Nosocomial Infections in Brazilian Pediatric Patients: Using a Decision Tree to Identify High Mortality Groups

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Nosocomial infections (NI) are frequent events with potentially lethal outcomes. We identified predictive factors for mortality related to NI and developed an algorithm for predicting that risk in order to improve hospital epidemiology and healthcare quality programs. We made a prospective cohort NI surveillance of all acute-care patients according to the National Nosocomial Infections Surveillance System guidelines since 1992, applying the Centers for Disease Control and Prevention 1988 definitions adapted to a Brazilian pediatric hospital. Thirty-eight deaths considered to be related to NI were analyzed as the outcome variable for 754 patients with NI, whose survival time was taken into consideration. The predictive factors for mortality related to NI ($p < 0.05$ in the Cox regression model) were: invasive procedures and use of two or more antibiotics. The mean survival time was significantly shorter ($p < 0.05$ with the Kaplan-Meier method) for patients who suffered invasive procedures and for those who received two or more antibiotics. Applying a tree-structured survival analysis (TSSA), two groups with high mortality rates were identified: one group with time from admission to the first NI less than 11 days, received two or more antibiotics and suffered invasive procedures; the other group had the first NI between 12 and 22 days after admission and was subjected to invasive procedures. The possible modifiable factors to prevent mortality involve invasive devices and antibiotics. The TSSA approach is helpful to identify combinations of predictors and to guide protective actions to be taken in continuous-quality-improvement programs.

Key-Words: Epidemiology, healthcare quality, mortality, nosocomial infection, pediatric hospital.

Nosocomial infection (NI) is a significant health problem in Brazil and requires institutional programs and efforts [1-4]. Lowering the risk of acquiring an infection and its lethal consequences during the period of hospitalization is the main goal of an NI control program. In 1992, the Ministry of Health established regulation 930 as mandatory [1]. This required obligatory active surveillance and data reporting; however, it was not stipulated how this should be done. In order to meet this requirement, a surveillance system was set up in 1992 in our hospital in Minas Gerais state in southern Brazil, as no active system had previously been in place.

The methodology reported in the medical literature [4-6] was adapted for our hospital; this program led to improvements in healthcare quality [7,8]. Nevertheless, few studies have analyzed mortality data [9,10], and this has not been done in Brazilian public pediatric hospitals. This is needed in order to make evaluate infection control programs.

The aim of our study was to identify predictive factors for mortality related to pediatric NI, based on survival time (survival analysis), to develop a tool for predicting that risk using a classification tree (tree-structured survival analysis - TSSA).

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Material and Methods

The Hospital

Ours is a public tertiary pediatric referral hospital, located in Belo Horizonte (2,399,920 inhabitants). It serves the state of Minas Gerais in Brazil and belongs to the Minas Gerais State Hospital Foundation (FHEMIG), which runs 22 hospitals throughout the state. Most of the pediatricians are professors and/or infectious disease specialists. All patients (there are no surgical patients) are also attended by pediatric and/or infectious disease medical residents [7,8].

Study Design

Prospective cohort nosocomial infection surveillance was undertaken for all acute-care patients according to the hospital-wide and intensive care NNIS components [5,6], adapted for Brazilian hospitals [1,4,8,11], since January 1992. There were 131,764 hospital patient-days and 14,892 discharges from January 1993 to December 1997. There were 1,174 nosocomial infections identified in 754 patients [8], who were admitted with the following diagnoses: meningitis (26%), pneumonia (11.5%), sepsis (11.3%), diarrhea (10.7%), malnutrition (7.8%), other infectious diseases (7.2%) and other problems, such as congenital abnormalities, syndromes, immune deficiencies (less than 7%).

The services that were surveyed were: Unit II- communicable diseases, Unit III- acute and clinical, and the Pediatric Intensive Care Unit (PICU) [7,8].

The Infection Surveillance and Control Team

The same medical coordinator oversaw data collection during the five-year period and performed retrospective surveillance whenever necessary. No automated system for

microbiological evaluations was available during that time. The standardized disk-diffusion method was used to determine resistance of bacterial strains. Other details about the active and prospective surveillance methods have been described previously [4,8].

