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Clinical and economic impacts of the hospitalization of patients with positive blood cultures

Impactos clínico e econômico da hospitalização de pacientes com hemoculturas positivas

Impactos clínicos y económicos de la hospitalización de pacientes con hemocultivos positivos

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ABSTRACT

Introduction: bloodstream infections are one of the most important nosocomial infections. And, although their impact on patients' morbidity and mortality is known, the financial impact is still poorly understood. The objective is to evaluate the clinical and economic impact of hospitalization of patients with positive blood cultures. **Outline:** study developed in a tertiary hospital, including patients hospitalized in 2017 and who collected blood cultures. **Results:** the sample consisted of 1,164 patients, 22.42% of whom had at least one positive blood culture. Positive blood cultures were associated with periods of hospitalization longer than 15 days, admission to the intensive care unit and deaths (p<0.001). All direct and total direct costs of patients with positive blood cultures were significantly higher than those with negative blood cultures. Hospitalization of patients with positive blood cultures had an average total cost of R$6,310.16, higher than those with negative blood cultures, which was R$2,808.07. Antimicrobial therapy in patients with positive blood cultures corresponded to three times the value of patients with negative blood cultures. **Implications:** positive blood cultures were associated with negative impacts on clinical variables and economic aspects, reflecting the increase in direct costs of hospitalization.

DESCRIPTORS

Health Care Costs; Drug Costs; Cross Infection; Blood Culture.

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INTRODUCTION

Among Health Care Related Infections (HAIs), Bloodstream Infection (BSI) is the most relevant, being responsible for high rates of morbidity and mortality. This lethality is justified by the invasion of the bloodstream by microorganisms, which can trigger sepsis and septic shock.[1-3] According to the Centers for Disease Control and Prevention,[4] it is estimated that in the United States 30 thousand BSI occur each year and these represent 12% to 25% of deaths in patients affected by the infection.

For the best prognosis of the patient with BSI, it is recommended that antimicrobial treatment be instituted early, and, for this, a fast and accurate diagnosis is necessary. This infection can be proven microbiologically by blood cultures, a test of high predictive value, performed in order to detect the presence of microorganisms in the bloodstream.[5]

The results of blood cultures indicate the etiologic agent of the infection, which favors the targeting of therapy and the efficient use of antimicrobials. Adequate treatment contributes to the control of BSI and the consequent reduction in mortality.[6] In addition to being associated with negative impacts on health, infections, in general contexts, have an impact on the increase in costs of health institutions.[7]

Several researches present epidemiological and microbiological results of BSI, however few are those that address the direct cost of hospitalization in the face of such infection.[8] The evaluation of the financial impact generated by the BSI, in a scenario of scarcity of resources and the need to formulate cost-effective measures, can support the incorporation of technologies and care processes that aim at preventing, controlling and treating these infections.[9]

Given the above, the objective of this study was to evaluate the clinical and economic impacts of hospitalization of patients with positive blood cultures.

METHOD

This is a cross-sectional, retrospective study, developed in a tertiary-level hospital. The research institution serves highly complex clinical and surgical cases. It consists of 191 beds of medical and surgical hospitalization, with 45 beds in the intensive care unit (ICU). Approximately 80% of the beds are assigned to patients from the Unified Health System (SUS). It has a laboratory for clinical and microbiological analysis with full-time operation.

The study included all patients who underwent at least one blood culture examination, aged 14 years or over and who were hospitalized for more than 48 hours in the clinical, surgical or intensive care sectors, from January to December 2017, and patients with exclusive positive blood cultures for fungi were excluded.

As for the processing of blood cultures, the collection was carried out by a trained technical team, according to medical request. The blood was collected using a sterile syringe and needle and inoculated into flasks containing culture media for aerobic, anaerobic bacteria, fungi and yeasts. Blood was collected using a sterile syringe and needle and inoculated into flasks containing culture media for aerobic, anaerobic bacteria, fungi and yeasts. After this stage, the samples were immediately sent to the institution's microbiology laboratory, which performed the detection of microbial growth by the automated method (BD BACTEC™). Positive samples were analyzed by the Siemens MicroScan® system, which identified the microbial species.

