Burden of disease of bloodstream infections (BSI) associated with long-term central venous catheter (LTC) in patients with haematological neoplasms (HN)

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INTRODUCTION

Bloodstream infections (BSIs) are one of the most frequently and severe healthcare associated infection (HI) (ANVISA 2013). About 60% of all BSIs acquired in the hospital environment are originated from vascular accesses (Cmich & Maki,2001). Catheter associated BSIs is related to high lethality, increased length of hospital stay and costs. However, it is estimated 65-70% of BSIs could be preventable (Umcheid, 2001). LTCs are the most commonly device used during the treatment of patients with neoplasm (Lebeaux et. al, 2012). Bloodstream infection associated with LTCs (BSI-LTC) in patients with HN are severe infections with additional risks and complications inherent to neoplastic disease such as delayed chemotherapy and difficulties to insert new catheter due to vascular anatomic damages. These infections are often caused by multidrug resistant microorganisms (MDR), with limited therapeutic options and high lethality. Infections due to these agents are a global public heath problem. MDR bacterias belonging to clonal complexes or specific genotypes have evolutionary advantages that facilitate their global spread (WHO, 2014). These agents have extremely limited or absence of therapeutic options and are associated with high lethality. The Global Burden of Disease (GBD) is a global project with the aim to estimate the burden of disease of 107 pathologies and ten risk factors through A new epidemiological parameter, Disability-Adjusted Life Year (DALY). However, the assessment of the disease burden of (HI) has not been included in the list of events studied so far. Despite the high occurrence and mortality associated with BSI-LTC in HN patients, the impact of this condition in terms of premature death or loss of health remains unknown. In view of the information previously presented, the following questions motivated this work: 1) What is the impact of BSI-LTCs in the years of life lost due to premature death or lived without full health conditions in HN patients? 2) What are the variables potentially associated with death by BSI-LTC? 3) Is there a difference in the disease burden attributed to the different microorganisms and prevalent bacterial genotypes that cause these infections? 4) Is the disease burden of BSIs caused By MDR higher than that caused by multisensitive ones?

OBJECTIVES

Main

- Measure the years of life lost due to premature death (YLL) and those lived without full conditions (YLD) in patients with HN who acquire BSI-LTC;
- Analyze the variables potentially associated with death in patients with HN and BSI-LTC.

Secondary

- Describe the microbiological profile of LTC-BSI;
- Characterize the genetic diversity the most prevalent bacterial species isolated;
- Calculate the Daly-gap between infections caused by different agents as well as MDR and multidrug susceptible microorganisms; vii) to calculate the Daly-gap between prevalent and sporadic bacterial genotypes.

METHODS

a) *Study environment:* Hospital do Câncer I (HCI / INCA), with 16-bed and 12-bed wards for admission of pediatric and adult patients with HN, respectively. In addition, there are a 10-bed Adult and 5-bed pediatric Intensive Care Unit. About 12 new adults and 3 pediatric patients are registered per month for treatment beginning in the Hematologic Section of HCI.

b) *Study design and period:* a prospective cohort from 01/04/2017 to 04/30/2019.

c) *Population:* patients with HN assisted in HCI/ INCA during the study period.

d) *Inclusion criteria:* patients assisted in HCI with HN and LTC inserted.

- For the calculation of the DALY, all episodes of BSI-LTC of each patient will be included.
- For the analysis of risk factors for death, only the first episode of BSI per patient will be included.

e) *Exclusion criteria:* palliative or end-of-life patients with no therapeutic possibilities for HN.

f) *Case detection and data collection dynamics:* BSI-LTC episodes are prospectively detected by laboratory-based surveillance; epidemiological, clinical and microbiological data are collected by bedside patient evaluation and medical records review; the number of LTC inserted is obtained by Technical and Logistic support/HCI/INCA.. Following information are collected with Magpi (Mobile data collector): demographics- date of birth, address, gender, place and date of admission to HCI; About the underlying diseases: type of hematologic cancer, staging, date of catheter placement, use of immunosuppressants or radiotherapy in the last 30 days, prediction of risk of death by Chalson comorbidity index, number of neutrophils at the time of positive blood culture; Data regarding the BSI episode: date of positive blood culture, time of blood culture positivity, microorganism (s) detected and antimicrobial susceptibility profile, BSI severity Pitt score, need for ICU admission, presence of sepsis (Sepsis-free, sepsis, or severe sepsis/septic shock); Data regarding the BSI treatment: antimicrobial (ATB) initiated, date of ATB beginning and end, adequacy of ATB therapy, “lock" therapy with ATB, withdrawal of LTC and date; BSI complications: endocarditis, septic thrombophlebitis; Outcome (30-day follow-up time): death and discharge, dates, or remains admitted.