Definitions

Definitions for nosocomial infections were based on 1988 CDC definitions [6] and the Centers for Disease Control and Prevention and National Nosocomial Surveillance System methods applied in Brazilian hospitals [1,4,5,6,8]. The relationship between mortality and NI was defined as follows: 1. Deaths related to NI: 1.1 Deaths caused by NI: the cause was the NI. No other condition led to death; 1.2. Deaths related to NI: the outcome was death, but the NI was not the cause, although it might have worsened a previous disease. 2. Deaths not related to NI: another condition led to death and the NI did not contribute. Rates were so defined: Mortality rate for NI = (deaths related to NI / discharges) x 100%. Mortality related to NI = (deaths related to NI / patients with NI) x 100% [4].

Variables

The outcome variable was defined as time from admission to the hospital until death related to NI and the event (or failure) was death related to NI. The potential explanatory variables that were analyzed were: number of admissions, age, gender, nutritional status on admission (by weight adjusted for gender and age and diagnosis of malnourished or not – Z score), underlying diseases (infectious or not), invasive procedures (central and peripheral catheters, venous cut-down, tubes, ventilators), number of antibiotics used, time from admission to onset of the first NI.

Data

Patient data were obtained from the infection control team data set (checked for consistency). The software packages used were EPI-INFO 6 [11] and SPSS 10.0 (data analysis) [12]. The study was approved by the ethical review board of FHEMIG and the ethics committee of the Federal University of Minas Gerais state.

Statistical Analysis

Univariate analyses were performed using the Kaplan-Meier method for fitting the survival curves and a *log rank* test for comparing two curves. At the beginning, variables considered to be potentially associated with death related to NI were the ones with $p < 0.25$, which were included in the multivariate analysis [13]. Multivariate analyses were performed using a Cox regression model to identify variables associated with deaths related to NI. Results were reported as relative risks (RR) and their 95% confidence intervals (CIs), which were calculated using standard methods. All values with $p < 0.05$ were considered significant [13]. TSSA [14] was used for identifying the patient profiles that were more susceptible to dying due to NI. A patient who had not died before the end of the study and the ones whose deaths were not related to NI were designated to be "censored data" [13].

Results

Among the 754 subjects who had NI, 74 had a fatal outcome (36 patients whose death was not related to NI, 38 related). The 680 survivors were followed in the survival analyses. The mortality rate for NI and the mortality related to NI during the study period were 0.2% (1.3% in PICU patients) and 5.0% (23% in PICU patients), respectively. The main characteristics of the patients are summarized in Table 1.

All the variables were tested by the Kaplan-Meier method, and the differences between the survival curves were compared by the *log rank* test. Factors significantly ($p < 0.05$) associated with death related to NI in the univariate analysis by the Kaplan-Meier method were: invasive procedures, infection on admission and use of two or more antibiotics to treat NI. The descriptive statistics are given in Table 2 (the mean is informed, since the median was not calculated because of the occurrence of more censored data than deaths related to nosocomial infection). The variables that had no significant effect were: number of admissions, age, gender, nutritional status on admission, and time from admission to onset of the first NI.

Based on the Kaplan-Meier method, the mean survival time was significantly ($p< 0.05$) longer for patients who had already been admitted with an infectious disease than for those who had not (310 days; $_{95\%}$CI=272-348 *versus* 198 days; $_{95\%}$CI=146-250), and it was shorter for patients who were subjected to invasive procedures than for those who were not (170 days; $_{95\%}$CI=130-210 *versus* 329 days; $_{95\%}$CI=290-368). It was also shorter for those who received two or more antibiotics to treat NI, compared to those who received less than two (216 days; $_{95\%}$CI=169-263 *versus* 324 days; $_{95\%}$CI=275-373).

The two factors that proved to be independent predictive factors for death related to NI according to the Cox regression model ($p = 0.00$) were: 1. invasive procedures - a risk 3.82 times greater for those who were subjected to such procedures compared those who were not (RR = 3.82; $_{95\%}$CI = 1.83-7.97); 2. two or more antibiotics to treat NI - a risk 3.10 times greater for such individuals compared to those who were treated with less than two (RR=3.10; $_{95\%}$CI=1.47-6.55). These two determinants were also significant when the analyses were repeated without censoring the 36 patients whose death was not related to NI.

Survival curves calculated by Kaplan-Meier product-limit estimates for specific subgroups are shown in Figures 1 and 2.

The classification tree for predicting the risk of dying related to NI for the 754 patients is presented in Figure 3. A maximum of three predictors can identify the significantly affected groups (time from admission to the first NI, number of antibiotics to treat NI and use of invasive procedures).

Table 1. Characteristics of 754 patients with nosocomial infections in a Brazilian public pediatric hospital.

