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Healthcare-Associated Infections in Paediatric Patients: A Decade of Experience in an Intensive Care Unit

Infeções Associadas aos Cuidados de Saúde em Idade Pediátrica: 10 Anos de Experiência num Serviço de Cuidados Intensivos

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ABSTRACT

Introduction: Healthcare-associated infections are an important cause of morbidity and mortality in the pediatric population and a growing problem in intensive care services. However, limited data are available on these infections in the Portuguese pediatric population. This study aimed to estimate its prevalence rate in a Portuguese pediatric intensive care unit, identifying the most frequent microorganisms and their antibiotic resistance profiles.

Methods: A retrospective cohort study was conducted, including patients admitted to a pediatric intensive care unit between January 1, 2014 and December 31, 2023, who were diagnosed with healthcare-associated infections during hospitalization.

Results: A total of 248 nosocomial infections were identified, corresponding to a prevalence rate of 6.3%, mostly in infants. Pneumonia (45.2%) and bacteremia (14.5%) were the most frequent infections. Gram-negative bacteria, specifically *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, were the most common pathogens. Over the last five years (2019 - 2023), there was a global increase in antibiotic resistance. The prevalence of infections with ESBL-producing bacteria, MRSA and ERC was 8.5%, 1.6%, and 0.4%, respectively, higher in the period from 2019 to 2023. Among 97 screening tests, 45 colonizations were identified in 41 patients: 40 with ESBL and 5 with ERC, with no MRSA colonizations detected. Sepsis occurred in 29.8% of cases, and the mortality rate was 11.7%, with 4.0% directly attributed to healthcare-associated infections. Risk factors for pneumonia included exposure to endotracheal tubes and prolonged invasive ventilation (OR = 2.5; 95% CI, 1.1 to 5.9, p = 0.03; and OR = 1.9; 95% CI, 1.1 to 3.4, p = 0.011; respectively).

Conclusion: Implementing effective strategies to prevent and control resistant bacteria is essential to safeguard current therapies, enhance patient safety, and protect public health.

Keywords: Child; Critical Care; Cross Infection; Drug Resistance, Microbial; Intensive Care Units, Pediatric

RESUMO

Introdução: As infeções associadas aos cuidados de saúde são uma causa importante de morbimortalidade na população pediátrica, representando um problema crescente nos serviços de cuidados intensivos. Contudo, existem poucos estudos que caracterizam a realidade destas infeções na população pediátrica portuguesa. Este estudo pretendeu avaliar a sua prevalência num serviço de cuidados intensivos pediátrico português, identificando os microrganismos mais frequentes e o respetivo perfil de resistência aos antibióticos.

Métodos: Estudo de coorte retrospetivo que incluiu os doentes admitidos num serviço de cuidados intensivos pediátrico entre 1 de janeiro de 2014 e 31 de dezembro de 2023, com diagnóstico de infeções associadas aos cuidados de saúde durante o internamento.

Resultados: Identificaram-se 248 casos, correspondendo a uma prevalência de 6,3%, a maioria em lactentes. As infeções mais frequentes foram pneumonia (45,2%) e bacteriemia (14,5%), sendo os agentes infeciosos mais comuns os Gram negativos, nomeadamente a *Escherichia coli*, a *Pseudomonas aeruginosa* e a *Klebsiella pneumoniae*. Observou-se um aumento global das resistências antibióticas nos últimos cinco anos (2019 - 2023). A taxa de infeção por bactérias produtoras de ESBL, MRSA e ERC foi, respetivamente, 8,5%, 1,6% e 0,4%, superior nos anos 2019 - 2023. Houve 45 colonizações em 41 doentes (num total de 97 pesquisas realizadas): 40 a ESBL e 5 a ERC (sem colonizações por MRSA). A sépsis ocorreu em 29,8% casos e a mortalidade foi de 11,7% (4,0% devido à IACS). A exposição a tubo endotraqueal e a ventilação invasiva de longa duração associaram-se a maior probabilidade de desenvolver pneumonia (OR = 2,5; IC 95%, 1,1 a 5,9; p = 0,03; e OR = 1,9; IC 95%, 1,1 a 3,4; p = 0,011; respetivamente).

Conclusão: É fundamental implementar estratégias eficazes para prevenir e controlar a disseminação das bactérias resistentes, assegurando a eficácia das terapêuticas atuais, a segurança dos doentes e a proteção da saúde pública.

Palavras-chave: Criança; Cuidados Intensivos; Infeção Hospitalar; Resistência Microbiana a Medicamentos; Unidades de Cuidados Intensivos Pediátricos

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KEY MESSAGES

- The prevalence of healthcare-associated infections (HAIs) found in this study was in line with other international studies. These mostly affected infants and children with a personal history of cardiac or perinatal pathology. The number of infections caused by ESBL(extended-spectrum beta-lactamase)-producing, CRE (carbapenem-resistant Enterobacteriaceae) and MRSA (methicillin-resistant *Staphylococcus aureus*) microorganisms has increased throughout the second study period (2019 - 2023), even though the colonisation rates by these microorganisms has been lower when compared to those described worldwide.
- There are few studies on HAIs in Paediatric Intensive Care departments, and continuous surveillance is crucial for the use of appropriate antibiotic therapy, based on the knowledge of the most common microorganisms involved, as well as the usual antibiotic resistances.
- An increase in antibiotic resistance was found which, even though not statistically significant, is a warning of the need for preventive strategies and wise antibiotic prescribing. These remain crucial to preventing cross-transmission and ensuring the protection of patients and the sustainability in healthcare.