g) *Statistical analysis:* proportions, means and medians will be calculated for categorical and continuous variables, respectively. As statistical tests will be used X2 test and Fisher's exact test for categorical variables; The Student t test or Mann-Whitney test for continuous variables, as appropriate. The primary outcome is death occurred within seven days after BSI-LCT diagnosis without other evident cause (BSI-LTC related deaths). The BSI mortality will be measured by dividing the number of BSI-LTC related deaths by the total number of BSI-LTCs. The estimate of the disease burden of HI will be done by calculating the DALY, which includes the sum of Years of life lost due to premature mortality (YLL) and the years of life lived without ideal conditions (Years lived with disability, YLD) (Murray et al, 2012B).

DALY=YLL + YLD

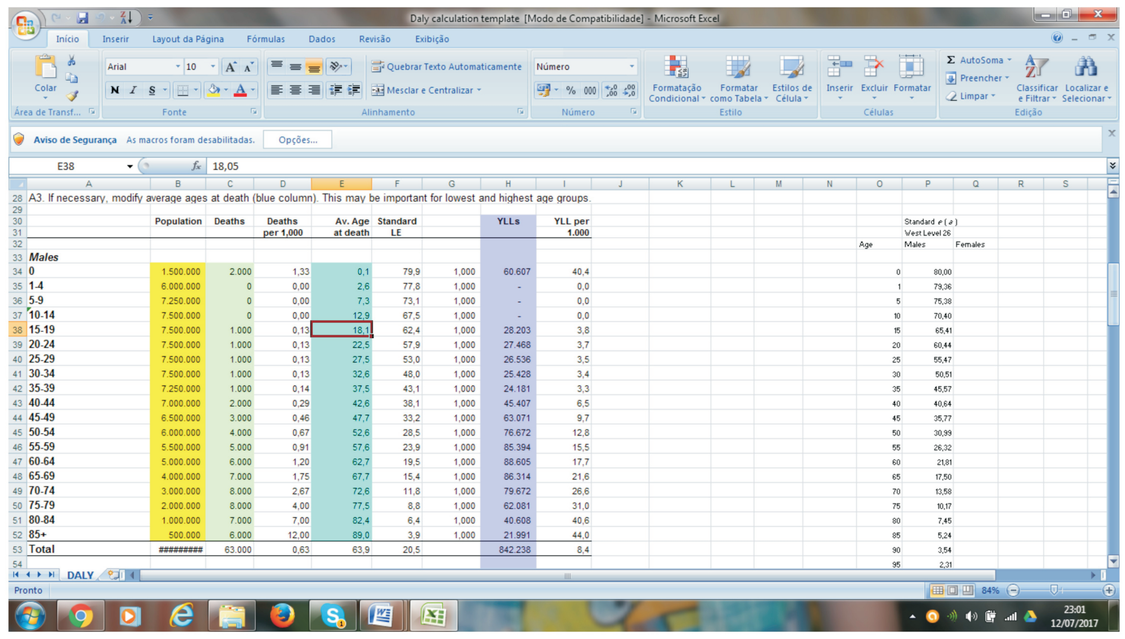
To calculate the years of life lost (YLL) due to premature death, the number of BSI-LTC related deaths in a given age and sex range will be multiplied by their life expectancy.

YLL = (number of deaths in the "X" age group by sex) x (life expectancy in the "X" age group by sex)

To estimate the years of life lived without ideal health conditions (YLD), the prevalence of the disease / injury "y" in the age and sex range is multiplied by the weight of the disability generated by this injury. However, for the study of BSI-LTC, the concept of incidence is more appropriate than of prevalence, since it is an acute event with no potential chronicity. In order to apply the weight of the disability generated by BSI-LTC, these will be classified as mild, moderate or severe acute infectious event. (Rocha et al, 2017), weights of 0.005, 0.053 and 0.21, as estimated by GBD 2010, respectively (Salomont et al, 2012). Sepsis-free, sepsis, or severe sepsis / septic shock / death within the first 72 hours of diagnosis will be categorized as mild, moderate, or severe acute infectious event, respectively. The incidence of each of these three categories will be calculated taking into account in the numerator the nº of cases of BSI-LTC and in the denominator the nº of LTCs installed in the same period. In this way, it will be possible to calculate the overall incidence of BSI-LTC. The YLD will be adjusted by the discount rate advocated by the GBD (0.03) and by the number of days lived without ideal annualized health conditions (days with disability / 365 or 366). The number of days lived without optimal health conditions will be considered as the time from the date of the positive blood culture or the beginning of the antibiotic (whichever comes first) until the end date of the antibiotic therapy for the treatment of CHF. (Rocha et al, 2017)