Characteristic	N	%
Sex		
Female	334	44.0
Male	420	56.0
Age		
Age ≤ 1 month	72	9.6
Age > 1 month	682	90.4
Age ≤ 1 year	654	86.7
Age > 1 year	100	13.3
Infectious diseases on admission		
Yes	660	87.5
No	94	12.5
Nutrition status		
Malnourished	67	8.9
Nourished	687	91.1
Score Z weight/age ≤ -3	154	20.4
Score Z weight/age > -3	600	79.6
Score Z weight/age ≤ -2	280	37.1
Score Z weight/age > -2	474	62.9
Number of admissions		
1	731	96.9
2	21	2.7
3 or more	2	0.4
Number of Antibiotics to treat nosocomial infections		
0	163	21.6
1	430	57.0
2	102	13.5
3 or more	59	7.9
Relationship between death and nosocomial infection		
No death + death not related to nosocomial infection	716	95.0
Death related to nosocomial infection	38	5.0
Relationship between death and number of nosocomial infections		
Related to the first nosocomial infection	21	55.3
Related to the second nosocomial infection	9	23.7
Related to the third nosocomial infection	3	7.9
Related to the fourth nosocomial infection	5	13.1
Median time from admission to death/discharge		
Median ≤ 27 days	380	50.4
Median > 27 days	374	49.6
Median time from admission to the first nosocomial infection		
Median ≤ 11 days	355	47.1
Median >11 days	399	52.9
Invasive procedures (catheters, venous cutdown, tubes, ventilators)		
Yes	132	17.5
No	622	82.5

TSSA identified two important groups (Figure 3) with high mortality: (1) The group of subjects that had an interval between admission and onset of the first NI of less than 11 days, were treated with two or more antibiotics and underwent invasive procedures (34 survived out of 41 = 17% mortality rate). (2) A group with an interval between admission and onset of the first NI of between 12 and 22 days and who underwent invasive procedures (30 survived out of 40 = 25% mortality rate).

Discussion

There are some limitations to our study. We were not able to assess the association between antimicrobial use and/or the need of invasive devices and the severity of the patient's

Table 2. Descriptive statistics for the variables associated with death related to nosocomial infections, in univariate analysis with p-values < 0.05, using the Kaplan-Meier method, for 754 patients with nosocomial infections in a Brazilian public pediatric hospital.

Variables	Mean (days)	Deaths (N)	Censored *	
			N	%
Invasive procedure				
Yes	170	24	108	81.8
No	329	14	608	97.8
Infection on admission				
Yes	310	29	631	95.6
No	198	9	85	90.4
Number of antibiotics				
≥ 2	213	25	136	84.5
< 2	324	13	580	97.8

*Censoring = occurrence of no death at all or till before the end of the study + deaths not related to nosocomial infection.

Figure 1. Kaplan-Meyer surviving curves (s indicates censoring) for 754 patients with nosocomial infections according to invasive procedures performed (broken line) and not (solid line) in a Brazilian public pediatric hospital.

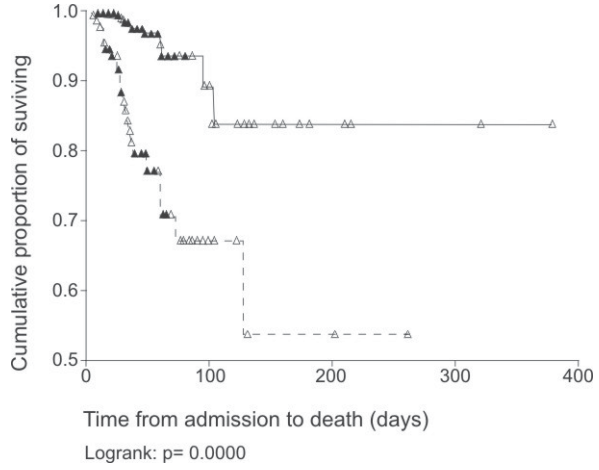
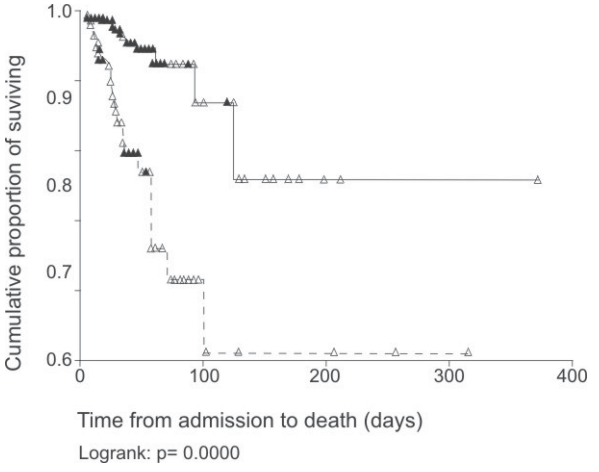