INTRODUCTION

Healthcare-associated infections (HAIs) or nosocomial infections represent the most frequent complications of hospital stays and are related to relevant morbidity and mortality in the paediatric population.[1-3] There is an increasing concern about this subject, especially in Paediatric Intensive Care Units (PICUs). Patients admitted to these units are twice as likely to develop a nosocomial infection as patients admitted to other wards.[4] One of the main risk factors associated with HAIs is the presence of invasive medical devices, widely used in intensive care services, carrying a significant risk of colonisation by bacteria and fungi.[5] The most frequently described HAIs include ventilator-associated pneumonia, urinary tract infection related to bladder catheters and bacteraemia associated with central venous catheters.[4] The causative agents include bacteria, viruses or fungi, in isolation or in combination.[6]

Among the paediatric patients admitted to PICUs, newborns (NB) are particularly vulnerable to these infections, including the presence of low birth weight, prematurity, mechanical ventilation, venipuncture and hypoxic-ischemic encephalopathy as relevant risk factors in this age group.[6] These are also associated with an immature immune system and the frequent use of invasive medical devices.[7-9]

In addition to being potentially fatal, HAIs are associated with prolonged hospital stays, increased resistance to antimicrobials and therefore poorer health outcomes,[5] in addition to increased health-related costs, affecting not only the patient's well-being, but also the quality of healthcare.[10-12]

Although antibiotics are the main tool against bacterial infections, multisensitive bacteria become resistant due to indiscriminate use, limiting therapeutic options and increasing the risk of therapeutic failure.[13] The highest number of infections with multidrug-resistant bacteria is found in the paediatric population, especially in infants.[13,14] Interpatient transmission, in addition to transmission from healthcare professionals and the irrational use of antibiotics are preventable factors involved in this type of infection.[2]

An estimated prevalence of infections acquired in PICU ranging between 9% and 37% has been found in Europe and the United States of America, while HAIs and multidrug resistance represent a threat to global public health.[4] There are few studies characterising HAIs in the Portuguese paediatric population.

This study was aimed at assessing the prevalence of nosocomial infections in a Portuguese PICU over the past 10 years and analysing the most frequent microorganisms involved and their antibiotic resistance profile.

METHODS

Study design and sample selection

A retrospective observational and analytical cohort study was carried out, including all children and adolescents (aged < 18 years) admitted to the PICU of the *Hospital Pediátrico* (Paediatric Hospital) (HP) of the Coimbra Local Health Unit (ULS) between January 1, 2014, and December 31, 2023, and diagnosed with HAI. This is a convenience sample, so the sample size was defined by the total number of HAIs found in the PICU during the study period.

The HP PICU is a neonatal and paediatric medical-surgical unit. It is the only paediatric intensive care unit in the Central region of Portugal.

Data collection

Data were obtained from the patient's clinical files, in accordance with the General Data Protection Regulation, complying with the ethical principles established by the Declaration of Helsinki of the World Medical Association and the study was approved by the Ethics Committee of the ULS Coimbra (registration number OBS.SF.191-2023).

HAI is defined as an infection diagnosed at least 48

hours upon admission to hospital and which was not diagnosed before or at admission. Diagnosis was based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-MC) for coding of diagnoses and procedures.

Demographic and clinical characteristics were analysed, including: patient's gender, age, personal history of previous hospitalisations and dates, origin, diagnosis at admission, medical devices used [central venous catheter (CVC), endotracheal tube (ETT), urinary catheter (UC), drains, parenteral nutrition or others] and dwell time, surgical intervention during hospitalisation, colonisation by methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL) or carbapenem-resistant Enterobacteriaceae (CRE), type of infection, isolated microorganism, biological product isolation, antimicrobial resistance, treatment, length of stay and clinical outcome.

ESBL and CRE screening (at admission and every 10 days during hospitalisation) were regularly obtained at the HP PICU in 2018, while MRSA screening was only started in 2020 (at admission). Initially, screening was only obtained from patients with risk factors for colonisation by multidrug-resistant microorganisms, namely previous hospital stays or surgery (Standard no. 018/2014 updated on 27/04/2015)[15] while more recently all admitted patients were involved, in accordance with the standard in force from the Directorate-General for Health for inpatient departments (Standard no. 004/2023 of 29/05/2023).[16]

Previous hospital stays were considered whenever patients had been admitted to hospital within the previous 30 days. Immunosuppression was considered whenever patients had undergone previous transplants, immunosuppressants (chemotherapy, radiotherapy, and corticoid therapy) or were diagnosed with primary immunodeficiency. Prematurity was considered in patients with a gestational age at birth of less than 37 weeks. Sepsis was defined as a suspected or confirmed infection with a Phoenix sepsis score ≥ 2, including respiratory, cardiovascular, coagulation and/or neurological dysfunction.[17] Short-term ETT was considered for a dwell time < 21 days and long-term ETT for ≥ 21 days.[18,19]

Infection rates were obtained by dividing the number of cases of each type of infection by the total number of infections. Colonisation rates were determined by dividing the number of ESBL/CRE/MRSA colonisations by the total number of screenings. The resistance rate (number of microorganisms resistant to a given group of antibiotics) was divided by the total number of microorganisms screened for that same group. The prevalence of HAIs was calculated by dividing the number of HAI cases by the total number of hospitalisations during the study period.

Statistical analysis

The statistical analysis involved the use of the IBM® SPSS® Statistics version 27 software. Categorical variables are presented as absolute frequencies and percentages. Continuous variables are presented as mean and standard deviation (SD) in the case of normal distribution or as median and interquartile range (IQR) in the case of non-normal distribution. The normality of the distribution was checked using the Shapiro-Wilk test. Bivariate analysis involved the use of chi-square test or Fisher's exact test whenever appropriate. A *p*-value of < 0.05 was considered statistically significant. The relationship between variables was investigated by calculating the odds ratio, which was only considered significant when the confidence interval did not include a value of 1. An a priori power analysis was carried out with the aim of achieving a statistical power of 0.8 and a significance level (α) of 0.05, leading to the conclusion that 88 was the minimum sample size.

In addition, a survival analysis was carried out using the Kaplan-Meier curve aimed at the assessment of the relationship between the dwell time and the development of infection.

RESULTS

A total of 3,913 paediatric patients were admitted to the HP PICU within the study period, corresponding to 391.3 mean ± 17.6 SD admissions per year. Within this period, 248 patients were diagnosed with HAI, corresponding to a 6.3% prevalence. A variable distribution of HAIs during the study period was found over the years (Fig. 1), ranging from a minimum of 19 patients diagnosed with HAI in 2020 and 2022 and a maximum of 32 in 2019 (24.8 mean ± 4.4 SD cases per year). The number of patients diagnosed with HAI per 1,000 device-days (data were only available from 2019 onwards) is shown in Fig. 2.

The characteristics of our group of patients are shown in Table 1. Most patients diagnosed with HAI (55.2%) were less than a year old at admission, with a median age of 6.3 months (IQR: 12 – 3,353 days, corresponding to 0.03 - 9.2 years). Clinical history included cardiac pathology (particularly congenital heart disease with heart failure or need for surgery), perinatal pathology (especially prematurity) and gastrointestinal pathology (with the need for surgery). In total, 160 (64.5%) patients underwent surgery during the hospital stay at the PICU. The median (IQR) length of stay in the PICU was 21 (13 - 37) days and the time from admission to diagnosis was 10 (5 - 18) days; 29 patients died (11.7%), 10 (34.5%) from which were related to nosocomial infections. At admission, a median Paediatric Index of Mortality 3 (PIM) score of 10.1 (5.6 - 13.2) has been found in deceased patients.

