International Journal of Nursing and Health Care Research
Maia dos Santos MLB, et al. Int J Nurs Health Care Res 5: 1274.
www.doi.org/10.29011/2688-9501.101274
www.gavinpublishers.com

GAVIN PUBLISHERS

Research Article

Prognostic Factors of Severely Ill Children with Klebsiella pneumoniae Carbapenemase Blood Stream

Maria Lucia Barbosa Maia dos Santos[1*], Mônica Taminato[2], Artur Figueiredo Delgado[1], Guilherme José Fernandes[1], Juliana Caires de Oliveira Achili Ferreira[1], Werther Brunow Carvalho[1]

[1]Department of Pediatrics, University of São Paulo, School of Medicine, São Paulo-Brazil

[2]Federal University of São Paulo, SP-Brazil

***Corresponding author:** Maria Lucia Barbosa Maia dos Santos, Department of Pediatrics, University of São Paulo, School of Medicine, Avenida Doutor Enéas Carvalho de Aguiar nº647 - Cerqueira Cesar, Instituto da Criança do Hospital das Clínicas da FMUSP. Av. Dr Enéas Carvalho Aguiar nº647 - Cerqueira Cesar -São Paulo-Brazil

Citation: Maia dos Santos MLB, Taminato M, Delgado AF, Fernandes GJ, de Oliveira Achili Ferreira JC, et al. (2022) Prognostic Factors of Severely Ill Children with *Klebsiella pneumoniae* Carbapenemase Blood Stream. Int J Nurs Health Care Res 5: 1274. DOI: 10.29011/2688-9501.101274

Received Date: 02 February, 2022; **Accepted Date**: 09 February, 2022; **Published Date**: 15 February, 2022

Abstract

Objective: To identify the prognostic factors of patients who had bloodstream infection by *Klebsiella pneumoniae* carbapenemase during hospitalization in the Pediatric Intensive Care Unit. Method: Historical cohort study of patients hospitalized in the Pediatric Intensive Care Unit of a tertiary care hospital who had *Klebsiella pneumoniae* carbapenemase bloodstream infection between 2013 and 2018. Results: All patients had chronic underlying diseases, one third had malnutrition and presented up to three organ dysfunctions on the day of diagnosis of infection. The main prognostic factors associated with the patients were: *PELOD-2* (Pediatric Logistic Organ Dysfunction) scores on the day of infection ($p=0.005$), 48 hours after infection ($p<0.001$) and on the day of discharge or on the day of death ($p<0.001$). The antibiogram showed *Klebsiella pneumoniae* carbapenemase resistant to 75% of the antibiotics available for treatment, the frequency of death was 67.6%. Conclusion: The *PELOD-2* score was the most relevant prognostic factor. Increasing the score by one unit on the day of infection increased the risk of death by 56%, and increasing the score by one unit 48 hours after infection increased the risk of death by 64%. These data corroborate the fact that measures to prevent and control infection by this multidrug-resistant bacteria are essential, especially in patients hospitalized in Intensive Care.

Keywords: *Klebsiella pneumoniae* carbapenemase; Gram-negative Resistance; Pediatrics; Nursing Care; Pediatric Intensive Care Units

Introduction

Bloodstream Infections (BSI) are among the seven leading causes of death in Europe [1], and those caused by carbapenem-resistant enterobacteria in children are increasingly prevalent, with poor clinical outcomes [2]. In the United States, between one-third of carbapenem-resistant enterobacteria isolates in adult patients are carbapenemase producers, and the class A serine carbapenemase of Ambler *K. pneumoniae* Carbapenemase (KPC) accounts for more than 90% of these [2].

The spread of carbapenem-resistant enterobacteria has been a global public health threat. Carbapenems have been used conventionally in the hospital setting to treat infections caused

by β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*, and to date are considered to be antibiotics of last resort [3].

Data from China Antimicrobial Surveillance Network show resistance rate of *K. pneumoniae* to meropenem and imipenem increase from 2.9 to 3.0% in 2005 and 26.3 and 25% in 2018, respectively. While in Europe, carbapenem-resistant *K. pneumoniae* are most common in Mediterranean and Balkan countries, with a prevalence of 60% in Greece and 40% in Italy [4].

The mortality rate of Health Care Related Infections (HAI) caused by carbapenem-resistant enterobacteria, specifically *K. pneumoniae*, ranges from 30% to 50%, with BSI being the most important infection, with a high risk of mortality [5]. In Brazil, this pathogen has become endemic in some regions of the country [2,6].