Figure 2. Kaplan-Meyer survival curves (s indicates censoring) for 754 patients with nosocomial infections treated with two or more antibiotics (broken line) or less than two (solid line) in a Brazilian public pediatric hospital.



clinical status. Whether the need for various antibiotics and invasive procedures was mostly due to the underlying condition or not could not be separated in our study. It also can not be resolved with NISS methodology. However, we tried to assess this question by determining if infection was present at admission or not (this factor was not significant in multivariate analysis). Severity of illness, as measured by an admission score such as Pediatric Risk of Mortality (PRISM), was not calculated since it is not routinely recorded in our hospital. Even if it were, its calculation only at admission, as in many hospitals, would not reflect the severity of illness at the time of the NI; this would be another limitation, and its calculation twice was not feasible (no grant support).

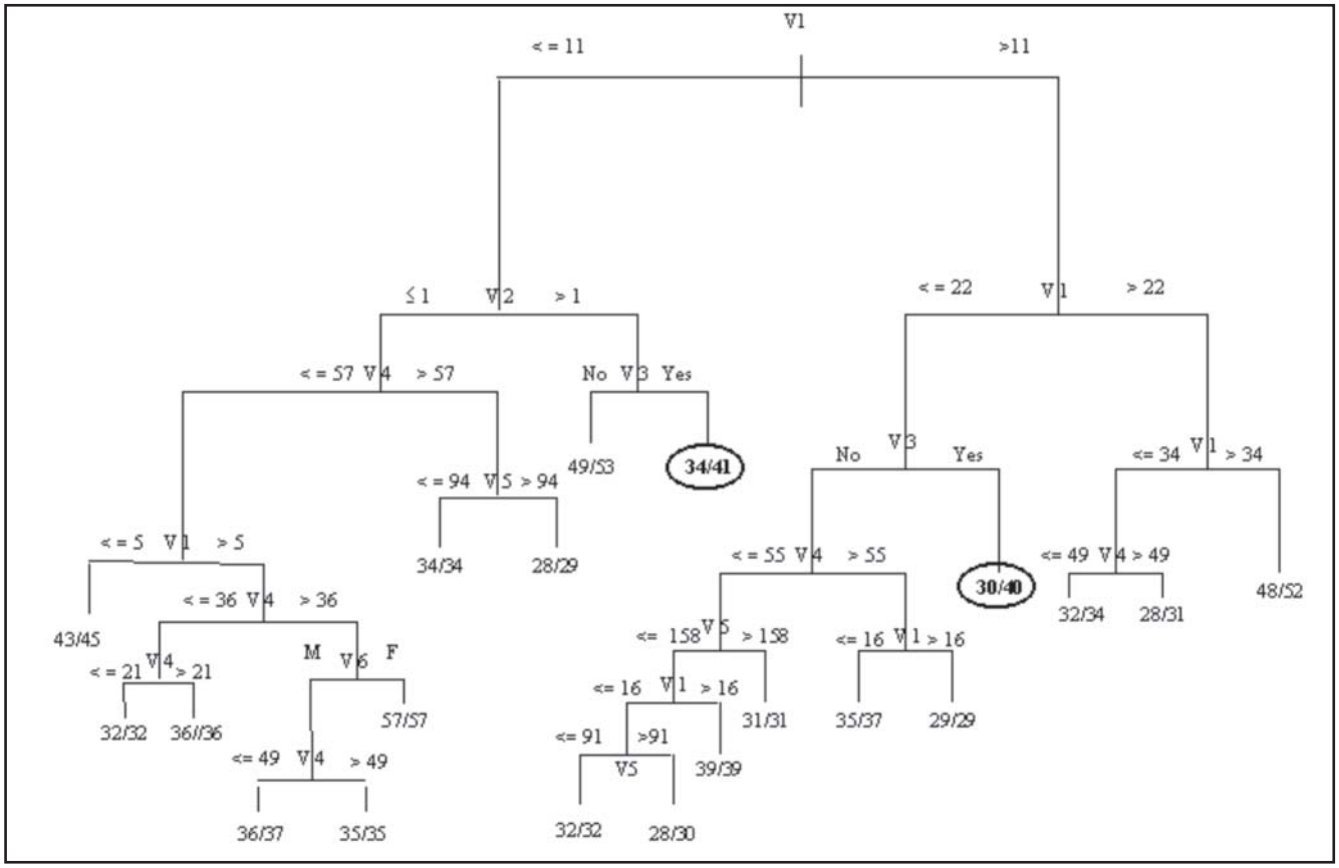
Various previous studies [9,10,15] reported intrinsic and extrinsic risk factors, according to where the research took place (different patient populations and medical practices); so, it is always important to know the institutional environment. Although our data were collected some time ago, our findings are similar to what has been reported recently; infection control teams must focus on the reduction/ appropriateness of invasive devices and decrease inadequate antimicrobial treatment of infection, since they cannot change the patient's clinical status or underlying diseases.