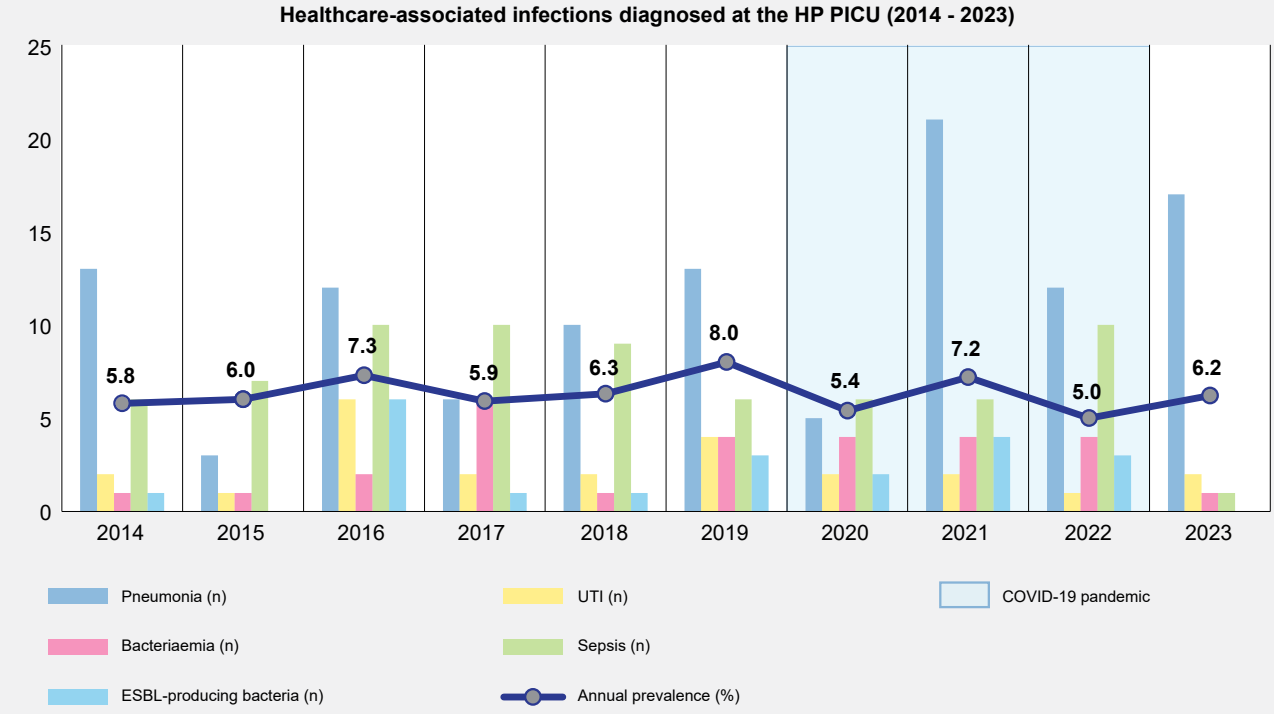

Figure 1 – Annual distribution of patients diagnosed with nosocomial infection (n = 248)
ESBL: Extended-spectrum beta-lactamase-producing Enterobacteriaceae; HP: Hospital Pediátrico (Paediatric Hospital); UTI: urinary tract infection; PICU: Paediatric Intensive Care Unit

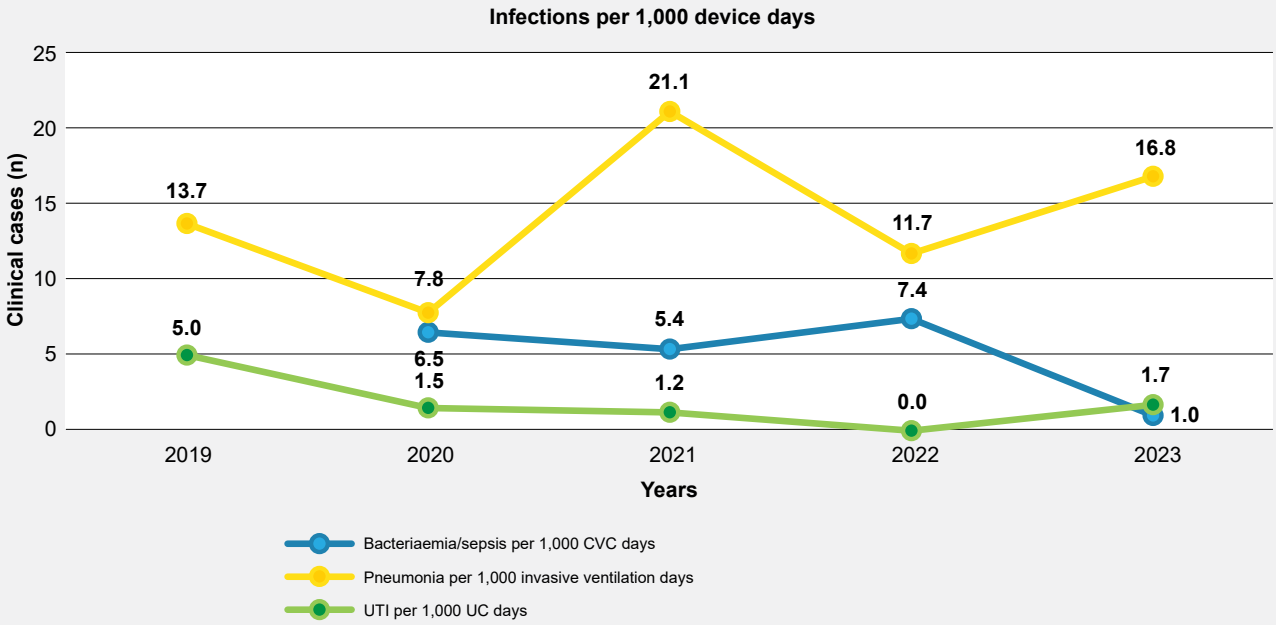

Figure 2 – Infections per 1,000 device days. Data were only available from 2019 onwards.
CVC: central venous catheter; UTI: urinary tract infection; UC: urinary catheter.