According to the Brazilian SCOPE study, 58.5% of BSI were caused by a Gram-negative. The overall mortality rate was 40% in patients with BSI, 49% of BSI occurred in patients admitted to Intensive Care and 5% had a polymicrobial origin (isolated more than one microorganism in the blood culture) [7,8]. Also in that same cohort, the 2013 data showed a total of 2,563 cases of BSI reported by the hospitals included in the study, of which 342 episodes of BSI in pediatric patients (≤16 years of age), 45% of which occurred in Pediatric and Intensive Care and 96% of BSI were monomicrobial and mortality was 21.6% [8].

The International Nosocomial Infection Control Consortium (INICC) [9] cohort, which includes 43 developing countries, reported a mortality rate of 17%. *Klebsiella pneumoniae* and *Acinetobacter spp* isolates ranked third and fourth, respectively, among the main agents isolated as cause of healthcare-associated infection in Brazil [7].

The National Program for Prevention and Control of Health-Related Infections described in its report that among the resistant Gram-negative bacilli that have been reported most frequently as etiologic agents of primary bloodstream infections associated with central venous catheters (IPCSL) in patients hospitalized in pediatric PICUs are: *Klebsiella pneumoniae* carbapenem-resistant to third and fourth generation cephalosporins and carbapenems. These data lead us to the need to know the prognostic factors of patients with positive blood cultures for bloodstream infection by KPC during hospitalization, and thus contribute to decision-making aimed at prevention and better prognosis of these patients.

Therefore, this study sought to identify the prognostic factors of patients who had presented laboratory-defined KPC bloodstream infection during hospitalization in the Pediatric Intensive Care Unit of a high-complexity Brazilian hospital between 2013 and 2018.

Methods

Historical cohort study with children hospitalized in the Pediatric Intensive Care Unit of a high-complexity university hospital, who were diagnosed with *Klebsiella pneumoniae* carbapenemase bloodstream infection confirmed in the laboratory. The institution has 226 beds, including 20 PICU-specific beds, between 2013 and 2018.

Data collection

The following variables were collected:

Outcome: positive blood cultures for *Klebsiella pneumoniae* carbapenemase, laboratory confirmed, after 48 hours in the PICU, at discharge or on the day of death.

Demographic data: age, weight, color, gender

Clinical characteristics: *PELOD-2* score, length of stay in PICU, exposure to broad spectrum antibiotics, PICU admission, invasive devices, solid organ transplantation, parenteral nutrition, combined therapy.

Definitions

Bloodstream Infection (BSI) results from blood cultures (HMC) positive for *Klebsiella pneumoniae* carbapenemase laboratory confirmed and identified by the service's Hospital Infection Control Subcommittee (SCIH) according to the diagnostic criteria of the National Agency for Sanitary Surveillance (ANVISA) [10] and Centers for Disease Control and Prevention/ National Healthcare Safety Network (CDC/NHSN) [11,12] described below:

Criteria 1	Patient older than 28 days with a pathogen identified in one or more blood cultures AND The microorganism identified is not related to another infectious focus
Criteria 2	Patient > 1 year presents with at least one of the following signs or symptoms: • Fever (>38°C) • Chills • Hypotension (systolic pressure ≤ 90 mmHg) AND Two or more blood cultures, collected at separate times on the same day or no later than the next day, positive for skin contaminating agents: *Corynebacterium spp*. (excludes C. diphtheriae), *Bacillus spp*. (excludes B. anthracis), *Propionibacterium spp*., *Coagulase negative Staphylococcus, Streptococcus viridans, Aerococcus spp. and Micrococcus spp*. AND The identified microorganism is not related to another infectious focus
Criteria 3	Children > 28 days and ≤ 1year present with at least one of the following signs or symptoms: • Fever (>38°C) • Hypothermia (<36°C) • Apnea • Bradycardia AND Two or more blood cultures, collected at separate times on the same day or no later than the next day, positive for skin contaminating agents: *Corynebacterium spp*. (excludes C. diphtheriae), *Bacillus spp*. (excludes B. anthracis), *Propionibacterium spp., Coagulase negative Staphylococcus, Streptococcus viridans, Aerococcus spp. and Micrococcus spp*. AND The identified microorganism is not related to another infectious focus

Primary catheter-associated bloodstream infection should be considered only if the patient has been using a central catheter for a period longer than two calendar days (with D1 being the day the device was installed) and that on the date of infection the patient was either wearing the device or the device was removed the day before.

All microbiological tests were performed according to the guidelines established by the Clinical and Laboratory Standards Institute [13].

Exposure to broad-spectrum antibiotics before infection: patients who had received a broad-spectrum antimicrobial (vancomycin, meropenem, piperacillin and tazobactam, linezolid, fluconazole, ceftriaxone, cefepime, ciprofloxacin, levofloxacin) up to 60 days before infection.