Blood cultures were classified as positive blood cultures (Positive-BC) or negative blood cultures (Negative-BC). Positive-BC being all samples that showed microbial growth and Negative-BC all samples with no microbial growth or with isolation of coagulase negative staphylococci. The presence of coagulase-negative staphylococci in the culture was

considered a negative sample because it is a skin-colonizing microorganism and a blood sample contaminant, according to the "Diagnostic Criteria for Health Care-Related Infections".[10]

The research compared direct costs of hospitalization of patients with Positive-BC and Negative-BC, correlating with clinical variables. Clinical variables were categorized into dichotomous variables: period of hospitalization (up to 15 days or> 15 days), hospitalization in the ICU (yes or no), length of stay in the ICU (up to 15 days or> 15 days), clinical outcome (survivors) or not survivors) and blood culture results regarding the presence of microorganisms (Positive-BC or Negative-BC).

Regarding costs, all data were provided by the financial sector of the hospital under study. The amounts were shown in reais (BRL-R$) and dollars (USD-US$), in which the Dollar quotation was related to the median period of data collection, corresponding to the amount of R$3.1301 in July 2017. The costs converted into dollars are available in the accompanying supplementary material, Table 3.

Direct costs were related to patient care, encompassing values of materials and drugs, including antimicrobials, as well as laboratory and imaging tests. Indirect costs such as water, energy, telephone and building maintenance were not accounted for, as they are considered imprecise values in the analysis of individual cost per patient.

Regarding the classification of costs, the full cost corresponded to the entire set of expenses with medications, materials and exams, and was subdivided for analysis into total direct cost and daily direct cost. The total direct cost accounted for the entire period of hospitalization of the patient, while the daily direct cost was calculated by dividing the total cost of hospitalization by the number of days of hospitalization.

The research data were extracted from the electronic medical record by the Business Intelligence® program and transported to Microsoft Excel® in spreadsheets, which were later analyzed using the Statistical Package for the Social Science (SPSS) version 20.

The clinical impact of hospitalization was assessed through the association between dichotomous clinical variables and the result of positivity or negativity in blood cultures. The analyzes were presented in simple frequency and the statistical association was analyzed by Fisher's Exact test, considering associations with p (p-value) less than 0.05, 95% confidence interval (95% CI) and statistically significant. the odds were determined by calculating *Odds Ratio* (OR).

Normality was assessed using the *Shapiro-Wilk* test and the data were analyzed using the *Mann-Whitney* non-parametric test. For all analyzes, the significance level was set at a p-value less than 0.05, within the 95% confidence interval (CI).

As a way of controlling the bias of hospitalization time in costs, it was decided to carry out an assessment of the daily cost through multivariate linear regression in order to distinguish daily costs between patients with Positive-BC and Negative-BC. For this multivariate linear regression, age (continuous), outcome (death or discharge) and whether he was admitted to the ICU (yes or no) were used as control.

The study is linked to the project entitled "Clinical and economic impact of antimicrobial resistance on hospital costs", approved by the Research Ethics Committee involving Human Beings at the State University of Londrina on December 20, 2018 (Evaluation No. 3,097,075) and Certificate of Presentation for Ethical Appreciation (CAAE: 97120618.3.3001.5231).

RESULTS

The study was composed of 1,164 patients who underwent at least one blood culture during hospitalization. Of these, 22.42% (261) had at least one Positive-BC, while 77.58% (903) had all Negative-BC, as shown in Table 1.

Table 1 – Association of patients' clinical variables (N=1,164) according to the microbiological result of blood cultures. Londrina-PR, 2019.

Variables	Patients (1.164)					
	Positive-BC n (%)	Negative-BC n (%)	OR	CI 95%		*p*-value*
Hospitalization period						
Up to 15 days	119 (15.97)	626 (84.03)	1.00			
>15 days	142 (33.89)	277 (66.11)	2.70	2.03	3.57	<0.001
UTI						
No	70 (16.32)	359 (83.68)	1.00			
Yes	191 (25.99)	544 (74.01)	1.80	1.33	2.44	<0.001
ICU Stay						
Up to 15 days	115 (18.52)	506 (81.48)	1.00			
>15 days	76 (66.67)	38 (33.33)	8.80	5.67	13.65	<0.001
Clinical Outcome						
Survivors	147 (18.35)	654 (81.65)	1.00			
No Survivors	114 (31.40)	249 (68.60)	2.04	1.53	2.71	<0.001