Table 1 – Demographic and clinical characteristics of our group of patients

Characteristics	n (%)
Gender	
Male	144 (58.1%)
Patient's age at admission to the PICU	
≤ 28 days	75 (30.2%)
[29 days - 1 year[	63 (25.4%)
[1 - 5 years]	37 (14.9%)
[6 - 9 years]	17 (6.9%)
≥ 10 years	56 (22.6%)
Personal history	
Cardiac pathology	56 (22.6%)
Perinatal pathology	37 (14.9%)
Gastrointestinal pathology	34 (13.7%)
Cancer	28 (11.3%)
Neurological pathology	16 (6.5%)
Endocrine pathology	5 (2.0%)
Urological pathology	3 (1.2%)
Other	7 (2.7%)
Immunosuppression	30 (12.1%)
Previous hospital stay	109 (43.9%)
Origin	
Other hospital	77 (31.0%)
Other medical ward	53 (21.4%)
Other surgical ward	44 (17.7%)
NICU	38 (15.3%)
Emergency Department	36 (14.5%)
Discharged	
To other medical ward	113 (45.6%)
To other surgical ward	70 (28.2%)
To other hospital	21 (8.5%)
To NICU	7 (2.8%)
Home	8 (3.2%)
Deceased	29 (11.7%)

PICU: Paediatric Intensive Care Unit; NICU: Neonatal Intensive Care Unit.

Table 2 – Characteristics of the medical devices and related infections

Devices and infections	n (%)
Devices	
Central venous catheter	219 (88.3%)
Endotracheal tube	218 (87.9%)
Urinary catheter	194 (78.2%)
Chest drain	51 (20.5%)
External ventricular drain	19 (7.7%)
Other devices	76 (30.6%)
Infection	
Pneumonia	112 (45.2%)
Bloodstream infections	36 (14.5%)
UTI	24 (9.7%)
Clinical sepsis	20 (8.1%)
Surgical site infections	20 (8.1%)
Gastrointestinal infections	14 (5.6%)
CNS infections	11 (4.4%)
Mediastinitis	5 (2.0%)
Skin and soft tissue infections	3 (0.8%)
Osteoarticular infections	2 (0.8%)

UTI: urinary tract infection; CNS: central nervous system.

The most frequently found infection cases and the medical devices used are shown in Table 2. CVC was mostly used, with a median (IQR) dwell time of 17 (9 - 33) days, ETT with a median (IQR) dwell time of 8 (3 - 21) days and UC with a median (IQR) dwell time of 7 (1 - 16) days. CVC was mostly inserted into the femoral vein (n = 106; 48.4%), the jugular vein (n = 100; 45.6%), the subclavian vein (n = 62; 28.3%) and the umbilical vein (n = 21; 9.6%). A percutaneous catheter was used in 53 (24.2%) patients. In 100 (40.3%) patients, two or more CVCs were inserted during hospitalisation. Parenteral nutrition was used in more than half of the patients with CVCs (n = 112; 51.1%).

Pneumonia was the most frequent HAI found, bronchoalveolar lavage was the most common isolation product (n = 89; 79.4%), followed by bacteraemia with the identification of the agent in blood culture obtained in most patients (n = 36; 64.3%). Sepsis developed in 74 (29.8%) patients, the most frequent starting point of which was bacteraemia (n = 35; 47.3%). No case of surgical wound infection, central nervous system infection, mediastinitis, osteoarticular infection or skin and soft tissue infection developed into sepsis. Almost half (n = 35; 47.3%) of the agents causing sepsis were isolated in blood cultures.

The responsible agent was isolated in 226 (91.5%) infections, corresponding to a total of 241 microorganisms (Table 3). The median number of agents identified by culture was 1 (1 - 3).

Meropenem (n = 31; 26.1%) and gentamicin (n = 18; 15.1%) were most frequently used for Gram-negative infections, while vancomycin (n = 54; 55.7%) and flucloxacillin (n = 11; 11.3%) were mostly used in Gram-positive infections.

The antibiotic resistance identified in Gram-positive and Gram-negative bacteria is shown in Tables 4 and 5, according to the antibiotic sensitivity test (n = 241), showing that

Table 3 – Type of microorganism

Microorganism	n (%)
Gram-negative	**119**
Enterobacteriaceae	**81 (68.1%)**
Klebsiella pneumoniae	30 (25.2%)
Escherichia coli	23 (19.3%)
Serratia marcescens	7 (5.9%)
Enterobacter cloacae	6 (5.0%)
Klebsiella oxytoca	4 (3.7%)
Proteus mirabilis	3 (2.5%)
Enterobacter aerogenes	2 (1.7%)
Enterobacter hormaechei	2 (1.7%)
Enterobacter amnigenus	1 (0.8%)
Enterobacter kobei	1 (0.8%)
Erwinia rhapontici	1 (0.8%)
Morganella morganii	1 (0.8%)
Pseudomonas aeruginosa	13 (10.9%)
Stenotrophomonas maltophilia	10 (8.4%)
Haemophilus influenzae	9 (7.6%)
Moraxella catarrhalis	2 (1.7%)
Acinetobacter baumannii	2 (1.7%)
Acinetobacter lowfi	1 (0.8%)
Acinetobacter junii	1 (0.8%)
Gram-positive	**97**
Coagulase negative *Staphylococci*	47 (48.5%)
Staphylococcus epidermidis	30 (30.9%)
Staphylococcus hominis	8 (8.2%)
Staphylococcus haemolyticus	6 (6.2%)
Staphylococcus capitis	3 (3.1%)
Staphylococcus aureus	34 (35.1%)
Enterococcus faecalis	11 (11.3%)
Streptococcus pneumoniae	2 (2.1%)
Streptococcus agalactiae	1 (1.0%)
Streptococcus mitis	1 (1.0%)
Staphylococcus ludgensis	1 (1.0%)
Fungi	**25**
Candida albicans	18 (72.0%)
Candida parapsilosis	4 (16.0%)
Candida tropicalis	1 (4.0%)
Candida cruzei	1 (4.0%)
Geotrichum capitatum	1 (4.0%)

Gram-negative bacteria were resistant to penicillin, beta-lactamase inhibitors and third-generation cephalosporins. An increase in strains of *Klebsiella pneumoniae* resistant to aminoglycosides (due to the emergence of strains resistant to amikacin), cotrimoxazole and third-generation cephalosporins was found between the two periods analysed. There was an increase in *Escherichia coli* strains resistant to aminoglycosides, third-generation cephalosporins and cotrimoxazole. It is also worth mentioning the presence of strains of *Pseudomonas aeruginosa* resistant to carbapenems (namely meropenem) and third-generation cephalosporins, and strains of *Serratia marcescens* resistant to aminoglycosides and cotrimoxazole. In the case of Gram-positive bacteria, most resistances were found against penicillin and oxacillin, and there was no resistance to vancomycin or linezolid.