Combined therapy: patients who received two or more antimicrobials in the same period with activity against the bacteria;

Death: the frequency of deaths occurring within 30 days after diagnosis of infection was verified;

Colonization: patients who had *Klebsiella pneumoniae* carbapenemase isolated in the rectal swab, urine and/or tracheal secretions when admitted to the unit, but without any clinical expression or detection of an immune response in patients, when this was isolated;

Early therapy: Administration of the prescribed therapy up to 24 hours before the blood culture and sensitivity results of the antibiogram.

Previous admission to the PICU: because there is no consensus in the literature about previous hospitalization, this study considered

patients who had been admitted to the PICU up to 120 days before the infection;

Invasive devices: Indwelling urinary catheter, invasive blood pressure, orotracheal cannula, drains, tracheostomy tube, gastrostomy tube, central venous catheter.

Date of infection: is the date when the first element (sign, symptom, or imaging or laboratory test results) used to define IPCSL occurred within the 7-day infection window period;

Infection window period: period of 7 days during which all elements (signs, symptoms, results of imaging and/or laboratory tests) necessary to define the infection are identified. To identify the IPCSL window period, three days before and three days after the date of the first positive blood culture should be considered;

Time frame for repeat infections: For IPCSL, a patient cannot have more than one event reported within a 14-day period.

The time limit for repeat infections applies only to a single admission to the health facility. This time limit does not extend to different hospitalizations, even if they are in the same institution.

Patient's discharge from the PICU was defined by the physician based on clinical improvement and laboratory test results.

To assess the severity of cases of organ dysfunction syndrome, we used the Pediatric Logistic Organ Dysfunction score (PELOD-2) [14], which includes ten variables corresponding to five organ systems and determines the severity of multiple organ dysfunction syndrome in the PICU on a scale to be continued. This tool is divided into four subsections and the scoring considers the cardiovascular, neurological, respiratory, hematological and renal systems. Based on the score for each system, a dysfunction score is assigned, and a mortality rate is estimated.

The comorbidities considered were those of primary character and liver disease was defined based on the criteria of the King's College and Pediatric Acute Liver Failure Study Group, which included: biochemical evidence of acute liver failure (increased transaminases and bilirubins associated with hepatic coagulopathy (INR>1,5 or PT >15 seconds compared to control, no response to vitamin K administration, in a patient with hepatic encephalopathy) [15,16].

Data Analysis

Categorical variables were presented by absolute and relative frequencies. Quantitative variables were calculated, including mean, median, standard deviation and minimum and maximum values. Association between categorical variables was accomplished by Pearson's chi-square test or Fisher's exact test. Comparison between quantitative variables between groups was obtained by the Mann-Whitney test, following a data normality test. Univariate and multiple logistic regression was used to calculate the odds ratio (OR), as well as the 95% confidence interval (95% CI) of the association measure. To analyze survival, we evaluated the period between infection and death, and used the Kaplan-Meier survival curve and survival probabilities at specific dates (7, 14, 21 and 28 days). The significance level was set at 5% for all statistical tests. All analyzes were carried out using a statistical software (SPSS 18 for Windows).

Results

During the period of data collection, 2.696 patients were admitted to the PICU, 92 patients had bloodstream infection (BSI) by different microorganisms, and only 34 of these BSIs were laboratory-confirmed *Klebsiella pneumoniae* carbapenemase isolates, as shown in Figure 1.

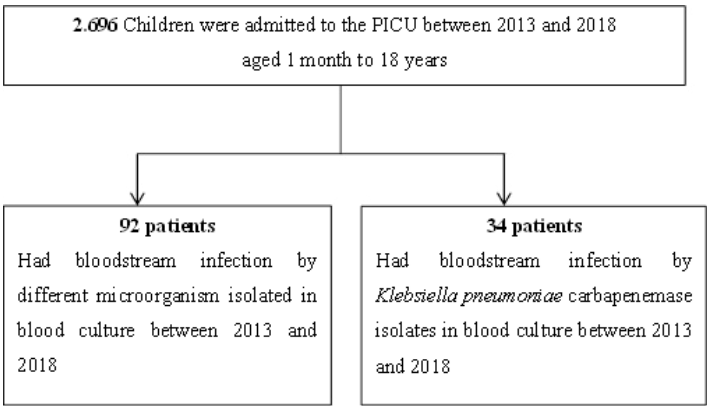

Figure 1: *Klebsiella pneumoniae* carbapenemase isolates.