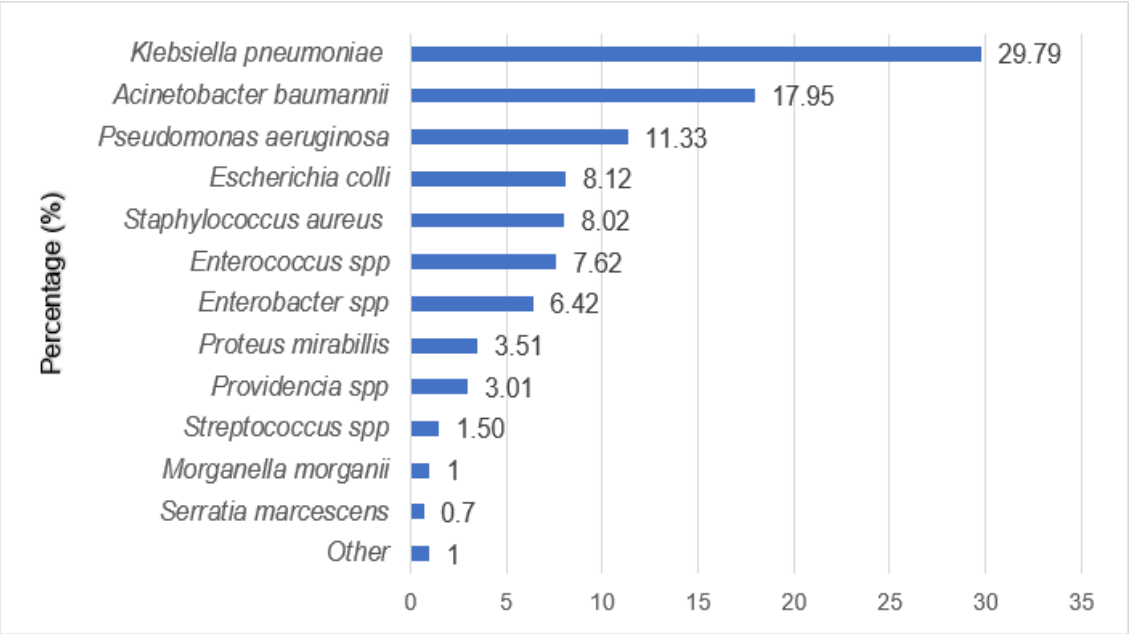
Caption: Positive-BC: blood cultures with microbial growth; Negative-BC: blood cultures with no microbial growth or isolation of coagulase-negative staphylococci; ICU: intensive care unit; OR: *Odds Ratio*; 95% CI: Confidence Interval; **Fisher's exact test*.

Regarding the length of hospital stay, the median days of hospitalization for patients with Positive-BC was 16 days (minimum 3 and maximum 112 days) and the average was 23.82 days (SD 20.61). For patients with Negative-BC, the median days of hospitalization was 10 days (minimum 3 and maximum 95 days) and the average was 13.61 days (SD 10.69). HMC positivity was associated with an increase of 10.21 days in the mean hospital stay (p<0.001).

The frequency of deaths was higher (p<0.001) among patients with Positive-BC, 43.7% (114/261), when compared to the group with Negative-BC, 27.6% (249/903).

Among the Positive-BC, 997 microorganisms were isolated, with 826 (82.85%) identified as Gram-negative bacteria and 171 (17.15%) as Gram-positive. The most frequent microorganism was *Klebsiella pneumoniae*, as shown in Figure 1.

Figure 1 – Frequency of microorganisms identified in positive blood cultures (N=997). Londrina-PR, 2019.



As for the total direct and daily cost, the means were statistically higher in patients with Positive-BC when compared with those of patients with Negative-BC (Table 2).

Table 2 – Association analysis of the averages and medians of the direct cost (total and daily) in reais (R$) attributed to the hospitalization of patients (N=1,164) according to the microbiological result of blood cultures. Londrina-PR, 2019.