No resistance to linezolid, imipenem, teicoplanin or vancomycin was recorded within the study period.

A total of 21 cases involving ESBL-producing bacteria have been found: *Klebsiella pneumoniae* (n = 16), *Escherichia coli* (n = 2), *Haemophilus influenzae* (n = 2) and *Moraxella catarrhalis* (n = 1), most of which (n = 12; 57.1%) were found within the last five years of the study (2019 - 2023). *Pseudomonas aeruginosa* (n = 1) was isolated in one patient as a CRE, also between 2019 – 2023; 11 MRSA microorganisms were identified, 7 from which (63.6%) were found within the second five years of the study.

There were 25 (10.4%) patients diagnosed with fungal infections, mostly (72.0%) caused by *Candida albicans*. There were no infections caused by *Aspergillus spp*.

During their stay at the PICU between 2018 and 2023, 97 of the 150 patients diagnosed with HAI within this period were screened for MRSA, CRE or ESBL, including 45 colonisations affecting 41 patients: 40 diagnosed with ESBL (41.2%) and 5 with CRE (5.2%). No patient was diagnosed with MRSA; 53 (35.3%) patients did not undergo any screening.

No statistically significant relationship was found between the type and location of catheters and the identification of positive blood cultures, or between the use of more than one CVC and positive blood cultures. The data related to the comparison between the type of catheter and positive blood cultures is shown in Table 1 [Appendix Table 1 (*Apêndice* 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22279/15571)].

There was also no significant association between the use of a bladder catheter and diagnosis of HAI (p = 0.311) [Appendix Table 2 (*Apêndice* 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22279/15571)].

Exposure to ETT was found to significantly increase the likelihood of pneumonia (OR = 2.5; 95% CI, 1.1 to 5.9;

p = 0.030) and patients on long-term invasive ventilation were also more likely to present with pneumonia (OR = 1.9; 95% CI, 1.1 to 3.4; p = 0.011). The comparison between the use of ETT and long-term invasive ventilation and the development of pneumonia are shown in Table 3 of the Appendix (*Apêndice* 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22279/15571). A higher mortality was also found in patients with sepsis (OR = 6.8; 95% CI, 2.9 to 15.8; $p < 0.001$) [Table 4 in the Appendix (*Apêndice* 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22279/15571)].

The survival analysis, represented in Kaplan-Meier charts, showed that 75% of positive blood cultures occurred up to day 40 of CVC dwell time and 75% of pneumonia cases occurred up to day 10 of ETT dwell time (Figs. 3 and 4, respectively).

Even though a percentage increase in resistance was found within the past five years (2019 - 2023) compared to the first five years (2014 - 2018), this difference was not statistically significant in any class of antibiotic, according to the chi-square test or Fisher's exact test (where applicable) [Appendix, Tables 5 and 6 (*Apêndice* 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22279/15571)].

Among the patients with documented ESBL colonisation, 10 (25.0%) patients developed an infection caused by an ESBL-producing microorganism during their stay at the PICU and there was only one case of ESBL-positive disease affecting a non-colonised patient. This difference was statistically significant *($p < 0.001$)* [Appendix Table 7 (*Apêndice* 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22279/15571)]. The only patient presenting with a culture positive for a CRE microorganism was not previously colonised.

DISCUSSION

The 6.3% prevalence of HAIs that was found in this study is in line with studies held in international PICUs (5% - 33%)[20-22] and below what has been described by the European Center for Disease Prevention and Control (12.7%) in adult intensive care units.[23] This was also lower, when compared to the only study carried out in a Portuguese medical-surgical PICU on HAIs in children, in which a 15% prevalence has been described.[21] However, it is worth mentioning that only paediatric patients (no newborns) were admitted to the unit involved in that study and only within one year.

Most patients diagnosed with HAI were under one year of age and a male predominance has been found in our group of patients. These results are in line with most studies in this area.[13,24] Heart disease was the most common pathology found, which is in line with the higher risk found in different studies. These patients are at a higher risk of HAIs, as well as device-associated adverse events and complications.[25,26] Perinatal pathology was also frequent, in line with other studies.[24,27] Therefore, risk anticipation is crucial, based on an increased susceptibility to HAIs, as well as the associated risk of morbidity and mortality, according to each patient's personal history.

A 21-day median length of stay has been found, longer than what has been found in other units and countries (3-9 days).[28] Longer stays have been associated with an increased risk of infection.[28]

The association between the use of invasive medical devices and the risk of hospital infection by resistant organisms[29,30] is well known, and this was also found in this study. CVC was most frequently used and in 40.3% of the cases two or more CVCs were inserted during the hospital stay. Previous studies have described prolonged duration and the use of multiple CVCs as the main risk factors for catheter-related bloodstream infections.[31] In this study, there were no statistically significant differences between the type and insertion site of CVC and positive blood cultures. These results are not in line with other studies, in which the femoral location showed a higher risk of CVC-related bloodstream infection, and the use of percutaneous catheters was shown to have an improved safety profile.[32,33]

ETTs are also widely used, which could explain the high number of cases of respiratory infection. According to Kohbodi *et al.*, ventilator-associated pneumonia underlies 7 to 32% of HAIs and, in PICUs, an incidence of 1.8 to 8.3 per 1,000 ventilator days is estimated.[34] In our group of patients, exposure to ETT was associated with the development of pneumonia and a higher incidence of ventilator-associated pneumonia (from 7.8 to 21.1 cases per 1,000 ventilator days) has been found, when compared to other studies.

Although a lower mortality has been found in our group of patients (n = 29; 11.7%) than what was shown by another Portuguese study carried out in a PICU (23%), it is also worth mentioning that this study was held over only one year and only paediatric patients were included.[21] From these, only around a third of the deceased patients were related to nosocomial infections.