Most patients were male (58.8%), infants (52.9%), 35.3% were malnourished, all had chronic underlying diseases and had hospitalization up to 6 months prior to admission to the PICU before infection. Hepatopathies were the most frequent underlying disease (47.1%). The median age was 22 months (2-208) and the median weight was 9 kg (3-50).

The clinical characteristics showed that 31 (91.2%) of the patients had central venous access, 21 (67.7%) located in the internal jugular vein, and 30 (88.2%) received combined antimicrobial therapy. In 24(70.6%) antibiotic therapy was prescribed and administered within 48h before the HMC result was released by the laboratory. 41,2% of patients had isolated KPC in other sites such as ascitic fluid, urine and tracheal secretion and 9 (26.5%) of patients were colonized (had the bacteria identified in rectal swab research). Also, mechanical ventilation was used in 23 (67.6%) of the patients, indwelling urinary catheter in 18 (52.9%), and hemodiafiltration in 14 (41.2%).

Antimicrobial resistance profile according to antibiogram and treatment

We observed a significant predominance of beta-lactams and carbapenems resistance. Colistin was the most sensitive antibiotic, followed by tigecycline and aminoglycosides (Table 1):

Antimicrobial	Sensitive n (%)	Intermediate n (%)	Resistant n (%)
Colistin	**33 (97.0)**	**0**	**1 (3)**
Tigecycline	**32 (94.)**	**0**	**2 (6)**
Amikacin	**28 (82.3)**	**1 (3)**	**5 (14.7)**
Gentamicin	**20 (58.8)**	**0**	**14 (41.2)**
Ampicillin	0	0	34 (100)
Cefepime	1 (3)	0	33 (97)
Cefoxitin	1 (3)	1 (3)	32 (94)
Ceftazidime	0	0	34 (100)
Ceftriaxone	0	0	34 (100)
Cefuroxime	0	0	34 (100)
Ciprofloxacin	0	0	34 (100)
Ertapenem	0	0	34 (100)
Imipenem	0	0	34 (100)
Meropenem	0	1(3)	33 (97)
Piperacillin + tazobactam	0	0	18 (53)
Results in number (%)			

Table 1: Sensitivity profile of children hospitalized in PICU with KPC bloodstream infection between 2013 and 2018.

The minimum inhibitory concentration (MIC) of Meropenem was ≥16 μg/ml (33/34, 97%) and 1/34 (3%) was intermediate for merepenem MIC (MIC, 8 μg/ml); Imipenem ≥16 μg/ml (34/34, 100%) and Ertapenem ≥8 μg/ml (34/34, 100%).

Demographic and clinical factors were evaluated in association to the death occurrence in this group of children and adolescents (n = 23). Table 2 shows the variables distributions according to the patient's vital status (discharge or death), revealing that parenteral nutrition (p=0.038), in addition to *PELOD-2* scores on the day of infection (p=0.005), *PELOD-2* scores 48 hours after infection were statistically significant regarding the patients' prognostic (survivors x non-survivors).

Variables	Discharge n=11	Death n=23	*p*
Gender[2]			1
Female	7 (63.6)	13 (56.5)	
Male	4 (36.4)	10 (43.5)	
Age group[2] Infant/preschool	9 (81.8)	14 (60.9)	0.271
School/adolescent	2 (18.2)	9 (39.1)	
Age (months)[3]	20 (4-69)	24 (2-208)	0.376
Nutritional status[1] Low weight	7 (63.6)	10 (43.5)	0.271
Normal, overweight or obese	4 (36.4)	13 (56.5)	
Hemodialysis[2]	4 (36.4)	10 (43.5)	1
Prior antibiotic therapy[2]	10 (90.9)	14 (60.9)	0.113
Late bladder catheter[1]	6 (54.5)	12 (52.2)	0.897
Parenteral nutrition[1]	8 (72.7)	8 (34.8)	0.038

Intubation[2]	7 (63.6)	16 (69.6)	1
Percutaneous abdominal decompression[2]	2 (18.2)	7 (30.4)	0.682
Patient receiving combination therapy[2]	11 (100)	19 (82.6)	0.280
Central venous access[2]	11 (100)	20 (87)	0.535
Other bacteria besides KPC in hemoculture[2]	2 (18.2)	3 (13.0)	1
Colonized Patients[2]	3 (27.3)	6 (26.1)	1
Presence of KPC in other sites before positive hemoculture[2]	3 (27.3)	11 (47.8)	0.295
Meropenem time of infection (days)[3]	27.5 (43.3)	10.6 (9.7)	0.172
Hepatopathies[1]	6 (54.5)	10 (43.5)	0.545
PELOD-2 at admission[3]	6.09 (2.63)	7.04 (2.10)	0.314
PELOD-2 on the day of infection[3]	7 (4-11)	11 (4-15)	0.005
PELOD-2 48 h after infection[3]	5 (2–9)	13 (2–17)	<0.001
PELOD-2 at death or day of discharge[3]	3 (2–7)	12 (6–17)	<0.001
Results presented in n (%), mean and median. [1]Pearson's chi-square test; [2]Fisher's exact test; [3]Mann-Whitney test.			