Variables	Total Direct Cost			Daily Direct Cost		
	Positive-BC	Negative-BC	*p*-value*	Positive-BC	Negative-BC	*p*-value*
	Average (DP) Median	Average (DP) Median		Average (DP) Median	Average (DP) Median	
Materials and medicine	4,786.65 (5,936.67) 2,718.46	1,821.79 (2,351.47) 1,165.44	<0.001	200.67 (298.29) 157.47	130.43 (107.36) 104.54	<0.001
Antimicrobials	1,687.41 (2,995.56) 651.44	569.57 (1,126.93) 272.63	<0.001	61.90 (126.78) 39.95	36.75 (42.15) 26.91	<0.001
Exams	1,523.51 (1,987.27) 972.59	986.27 (1,897.12) 488.53	<0.001	89.17 (334.37) 49.46	84.81 (183.61) 44.59	0.012
Integral**	6,310.16 (6,914.52) 3,959.77	2,808.07 (3,289.07) 1,765.71	<0.001	289.94 (494.53) 207.74	215.24 (219.74) 158.17	<0.001

Caption: Positive-BC: blood cultures with microbial growth; Negative-BC: blood cultures with no microbial growth; SD: *Standard deviation*; **Mann–Whitney test*; Integral**: sum of material and medication costs and exams.

The association analysis showed a significant increase in the total and daily costs corresponding to the consumption of materials, drugs and tests among patients with Positive-BC. Such patients had a median of total costs approximately twice the value when compared to patients with Negative-BC.

Patients who had at least one Positive-BC during the hospitalization period presented, according to multivariate linear regression controlled by age, outcome and ICU admission, higher average daily costs with antimicrobials (R$19.43, Standard error (EP): 4.75; $p<0.001$), materials and medicines

(R$47.58, EP: 11.07; p<0.001) and full daily cost (R$58.92, EP: 19.96; p=0.003). This analysis indicates that regardless of the aforementioned variables, the patient with Positive-BC spent more daily expenses during hospitalization, in relation to those with negative blood culture. In the regression, there was no significant daily increase in the exams (R$11.34, EP: 15.18; p=0.455).

DISCUSSION

The presence of Positive-BC influenced clinical variables and hospitalization costs. It was observed that patients who were hospitalized for more than 15 days showed greater positivity in blood cultures. Findings close to this result were presented in a cohort study carried out in North Carolina and Virginia, where the average hospitalization period in the two health services was 12 and 9 days before the infectious diagnosis, respectively.[11]

Another study carried out in a Brazilian hospital of high complexity, found that the length of hospital stay greater than three days in an ICU was associated with positivity in blood culture.[6] Both of the aforementioned studies identified that the length of stay of the patient in hospitalization, influenced positivity blood cultures, since the more days of hospitalization, the greater the risk of the patient developing BSI. This result was also observed in the current study, where there was an association between hospitalization for more than 15 days and Positive-BC, with emphasis on those who were hospitalized in the ICU.

Regarding the economic impact, it was observed that patients with Positive-BC had higher direct costs in relation to those with Negative-BC, this is identified in all statistical analyzes, including expenses with laboratory and imaging tests, materials, antimicrobials and other medicines. In view of this result, it is possible to indicate that patients with Positive-BC have greater assistance and therapeutic needs, consequently generating higher costs for the health system.

A North American study identified that patients with Positive-BC had significantly higher hospital costs, whose average was US$43,208 (95% CI = US$30,663-58,540). In that same study, it was observed that the frequency of deaths was twice as high in patients with infection related to Positive-BC. 11 Both analyzes corroborate the present study, which identified that Positive-BC was associated with increased hospital costs and deaths.

Regarding mortality, a study carried out in Germany found that 18.6% of patients hospitalized with BSI died. 12 However, a retrospective cohort study obtained a significantly higher result, with deaths in patients with BSI corresponding to 72.4 %.[13] In line with the result of the current study, in which the frequency of deaths was twice as high among patients with Positive-BC.