Most infections were related to Gram-negative agents, in line with European statistics, particularly involving the Enterobacteriaceae family.[23,35]

The antibiotic therapy used in our study was in line with other PICUs, with a predominance of vancomycin, carbapenems and aminoglycosides.[36,37]

There was an overall increase in the number of antibiotic resistances from the first five (2014 - 2018) to the last five years of the study (2019 - 2023). When comparing these two periods, antibiotic susceptibility testing showed an increase in strains of *Klebsiella pneumoniae* and *Escherichia coli* resistant to aminoglycosides, cotrimoxazole and

Table 4 – Screening results for resistance in Gram-negative bacteria related to HAI at the HP-PICU (comparison between both five-year periods)

Gram-negative (n = 119)	Antibiotic							
	Aminoglycosides		Penicillin		2nd generation cephalosporin		3rd generation cephalosporin	
	2014 - 2018	2019 - 2023	2014 - 2018	2019 - 2023	2014 - 2018	2019 - 2023	2014 - 2018	2019 - 2023
Klebsiella pneumoniae (n = 30)	31% 4/13	67% 8/12	100% 12/12	100% 12/12	55% 6/11	50% 3/6	71% 5/7	100% 8/8
Escherichia coli (n = 23)	13% 1/8	25% 3/12	75% 6/8	62% 8/13	0% 0/6	33% 1/3	NA	60% 3/5
Pseudomonas aeruginosa (n = 13)	0% 0/6	0% 0/6	100% 2/2	NA	NA	NA	0% 0/2	17% 1/6
Stenotrophomonas maltofilia (n = 10)	NA	NA	NA	NA	NA	NA	0% 0/1	13% 1/8
Haemophilus influenzae (n = 9)	NA	NA	17% 1/6	100% 1/1	NA	NA	0% 0/6	0% 0/1
Serratia marcescens (n = 7)	0% 0/1	17% 1/6	100% 1/1	100% 6/6	100% 1/1	NA	NA	100% 1/1
Enterobacter cloacae (n = 6)	0% 0/2	0% 0/3	100% 2/2	100% 3/3	100% 1/1	0% 0/3	100% 1/1	0% 0/2

HP: *Hospital Pediátrico* (Paediatric Hospital); HAI: healthcare-associated infection; NA: non-applicable (non-screened antibiotic group); PICU: Paediatric Intensive Care Unit

third-generation cephalosporins. As regards to other Gram-negative bacteria, the emergence of strains of *Pseudomonas aeruginosa* resistant to carbapenems and third-generation cephalosporins and strains of *Serratia marcescens* resistant to aminoglycosides and cotrimoxazole stood out. The resistance of Gram-negative microorganisms to third-generation cephalosporins ranged from 13% to 100% and was mostly found in *Klebsiella pneumoniae* bacteria (between 2019 and 2023 these were all resistant to this antibiotic group). As a result, this class of antibiotics has become inappropriate for the empirical treatment of these infections. This pattern of increased resistance found in Gram-negative bacteria in recent years was expected and has already been described in Europe and other PICUs.[13,23,38-40] On the other hand, contrary to what has been described by other authors,[39] there was in this study no overall increase in infections caused by multidrug-resistant Gram-negative bacilli, particularly to carbapenems (only one strain of *Pseudomonas aeruginosa* resistant to this group of antibiotics was found).

In the group of Gram-positive bacteria, 31.4% of *Staphylococcus aureus* were MRSA, and all were sensitive to vancomycin. Other authors have found up to 64% resistance rates to vancomycin.[13] In view of our results, in this population, this antimicrobial agent continues to be the most effective in the treatment of severe infections caused by *S. aureus* and is the preferred empirical treatment for suspected Gram-positive cocci. No isolated agent has shown resistance to linezolid; therefore, with a resistance to vancomycin, or when its use is not feasible, it appears to be a second-line therapeutic option. The overall increase in these resistances over the last five years of the study, although not statistically significant, is in line with the trend found both nationally and internationally.[13,23,38-40] In this context, the department has adopted screening strategies at admission and isolation measures to prevent cross-transmission, as well as education in the rational use of antibiotics. The appropriate prescription of antibiotics in our unit (i.e., only when clinically justified, with the appropriate treatment duration for each type of infection/pre- and post-surgical prophylaxis and with the choice of antibiotic with a targeted spectrum) is also a key factor in reducing the risk of developing antibiotic resistance.

The rate of infection caused by ESBL-producing bacteria

Table 5 – Screening results for resistance in Gram-positive bacteria related to HAI at the HP-PICU (comparison between both five-year periods)

Gram-positive (n = 97)	Antibiotic					
	Aminoglycosides		Penicillin		Oxacillin	
	2014 - 2018	2019 - 2023	2014 - 2018	2019 - 2023	2014 - 2018	2019 - 2023
Coagulase-negative *Staphylococcos* (n = 47)	61% 11/18	72% 18/25	100% 18/18	83% 20/24	84% 16/19	78% 18/23
Staphylococcos aureus (n = 34)	0% 0/15	6% 1/16	75% 12/16	87% 13/15	25% 4/16	47% 7/15
Enterococcos faecalis (n = 11)	20% 1/5	100% 1/1	29% 2/7	67% 2/3	100% 2/2	NA

HP: *Hospital Pediátrico* (Paediatric Hospital); HAI: healthcare-associated infection; NA: non-applicable (non-screened antibiotic group); PICU: Paediatric Intensive Care Unit.
Coagulase-negative *Staphylococci: Staphylococcos epidermidis, Staphylococcos hominis, Staphylococcos haemolyticus, Staphylococcos capitis*

	Antibiotic									
	4th generation cephalosporin		Beta-lactamase inhibitors		Fluoroquinolones		Carbapenem		Cotrimoxazol	
	2014 - 2018	2019 - 2023	2014 - 2018	2019 - 2023	2014 - 2018	2019 - 2023	2014 - 2018	2019 - 2023	2014 - 2018	2019 - 2023
	0% 0/1	50% 1/2	54% 7/13	58% 7/12	23% 3/13	25% 3/12	0% 0/7	0% 0/6	21% 3/14	50% 5/10
	NA	0% 0/2	25% 2/8	30% 4/13	0% 0/8	15% 2/13	NA	0% 0/2	8% 1/3	56% 5/9
	100% 2/2	0% 0/2	50% 2/4	0% 0/1	0% 0/4	17% 1/6	0% 0/3	50% 1/2	33% 1/3	0% 0/3
	NA	NA	0% 0/1	0% 0/9	0% 0/1	13% 1/8	NA	NA	NA	17% 1/6
	NA	NA	29% 2/7	100% 1/1	0% 0/6	0% 0/1	NA	NA	33% 2/6	0% 0/1
	NA	100% 1/1	100% 1/1	100% 6/6	0% 0/1	0% 0/6	NA	0% 0/1	0% 0/1	33% 1/3
	NA	NA	100% 2/2	100% 3/3	0% 0/2	0% 0/3	0% 0/1	NA	33% 1/3	0% 0/2

in our population (8.5%) was lower than what has been described by other authors (11.8% - 30.0%).[22,38] Nevertheless, the percentage of disease caused by these microorganisms in previously colonised patients (25.0%) was higher than in other studies.[41]

As regards fungal infections in our population, both their prevalence (10.4% of HAIs) and the most frequently isolated agent (*Candida albicans*) were in line with data described by other authors.[42] Although *Aspergillus spp.* is one of the most frequent causative agents of fungal infection in critically ill children, there were no infections caused by this microorganism in our population.