Table 2: Factors related to mortality of children hospitalized in PICU with KPC bloodstream infection between 2013 and 2018.

The HMC negative control after starting antibiotic therapy was unavailable in 23/16 (69.6%) died patients at the time of death, and the median time between positive blood culture (BSIs) and the death event was 1,5 (0 -14) days. The median time to treat the infection in this group of patients was 6 (4-57) days.

To determine the risk factors associated with mortality, the Odds Ratio (OR) and its respective 95% confidence interval were calculated, using logistic regression for the variables that presented statistical significance in the univariate analysis: *PELOD-2* on the day of infection, *PELOD-2* 48h after infection and *PELOD-2* in the occurrence of death or discharge. An increase of one unit in the *PELOD-2* score on the day of the diagnostic of infection increased the risk of death by 56% and in the score 48 hours after infection, by 64%, as shown in Table 3.

Characteristics	**Death n = 23**	**OR_{crude} (95% CI)**	**p-value**	**$OR_{adjusted}$ (95% CI)**	**p**
Parenteral nutrition					
No	15 (65,2)	1		1	
Yes	8 (34,8)	0,20 (0,04-0,97)	**0,046**	0,06 (0,003-1,10)	0,058
***PELOD-2* on day of infection**					
Mean (SD)	10,17 (2,82)	1,56 (1,12-2,18)	**0,009**		
Median (min-max)	11 (4-15)				
***PELOD-2* 48h after infection**					

Mean (SD)	11,39 (4,03)	1,64 (1,16-2,32)	**0,005**	1,81 (1,22-2,68)	**0,003**
Median (min-max)	13 (2-17)				
***PELOD-2* at death or day of discharge**					
Mean (SD)	12,24 (3,19)	4,22 (0,89-20,13)	0,071		
Median (min-max)	12 (6-17)				
SD: standard deviation; min: minimum value; max: maximum value.					

Table 3: Factors associated with death in children hospitalized in PICU with KPC bloodstream infection between 2013 and 2008.

Survival Analysis

The time between hospitalization and death in children with carbapenem-resistant *Klebsiella pneumoniae* infection was analyzed in the survival curve, according to the follow-up period (7, 14, 21 and 28 days) as showed in Figure 2.

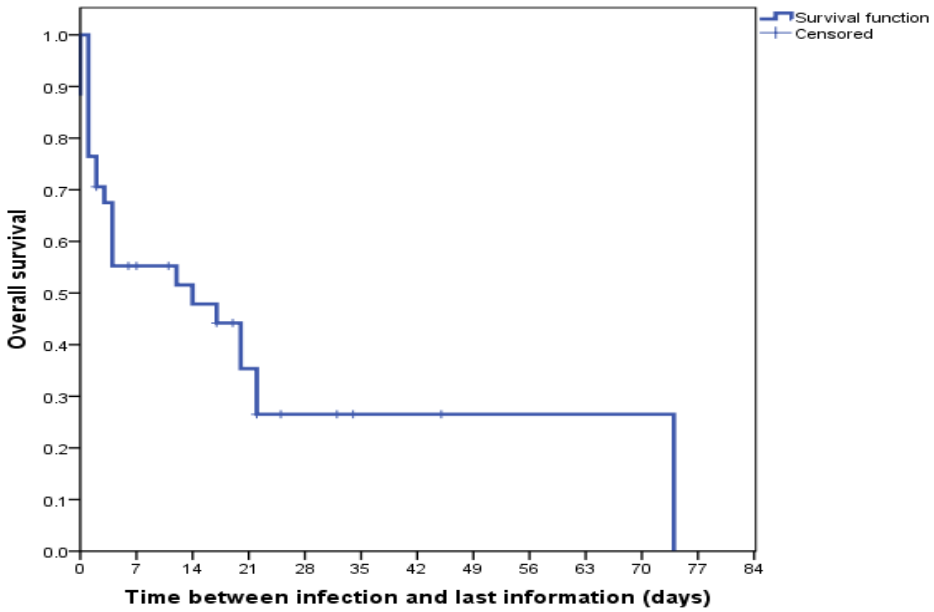

Figure 2: Survival probability in children with KPC-induced BSI, who are hospitalized in the PICU between 2013-2018.

