 32.4%, inferring a nearly twice as high death risk.[22] Such risk was higher than the risk found in the present study, which varied between 1.28 and 1.37 among patients infected and colonized by multidrug resistant bacteria (Table 2).

CONCLUSION

The present study showed that the majority of deaths among patients with HAI was related with this type of infection, and that deaths were associated with comorbidities, patient's clinical status, performance of invasive procedures, pneumonia, cardiovascular system infection, sepsis, and multidrug resistant microorganisms. The factors that enhanced death risks among patients with HAI were: comorbidities, pneumonia associated or not with mechanical ventilation, orotracheal intubation, and tracheotomy.

In face of the results of the present study, and taking into account the high rates, complexity and severity of the HAI, the implementation of prevention strategies and efforts toward improving the care quality would be quite a relevant action. As such, specific epidemiological surveillance and case monitoring actions toward more improved treatment processes, as well as disclosure of data to the professionals involved in the institutional work process, employment of tools that allow for a more effective identification of patients at risk, strict control of care procedures, and immediate and adequate interventions, are critical steps in the hospital environment, tending to dramatically reduce the rates of these infections and consequently related deaths.

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