Another limitation is that cutoff points for continuous covariables need to be established for any analyses to be performed. So, we used TSSA in an attempt to obtain appropriate cutoff points.

Among many possible cutoff points between nutrition and malnutrition, the Z score was chosen and the reference pattern of the National Center of Health Statistics (NCHS) was used. The software Epi Info provided an infantile nutritional evaluation based on anthropometric indicators [11]. Malnutrition was not significantly associated with NI, as also reported in the literature.

As 593 patients (78.65%) were treated with less than two antibiotics to treat their NI and 161 (21.35%) were treated with two or more, the cutoff point was so defined. Time from admission to diagnosis of NI was analyzed using quartiles and the median time as a cutoff point. Number of admissions

Figure 3. Classification tree for predicting the risk of dying due to nosocomial infection for 754 patients in a Brazilian public pediatric hospital. The predictive factors: V1 = median time from admission to the first nosocomial infection (days), V2 = number of antibiotics (≤ 1 and > 1), V3 = invasive procedure (performed or not) as well as the other factors deemed as potentially predictive, such as V4 = age (months) are displayed on the tree nodes. The branchings are "less than or equal to" on the left and "more than" on the right. The first major branching in the tree is the predictor "at most 11 days from admission to the onset of the first NI (on the left) *versus* "more than 11 days to onset" (on the right). The second branching, on the left, is number of antibiotics to treat NI (cut off point = two or more) and, on the right, between 12 and 22 days from admission to the onset of the first NI *versus* more than 22 days till onset of the NI. The third branching is related to age, but it was not significant. The fourth branching is use or not of invasive procedures. Other branchings are related to the other variables studied, which were not significant and should not be taken into consideration. The fractions indicate the survival proportions; therefore, the highlighted end groups (high mortality groups) are the ones that deserve most attention from healthcare workers and administrators.



were cutoff as one and two or more since 97% of the patients had only one. And various different ages, such as, one month, two months, one and two years or more were tested as they are supposed to be well established pediatric periods (Table 2). Age and Z score were not significantly associated with NI, including those provided by TSSA [14] (Figure 3).

This is the first study using TSSA [14] for the development of a classification tree for the prediction of death related to NI. It was used for identifying the patient profiles more susceptible to NI - related death. An analysis of survival using a tree-structured approach may be helpful to identify combinations of predictors (Figure 3). It is a tool that can be applied at any time. Therefore, it does not matter how old the data might be. It can identify subjects who are eligible for preventive measures in public health strategies.

In Group 1, there were 12 NIs in seven patients (three patients with one NI each, one patient with three NIs and three patients with two NIs each). Five out of those 12 NIs were laboratory confirmed blood stream infections (LCBSI): 2 *Klebsiella sp*, 1 *S. pneumoniae*, 1 *S. aureus*, 1 *Candida sp*). Two patients were admitted malnourished and with diarrhea (ages: two and five months; 2.9 Kg and 3.3 Kg;), one (12 years old, 32 Kg) with Stevens Johnson Syndrome, one (18 days, 3.5 Kg) with Pertussis Syndrome, one with meningitis (three months old and 5.4 Kg), and two with BSI (five months old, 6.8 Kg and one month, 4 Kg). The invasive and risk procedures they had been performed were: venous catheters, naso-gastric tubes, parenteral nutrition, and ventilator use.