Discussion

Increased microbial resistance by enterobacteria is considered a global and public health problem, associated with little research on KPC bloodstream infection in critically ill children.

Knowing evidence-based interventions can contribute to reduce the risk of KPC ICS and is fundamental for improving care for critically ill patients, as this bacteria has a high power of dissemination [17].

The profile of patients who had positive blood cultures for *Klebsiella pneumoniae* carbapenemase during hospitalization in the PICU is similar to that described in other publications conducted in hospitals with tertiary care level, showing patients with chronic underlying disease, predominance of males, infants, malnourished with comorbidities, in addition to previous hospitalization [17-19].

The mortality rate in the present series was 23/34 (67.6%) being higher when compared to other similar studies, however it was influenced by several factors such as: presence of various

comorbidities, invasive devices, high number of surgical procedures with solid organ transplants and number of organic dysfunctions after infection [5-7,25,29].

In a systematic review6 with 51 studies to estimate the evolution of patients infected with KPC, overall mortality was 41.0% (95% CI 37.0-44.0) and significant differences were found in the analysis of subgroup by countries being higher in Brazil, with mortality of 51.0% (95%CI 43.0-60.0). In addition, Brazil was also the country with the lowest number of studies in critically ill patients, and no study evaluated a specific type of infection and factors that could increase the risk of mortality in patients [6].

In another study [5] with 4,701 patients, the mortality of patients with bloodstream infection (BSI) was 54.30%, and 48.9% of them were admitted to an Intensive Care Unit (ICU) or underwent solid organ transplantation (SOT). The mortality rate in patients with carbapenem-resistant *K. pneumoniae* infection was 42.14% versus *K. pneumoniae* susceptible to carbapenem 21.2%.

Although 16/23 (69.6%) of the patients who progressed to death still did not have negative control blood culture, even so due to the large number of comorbidities that patients had, it is not possible to directly relate deaths only to blood cell infection by KPC.

In the present study, the *PELOD-2* score was significantly higher in the patients who did not survived. The most present dysfunctions were respiratory, hematological and renal, and explained, respectively, 56% and 64% of the variation in relation to mortality risk, besides the fact that 67.6% of the patients presented two to three dysfunctions from the date of infection. The presence of new organ dysfunctions during the PICU stay is associated with an increased risk of mortality [14].

Regarding the use of combination therapy, the literature shows results of studies with the adult population with blood bloodstream infections by KPC and found benefit of related mortality with combined antimicrobial therapy, in particular, with combinations containing carbapenem [20]. In contrast to other studies [21,22] have suggested that this benefit is limited to patients at higher risk of mortality (including patients with septic shock, fatal underlying diseases and bacteremia from non-urinary/ non-biliary sources) specifically, for combinations containing carbapenem, for isolates with carbapenem MICs ≤8 μg/mL, a result that is in line with the findings of the present study.

The literature [1] shows that several mechanisms of resistance to carbapenem in vitro result in varyingly elevated meropenem CIMs, it is already known that meropenem plays an important role in the treatment of resistant enterobacteria infections in clinical scenarios where meropenem CIMs are ≤2 μg /mL.

Bacterial death from carbapenems depends on the drug's free time above MIC, considered an optimal effect if the time above MIC exceeds 40% [1]. Pharmacokinetic data in pediatrics showed that, in healthy children, a prolonged infusion of meropenem for more than 3 hours can reach this goal for isolates with meropenem CIMs until 8 μg/mL [23]. However, in critically ill children, target serum concentrations are reliably achieved only for isolates with meropenem CIMs ≤2 μg/mL due to changes in the expected distribution volumes with sepsis [24]. In the present study, the MIC value was ≥16 μg/ml (33/34, 97%) for meropenem.

The antimicrobial therapy prescribed in this study coincides with the guidelines of ANVISA [28] Technical Note 01/2013, and in international studies [21,27] where the appropriate empirical therapy for multidrug-resistant enterobacteria infections is the use of polymyxin B or polymyxin E (colistin), in association with one or more antimicrobials such as aminoglycosides (gentamicin or amicacin), carbapenems (meropenem or doripenem) and tigecycline, avoiding the use of monotherapy due to the risk of developing resistance.

Studies with adults show that the institution of appropriate therapy is directly related to the reduction of mortality [27].

Early therapy was used in 19/34 patients (56%) of this population, and in 8/34 cases (23.5%) it was prescribed within 12 hours after blood culture results, and in 7/34 cases (20.5%) the appropriate therapy was prescribed within 48 hours after blood culture release. A study [29] demonstrates that for each hour of delay in administration there was an increase of 0.095 days in the length of stay in the ICU after infection.