In this group of patients, the rates of colonisation by ESBL-producing strains (25.0%), CRE (3.3%) and MRSA (0.0%) were significantly lower than those described in literature.[43-47] Hospital surveillance of MRSA, CRE and ESBL colonisations is crucial for the early-stage identification of patients and environments colonised by multidrug-resistant bacteria, preventing cross-transmission. Measures including contact isolation precautions, hand hygiene and the rational use of antibiotics are crucial to controlling these infections, and continuous analysis of these data allows control strategies to be adjusted, ensuring patient protection and sustainability of the healthcare system.

Strengths and limitations

As far as we know, this is only the second study analysing the prevalence and characteristics of HAIs in the Portuguese paediatric population. Units in Europe and the United States of America have been involved, with different population characteristics and realities. In addition, although there are different studies on the epidemiological variables of nosocomial infections in the paediatric population, few have been focused on the characterisation of the agents isolated in cultures and their antibiotic resistance profiles. It should also be noted that ESBL, MRSA and CRE colonisations were also analysed, which are not considered in most of the available studies and seem to affect the development of HAIs. A comprehensive knowledge of these subjects, applied to the reality of each region, is crucial for a better use of the antibiotic therapy, curbing the spread of multidrug-resistant bacteria and ensuring better care for paediatric patients and, subsequently, the general population. Finally, our sample size and the collection of data over

	Antibiotic					
	Vancomycin		Linezolid		Fluoroquinolones	
	2014 - 2018	2019 - 2023	2014 - 2018	2019 - 2023	2014 - 2018	2019 - 2023
	0% 0/17	0% 0/20	0% 0/7	0% 0/12	20% 1/5	100% 2/2
	0% 0/6	0% 0/12	0% 0/2	0% 0/2	20% 1/5	75% 3/4
	0% 0/7	0% 0/3	0% 0/1	0% 0/2	33% 1/3	0% 0/3

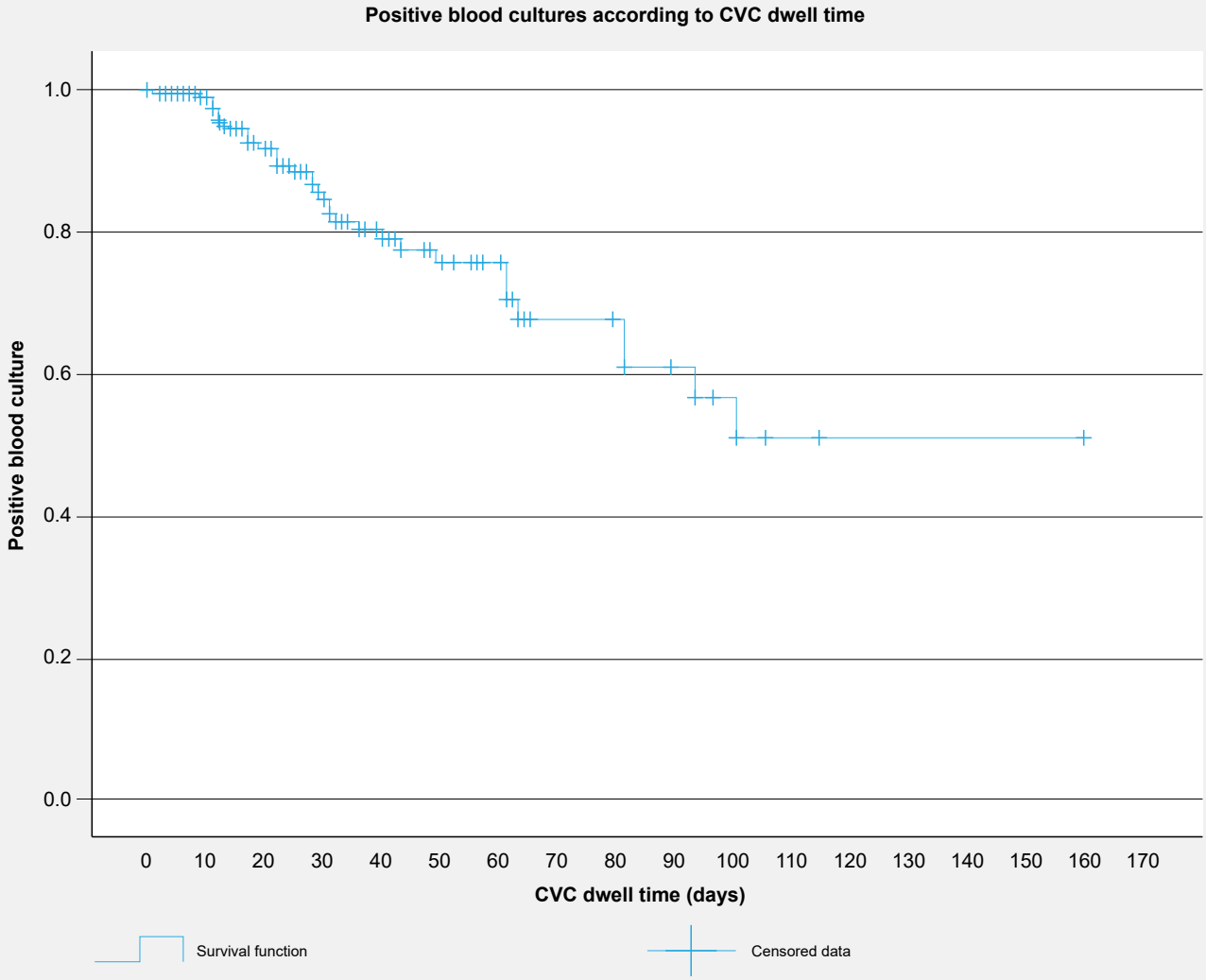

Figure 3 – Positive blood cultures according to CVC dwell time (days)
CVC: Central venous catheter

a prolonged period showed the reality of our region over the past decade.