In Group 2, there were 21 NIs in 10 patients (five patients with one NI each, one patient with two NIs, two patients with

three NIs each and two patients with four NIs each). All of them had severe diseases on admission and were in need of invasive and risk procedures (venous catheters, naso-gastric tubes, parenteral nutrition, and ventilator). Two patients were admitted malnourished and with diarrhea (2 months old and 2.5 Kg each), one with meningitis (one year old and 7.8 Kg), one with chickenpox, skin infection and pneumonia (four months, 5.6 Kg), two with BSI (one month and 6 Kg; one month and 3.7 Kg), one with respiratory distress (three months and 3.5 Kg), one with meningitis and BSI (four months and 4.3 Kg), another with myelomeningocele (three months and 6 Kg) and one (two months and 3.3 Kg) with pneumonia and BSI. The pathogens that were isolated were: 2 *Klebsiella sp.*, 1 *Candida sp.*, 1 *Pseudomonas sp.* and 1 *P. aeruginosa*. All of them were treated with antimicrobial agents to which the causative pathogen was susceptible, after and whenever this identification was possible.

Previously published data specific to prognosis on death of pediatric patients with NI are scarce. Thus, comparisons are difficult to draw. Previous similar studies were as follows: A report from the Department of Critical Care Medicine, University of Pittsburgh School of Medicine [9], among other conclusions, concluded that prolonged lymphopenia (absolute lymphocyte count less than 1,000 for more than seven days) was associated independently with nosocomial infection [odds ratio (OR), 5.5, 95% confidence interval (CI), 1.7-17, p <.05], death (OR, 6.8, 95% CI, 1.3-34, p <.05), and splenic and lymph node hypocellularity (OR, 42, 95% CI, 3.7-473, p < 0.05). Data (analysis of 24,179 cases) from a nationwide, concurrent surveillance study (Surveillance and Control of Pathogens of Epidemiological Importance [SCOPE]) were used to examine the trends in epidemiology and microbiology of nosocomial blood stream infections (BSIs). In this study [15], one of the largest multicenter studies performed to date, it was found that the proportion of nosocomial BSIs due to antibiotic-resistant organisms is increasing in US hospitals. Why is it not increasing in Brazil?

Our study revealed previously unknown prognosis factors for death related to NI in a Brazilian public tertiary pediatric referral hospital; it also enabled us to predict the risk of death using TSSA [14]. Our data provided some support (the findings are consistent with current infection control knowledge) that the number of antibiotics and invasive procedures are risk factors not only for infection but are also prognostic for death. Kollef et al. [10] identified potential risk factors for the administration of inadequate antimicrobial treatment of infections, including the prior administration of antibiotics, presence of a bloodstream infection, severity of illness, and patient age. The prior administration of antibiotics to hospitalized patients, particularly to patients in ICUs, appears to predispose to colonization with bacteria that are often resistant to previously prescribed classes of antibiotics. The timing of the administration of adequate antimicrobial therapy is also an important determinant of outcome for patients. It is important to have antibiograms updated on a regular basis in order to detect changes in the antimicrobial resistance patterns of pathogens.

The LDS Hospital has used an automated antibiotic consulting service, which has been shown to increase the rates of adequate antimicrobial treatment compared to individual physician antibiotic practices [16].

In a previous study, we found a gradual increase in the attempt to isolate pathogens in our hospital: 7.5% in 1993, 16.1% in 1995, 33.8% in 1996 (p< 0.001). The time needed for lab results (from specimen collected to microbiology result) had decreased from a mean of 10 days in 1993 to six days in 1996 (p = 0.001). A microbiology task force was set up based on the understanding of all pediatricians that it is important to treat their patients specifically [7].

Our local managers and administrators were alerted that it was necessary to implement automation, MIC and ESBL identification in the Microbiology Laboratory, speeding final culture results, enabling continuous quality improvement in healthcare, since qualified interventions, with correct timing, can decrease mortality.

We learned that a long range surveillance plan [7,8] enabled us to increase our knowledge about the hospital environment, not only to fulfill administrative requirements, but especially to find processes in need of improvement to upgrade healthcare quality. Healthcare facilities were encouraged to implement antimicrobial stewardship programs in recent Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines [17].

Conclusions

Our study demonstrated that number of antibiotics and invasive procedures received by the patient are prognostic for death; there has always been room for improvement in this field! A useful tool is the analysis of survival using a tree-structured approach to help identify combinations of predictors in order to take protective actions.

Our literature review showed some contradictory conclusions and non-answers, especially regarding mortality of pediatric patients related to or associated with NI. A global Brazilian perspective remains a great challenge [18].

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