The main prognostic factors associated with *Klebsiella pneumoniae* carbapenemase infection in children admitted to the PICU described in another study [26], conducted in Istanbul, were the use of mechanical ventilation, use of vasoactive drugs, previous hospitalization, acute renal injury, use of total parenteral nutrition, need for red blood cells transfusion and surgical procedures.

The resistance profile found in this study is similar to previously published studies [23], showing high resistance of KPC to carbapenems and cephalosporins, and consequent need for prevention studies, considering the susceptibility of the pediatric population.

When pathogenic bacteria develop resistance to multiple classes of antimicrobials, previously treatable diseases become lethal. Combating this challenge requires not only the discovery of new antimicrobial drugs, but also technological investment in rapid diagnosis and education of health professionals in the proper indication of antimicrobials, in addition to the participation of industry in the development of devices with technologies that also contribute to reduce the risk of infections related to health care.

Optimal therapy for the treatment of KPC bloodstream infection is not yet well defined for critically ill paediatric patients. It depends on the susceptibility of individual isolates of each patient and the choices that are very limited, based on the therapy used in adults.

The main limitation of this research was the fact that it was carried out in a single center, with retrospective design, being subject to data loss due to incomplete completion of medical records and small sample size.

Conclusion

The frequency of deaths was 23/34 cases, with mortality of 67.6% and the *PELOD-2* score was the most relevant prognostic factor. The increase of one unit of the score on the day of infection increased the risk of death by 56% and the increase of one unit of the score in 48 hours after infection increased the risk of death by 64%.

Considering that the result of blood culture with antibiogram can take up to 72 hours to be obtained, these data corroborate the fact that measures aimed at the prevention and control of Carbapenem-resistant *K. pneumoniae* infection are of great relevance especially in patients admitted to Intensive Care.

Contribution

Santos MLBM, Carvalho WB e Ferreira JCOA: Conception and design of the study, data collection, analysis and interpretation of the data, writing of the article and critical review of the important intellectual content, final approval of the version to be submitted.

Taminato M, Fernandes GJ e Delgado AF: Data collection, or analysis and interpretation of the data, writing of the article or critical review of the important intellectual content, final approval of the version to be submitted.

Ethical Considerations

The study was approved by the Research Ethics Committee. Certificate of Presentation for Ethical Appreciation (CAAE): 55779116.6.0000.0068. Research Ethics Committee Approval: 1.552.715.

References

1. Chiotos K, Hayes M, Gerber JS, Tamma PD (2020) Treatment of Carbapenem-Resistant Enterobacteriaceae Infections in Children. J Pediatric Infect Dis Soc 29: 56-66.
2. Goto M, Al-Hasan MN (2013) Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. Clin Microbiol Infect 19: 501-509.
3. Han R, Shi Q, Wu S, Yin D, Peng M, et al. (2020) Dissemination of Carbapenemases (KPC, NDM, OXA-48, IMP, and VIM) Among Carbapenem-Resistant Enterobacteriaceae Isolated From Adult and Children Patients in China. Front Cell Infect Microbiol 10: 314.
4. Feil EJ (2017) Enterobacteriaceae: joining the dots with pan-European epidemiology. Lancet Infect Dis 17: 118-119.
5. Xu L, Sun X, Ma X (2017) Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant *Klebsiella pneumoniae*. Ann Clin Microbiol Antimicrob 16:18.
6. Ramos-Castañeda JA, Ruano-Ravina A, Barbosa-Lorenzo R, Paillier-Gonzalez JE, Saldana-Campos JC, et al. (2018) Mortality due to KPC carbapenemase-producing *Klebsiella pneumoniae* infections: Systematic review and meta-analysis: Mortality due to KPC *Klebsiella pneumoniae* infections. J Infect 76: 438-448.
7. Marra AR, Camargo LFA, Pignatari ACC, Sukiennik T, Behar PRT, et al. (2011) Nosocomial bloodstream infections in Brazilian hospitals: analysis of 2,563 cases from a prospective nationwide surveillance study. J Clin Microbiol 49: 1866-1871.
8. Pereira CAP, Marra AR, Camargo LFA, Pignatari ACC, Sukiennik T, et al. (2013) Nosocomial bloodstream infections in Brazilian pediatric patients: microbiology, epidemiology, and clinical features. PLoS One 8: e68144.
9. Rosenthal VD, Maki DG, Mehta Y, Leblebicioglu H, Memish ZA, et al. (2014) International Nosocomial Infection Control Consortium (INICC) report, data summary of 43 countries for 2007-2012. Device-associated module Am J Infect Control 42: 942-956.
10. (2017) Agência Nacional de Vigilância Sanitária. Critérios Diagnósticos de Infecções Relacionadas à Assistência à Saúde. Agência Nacional de Vigilância Sanitária. Brasília: ANVISA.
11. (2009) Centers for Disease Control and Prevention. CDC. The National Healthcare Safety Network (NHSN) Manual. Patient Safety Component Protocol. Division of Healthcare Quality Promotion. Division of Healthcare Quality Promotion National Center for Preparedness, Detection and Control of Infectious Diseases.
12. Disease (ESCMID), & Hellenic Society of Chemotherapy (HSC) and Società Italiana di Terapia Antinfettiva (SITA) (2018). Management of KPC-producing *Klebsiella pneumoniae* infections. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 24: 133-144.
13. (2013) Performance Standards for Antimicrobial Susceptibility Testing; 23st Informational Supplement. CLSI document M100-S23. Clinical and Laboratory Standards Institute. 33.
14. Leteurtre S, Duhamel A, Deken V, Lacroix J, Leclerc F, Groupe Francophone de Réanimation et Urgences Pédiatriques (2015) Daily estimation of the severity of organ dysfunctions in critically ill children by using the *PELOD-2* score. Crit Care 19: 324.
15. Pham YH, Miloh T (2018) Liver Transplantation in Children. Clin Liver Dis 22: 807-821.
16. Bhatt H, Rao GS (2018) Management of Acute Liver Failure: A Pediatric Perspective. Curr Pediatr Rep 6: 246-257.
17. Bassetti M, Giacobbe DR, Giamarellou H, Viscoli C, Daikos GL, et al. (2018) Management of KPC-producing *Klebsiella pneumoniae* infections. Clin Microbiol Infect 24: 133-144.
18. Dong F, Zhang Y, Yao K, Lu J, Guo L, et al. (2018) Epidemiology of Carbapenem-Resistant *Klebsiella pneumoniae* Bloodstream Infections in a Chinese Children's Hospital: Predominance of New Delhi Metallo-β-Lactamase-1. Microb Drug Resist 24: 154-160.