This study has some limitations. A single PICU was involved; therefore, these results should be interpreted with caution and may not reflect the patterns found at other hospitals. Nevertheless, the HP PICU is the only paediatric intensive care unit in the Central region of Portugal, providing differentiated care to the paediatric population of this region (estimated at 313,274 children and adolescents - INE 2021 census data).[48] In addition, no patients were diagnosed with infection upon discharge from the unit, and retrospective data collection may favour underdiagnosis. However, records of all clinical data and patient progression during hospitalisation are accurate, so we believe that all data used in this study reflect the reality of the unit.

Future research

To date, there are few studies on the epidemiology of PICUs in Portugal, which should be analysed in the future to establish a comparison between the Portuguese and the international (European and worldwide) reality. In addition, the analysis of the personal background and origin of the patients is worth mentioning, aimed at developing a predictive model of severity and mortality. The use of metrics to account for antibiotic use should be relevant to ensure the appropriate use of antibiotics, preventing antimicrobial resistance and promoting safe prescribing practices. The use of these metrics would guide policies for the rational use

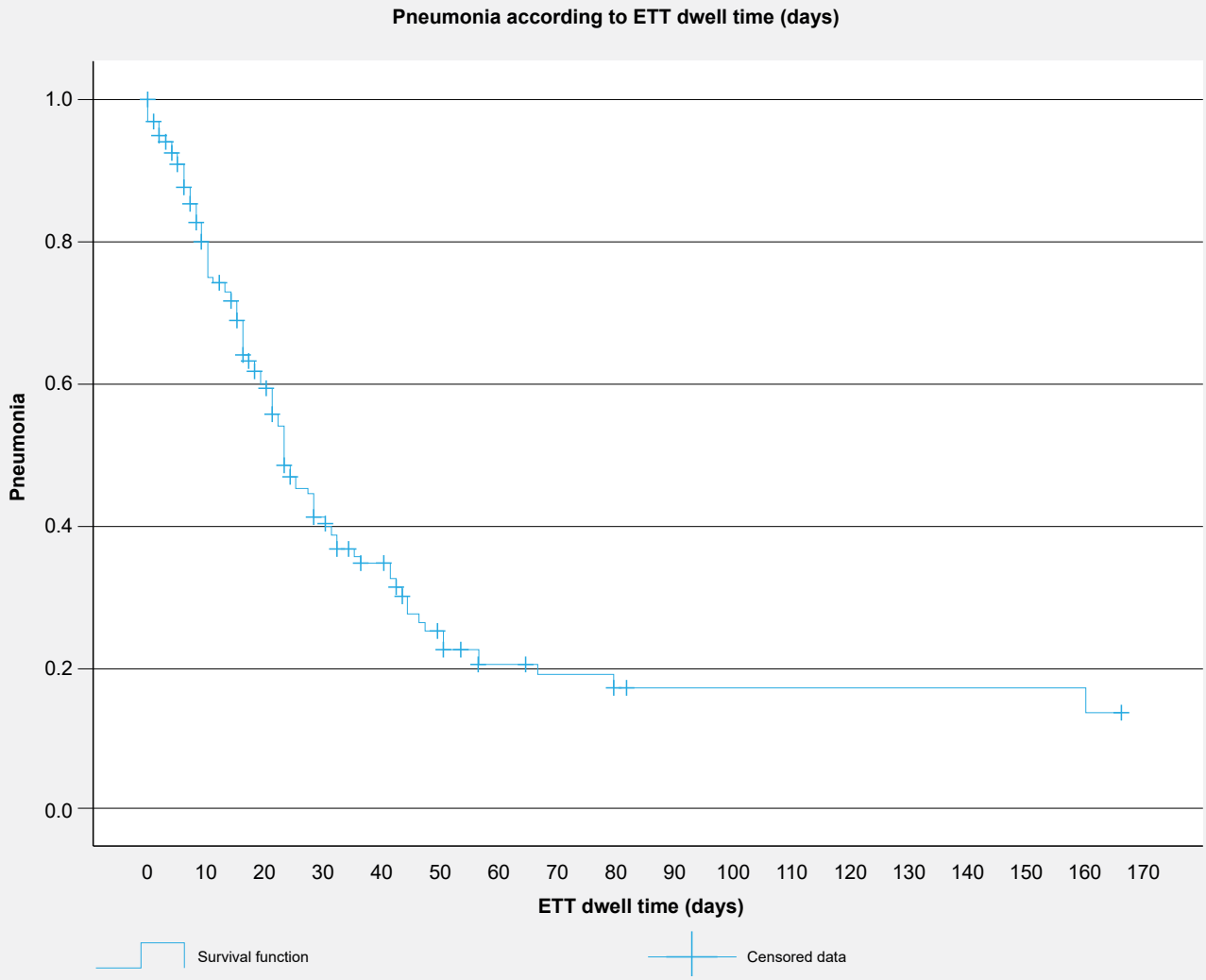

Figure 4 – Pneumonia according to ETT dwell time (days)
ETT: endotracheal tube

of antibiotics, improving the optimisation of the use of antibiotics and assessing the impact of specific interventions. Finally, this study did not assess the resistance of fungal agents, which could be the subject of future research.

CONCLUSION

This study has provided a detailed analysis of nosocomial infections in patients admitted to a Portuguese PICU within the past 10 years. Although the incidence was within the range described by other units, the lack of epidemiological studies in Portugal highlights the need for further research leading to a better understanding of this issue in the national context. The results highlighted the increased susceptibility to infection in patients with a specific medical history, including the presence of cardiac and perinatal pathology, emphasizing the relevance of surveillance and prevention in these vulnerable populations. The use of medical devices, especially ETT, was associated with an increased risk of infection, highlighting the need for effective strategies to prevent infections related to the use of these devices.

The antibiotic therapy patterns were in line with what has been described in other PICUs. However, the increase in bacterial resistance over the past five years shows the need for a wise use of antibiotics and ongoing surveillance of such resistance.

The implementation of strategies for the effective prevention and control of the advance of resistant bacteria is becoming increasingly crucial to ensure the effectiveness of

current therapies and patient safety and to prevent a major threat to global public health.

AUTHOR CONTRIBUTION

CM, DL, MCF: Study concept, data acquisition, writing of the manuscript.

JVA, AD: Study concept and critical revision of the manuscript.

The final version has been approved for publication by all authors.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2024 update of the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working centre regarding patients' data publication.

COMPETING INTERESTS

The authors declare not having any conflicts of interest related to the manuscript.

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