The primary therapy in cases of BSI corresponds to antimicrobials. The costs with these drugs were approximately three times higher among patients with Positive-BC in the present study, with a median cost of US$539.09. This result is similar to another Brazilian study that analyzed the cost of patients with both clinical suspicion of BSI and laboratory confirmation and presented a median of US$874.50.[14] It is believed that this small difference is justified by the study location, considering that at present patients hospitalized in other sectors of less complexity were also included.

A study that assessed the economic impact of HAIs on patients hospitalized in the ICU, showed that BSI was the second most frequent infection and that it presented higher costs. The median direct costs per day for medication and materials among patients with BSI was R$666.47 and for patients without infection the cost was R$374.59.[15] On the contrary, these values were higher than the findings in the current study (R$157.47 and R$104.54 respectively). The high cost in the aforementioned study can be justified by the fact that the patients evaluated are hospitalized in the ICU, and need greater resources related to life support due to the criticality of the clinical condition.

Considering the small number of studies that evaluated the clinical and economic impacts of hospitalization of patients with laboratory confirmed BSI, it is necessary to make a parallel with studies of HAIs that encompass multiple infections.

In this sense, a study carried out in a Brazilian ICU showed that the average cost of full hospitalization per patient with HAIs, using antimicrobials was similar to that found in the current research, corresponding to US$1,514.79, an approximate difference of US$500.00 from current study.[16] Another analysis carried out at an international hospital showed that the median spending on antimicrobial treatment was US$132.5 in patients with HAIs, compared to US$4.7 for patients without infection.[17] Therefore, it is identified that patients with HAIs spend greater investment, as they need specialized assistance and costly treatments, which have a negative impact on the institution.

In this sense, antimicrobial use management programs "Antimicrobial Stewardship" guide safe and cost-effective strategies for the use of antimicrobials, implementing care results as well as reducing the development of antimicrobial resistance.[18]

The On the CUSP: Stop BSI (Comprehensive Unit-based Safety Program: Stop Bloodstream Infections) initiative, carried out by the Health Research and Education Trust, showed that preventive interventions reduce infections and consequently the costs for healthcare institutions. This initiative saved more than US$34 million and prevented more than two thousand new cases of BSI.[10]

Considering the results of this study, cost-effective interventions aimed at reducing the incidence of Positive-BC by 10%, would represent approximately 26 patients who would not develop BSI per year. Among them, the average cost of hospitalization would fall from R$6,310.16 to R$2,808.07, corresponding to savings of R$3,502.09 per patient, saving R$91,054.34 per year, or R$7,587.86 per month.

In view of this scenario, knowledge of the clinical and economic impact of Positive-BC is of fundamental importance among managers and health professionals. Since, they need to develop and implement cost-effective measures aimed at preventing infection and provide benefits such as improved flow of hospital bed occupation, especially in ICU hospitalization. In addition, this economy makes it possible to hire professionals specialized in infection control, contributing to further reduce the incidence of Positive-BC and increase the economy of the health service.

In this sense, more studies should address the cost-effectiveness of infection prevention and control measures, a limitation of this research, which did not consider investments in prevention in the period studied.

CONCLUSION

In this study, it was evidenced that the Positive-BC were associated with negative impacts, both in the clinical variables, mainly in the period of hospitalization over 15 days, stay in the ICU and in the frequency of deaths, as well as in the economic variables, causing an increase in direct hospitalization costs.

RESUMO

Introdução: As infecções de corrente sanguínea são uma das mais importantes infecções hospitalares. E, embora saiba-se o impacto destas na morbimortalidade dos pacientes, o impacto financeiro ainda é pouco conhecido. O objetivo é avaliar os impactos clínico e econômico da hospitalização de pacientes com hemoculturas positivas. **Delineamento**: Estudo desenvolvido em um hospital terciário, incluindo pacientes hospitalizados em 2017 e que coletaram hemoculturas. **Resultados**: Amostra foi composta por 1.164 pacientes, dos quais 22,42% apresentaram pelo menos uma hemocultura positiva. As hemoculturas positivas foram associadas a períodos de hospitalização maior que 15 dias, internação em unidade de terapia intensiva e aos óbitos (p<0,001). Todos os custos diretos totais e diários de pacientes com hemoculturas positivas foram significativamente superiores aos com hemoculturas negativas. A hospitalização dos pacientes com hemoculturas positivas apresentou média de custo total de R$6.310,16, valor superior aos com hemoculturas negativas, que foi de R$2.808,07. A terapia antimicrobiana em pacientes com hemoculturas positivas correspondeu a três vezes o valor dos pacientes com hemoculturas negativas. **Implicações**: Hemoculturas positivas estiveram associadas a impactos negativos nas variáveis clínicas e nos aspectos econômicos, refletindo no aumento dos custos diretos da hospitalização.