19. Díaz A, Ortiz DC, Trujillo M, Garcés C, Jaimes F, et al. (2016) Clinical Characteristics of Carbapenem-resistant *Klebsiella pneumoniae* Infections in Ill and Colonized Children in Colombia. Pediatr Infect Dis J 35: 237-241.

20. Qureshi ZA, Paterson DL, Potoski BA, Kilayko M, Sandovsky G, et al. (2012) Treatment outcome of bacteremia due to KPC-producing *Klebsiella pneumoniae*: superiority of combination antimicrobial regimens. Antimicrob Agents Chemother. 56: 2108-2113.

21. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, et al. (2017) Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. Lancet Infect Dis 17: 726-734.

22. Daikos GL, Tsaousi S, Tzouvelekis LS, Anyfantis I, Psichogiou M, et al. (2014) Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. Antimicrob Agents Chemother. 58: 2322-2328.

23. Courter JD, Kuti JL, Girotto JE, Nicolau DP (2009) Optimizing bactericidal exposure for beta-lactams using prolonged and continuous infusions in the pediatric population. Pediatr Blood Cancer. 53: 379-385.

24. Cies JJ, Moore WS 2nd, Enache A, Chopra A (2017) Population Pharmacokinetics and Pharmacodynamic Target Attainment of Meropenem in Critically Ill Young Children. J Pediatr Pharmacol Ther 22: 276-285.

25. Zhang Y, Guo LY, Song WQ, Wang Y, Dong F, et al. (2018) Risk factors for carbapenem-resistant K. pneumoniae bloodstream infection and predictors of mortality in Chinese paediatric patients. BMC Infect Dis. 18:248.

26. Aygun F, Aygun FD, Varol F, Durak C, Cokugras H, et al. (2019) Infections with Carbapenem-Resistant Gram-Negative Bacteria are a Serious Problem Among Critically Ill Children: A Single-Centre Retrospective Study. Pathogens. 8: 69.

27. Liang Q, Huang M, Xu Z (2019) Early use of polymyxin B reduces the mortality of carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection. Braz J Infect Dis 23: 60-65.

28. (2013) Agência Nacional de Vigilância Sanitária (ANVISA). Nota Técnica n° 1/2013-Medidas de prevenção e controle de infecções por enterobactérias multiresistentes. Brasília (DF): ANVISA.

29. Zhang D, Micek ST, Kollef MH (2015) Time to Appropriate Antibiotic Therapy Is an Independent Determinant of Postinfection ICU and Hospital Lengths of Stay in Patients With Sepsis. Crit Care Med 43: 2133-2140.