DESCRITORES

Custos de Cuidados de Saúde; Custos de Medicamentos; Infecção Hospitalar; Hemocultura.

RESUMEN

Introducción: Las infecciones del torrente sanguíneo son una de las infecciones nosocomiales más importantes. Y, aunque se conoce su impacto en la morbilidad y la mortalidad de los pacientes, el impacto financiero aún se conoce poco. El objetivo es evaluar el impactos clínico y económico de la hospitalización de pacientes con hemocultivos positivos. **Delineación**: Estudio desarrollado en un hospital terciario, que incluye pacientes hospitalizados en 2017 y que recogieron hemocultivos. **Resultados**: La muestra estuvo compuesta por 1.164 pacientes, el 22,42% de los cuales tenían al menos un hemocultivo positivo. Los hemocultivos positivos se asociaron a periodos de hospitalización superiores a 15 días, ingreso a la unidad de cuidados intensivos y fallecimientos (p<0,001). Todos los costos directos totales y diarios de los pacientes con hemocultivos positivos fueron significativamente más altos que aquellos con hemocultivos negativos. La hospitalización de los pacientes con hemocultivos positivos tuvo un costo total promedio de R$6.310,16, superior al de los pacientes con hemocultivos negativos, que fue de R$2.808,07. La terapia antimicrobiana en pacientes con hemocultivos positivos correspondió a tres veces el valor de los pacientes con hemocultivos negativos. **Implicaciones**: Los hemocultivos positivos se asociaron con impactos negativos en variables clínicas y aspectos económicos, reflejando el aumento de los costos directos de hospitalización.

DESCRIPTORES

Costos de la Atención en Salud; Costos de los Medicamentos; Infección Hospitalaria; Cultivo de Sangre.

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COLLABORATIONS

NLP, GC and GK: Substantial contributions to work conception or outline, to data collection, analysis and interpretation. MREP, RR, MCFLH: Contributions article writing or to its critical review. All the authors agree and take responsibility for the content of this manuscript version to be published.

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AVAILABILITY OF DATA

Data in this study were presented in tables and charts, from the analysis by SPSS statistical software. Data collected are stored in Microsoft Excel® software.

FUNDING SOURCE

There were no costs in the execution of this study, and there was no funding source as well.

CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

COMPLEMENTARY MATERIAL

Table 3 – Association analysis of the averages and medians of the direct cost (total and daily) in dollar (US$) attributed to the hospitalization of patients (N=1,164) according to the microbiological result of blood cultures. Londrina-PR, 2019.

Variables	Total Direct Cost			Daily Direct Cost		
	Positive-BC	Negative-BC	*p*-value*	Positive-BC	Negative-BC	*p*-value*
	Average (DP) Median	Average (DP) Median		Average (DP) Median	Average (DP) Median	
Materials and medicine	1,529.23 (1,896.63) 868.48	582.02 (751.24) 372.33	<0.001	64.10 (95.29) 50.30	41.66 (34.29) 33.39	<0.001
Antimicrobials	539.09 (957.01) 208.12	181.96 (360.03) 87.09	<0.001	19.77 (40.50) 12.76	11.74 (13.46) 8.59	<0.001
Exams	486.72 (634.89) 310.72	315.09 (606.08) 156.07	<0.001	28.48 (106.82) 15.80	27.09 (58.65) 14.24	0.012
Integral**	2,015.96 (2,209.04) 1,265.06	897.11 (1,050.78) 564.10	<0.001	92.62 (157.99) 66.36	68.76 (70.20) 50.53	<0.001

Caption: Positive-BC: blood cultures with microbial growth; Negative-BC: blood cultures with no microbial growth; SD: *Standard deviation*; **Mann–Whitney test*; Integral**: sum of material and medication costs and exams.