YLD = incidence of BSI-LTC without sepsis in the "X" age group by sex x 0.005 x 0.03 x number of days per year) + (incidence of laboratorial BSI-LTC with sepsis in the "X" age group by sex x 0.053 x 0.03 x number of days annualized) + (incidence of BSI-LTC with severe sepsis or septic shock or death in the "X" age group by sex x 0.21 x 0.03 x number of days annualized). The DALY will be adjusted for 1,000 hospitalized patients. The DALY-gap will be calculated by subtracting the DALY / 1,000 from the comparison groups. The WHO excel spreadsheet will be applied (Figure 1)

Figure 1: WHO excel spreadsheet for Years lived with disability (YLD), Years of life lost (YLL) and Disability_ adjusted life year (DALY) calculation. (WHO, 2014)



The risk of death related to BSI-LTC (death in 7 days) will be measured through the Kaplan Meier survival analysis. For the evaluation of the variables potentially associated with the death outcome related to BSI (dependent variable) will be initially performed univariate analysis. The covariables (independent variables) with $p \leq 0.25$ in univariate analysis and those considered of clinical significance, will be included for the multivariate analysis by logistic regression in a saturated model. The backwards strategy will be used (successive withdrawal of the covariables) accompanied by the evaluation of the value of the 2-log likelihood of the model generated. Those variables with withdrawn from the model related to the 2-log likelihood difference ≥ 3.84 ($p \leq 0.05$) will be maintained in the adjusted final model. As a measure of association, the odds ratio (OR) and, as the test statistic, the 95% confidence intervals (95% CI) and p values will be calculated. It will be considered that the value of $p \leq 0.05$ will be as statistically significant. The data will be analyzed by Stata11.0 program (Stata Corp LP, College Station, Texas).

h) Microbiological analysis: the cultures are being processed in the Clinical Microbiological Laboratory of HCI/INCA. The collection of blood samples for blood culture will be indicated and performed by the hospital's care team, according to a routine already established in CHI / INCA. Positive blood cultures are detected by automated method, BactecTM 9240 system (Becton Dickinson, Cockeysville, MD, EUA). Bacterial samples will be identified by Vitek2® automated system (BioMérieux Vitek Inc., Hazelwood, Mo., EUA). Complementary biochemical tests are performed according to protocol already established by the Laboratory. Antimicrobial susceptibility testing will be performed using the agar - diffusion method, according to The Clinical and Laboratory Standards Institute (CLSI) in force in the period.

I) Molecular analysis: genotypes and CC will be characterized by random amplification of polymorphic DNA (RAPD-PCR) (Martins et al, 2013), pulsed-field gel electrophoresis (Pellegrino et al, 2002) and multilocus sequence typing (MLST) by the scheme of the University of Oxford (UO) and the Institut Pasteur (IP) (Martins et al, 2013 and Girão et al, 2013). This analysis will be carried out in collaboration Laboratory of Research in Medical Microbiology (LIMM), Institute of Microbiology Paulo de Goés, Federal University of Rio de Janeiro.

PRELIMINARY STUDY

Between April and June 2017, 35 LTC were installed in 35 patients with HN (Table 1). Of these, eight LTC-BSI episodes was detected, five of them in male patients. The median age of patients with LTC-BSI was 11 years (range:4-41). The median time of BSI treatment was 13 days (range: 10-18). There was one death, occurred in 30 days, in a female adult patient. Four infections were caused by Gram-negative, three by Gram-positive, and one by fungi. No MDR agent was detected (Table 2).

Table 1: Distribution of long-term catheters (LTC) inserted and associated bloodstream infections (BSI) in patients included in the study between April and June / 2017

Variable		LTC (n=35)	BSI (n=8)	Cumulative Incidence (%)
Sex				
	Male	20	5	25
	Female	15	3	20
Age in years				
	0	0	0	0
	0-4	5	1	20
	5-9	5	1	20
	10-14	6	4	67
	15-19	5	0	0
	20-24	1	0	0
	25-29	1	0	0
	30-34	1	0	0
	35-39	0	0	0
	40-44	4	2	50
	45-49	1	0	0
	50-54	1	0	0
	55-59	0	0	0
	60-64	4	0	0
	65-69	0	0	0
	70-74	0	0	0
	75-79	0	0	0
	80-84	0	0	0
	85	0	0	0
Treatment time, days				
Median, (range)		13 (10-18)		
Death				
	30 days	1		
	7 days	0		

Table 2: Distribution of bloodstream microorganisms associated with long term catheter of patients with HN - April to June / 2017 (n = 8)

Microrganism	Total (n=8)	Multidrug resistant (n=0)
Gram-negative	4	
Acinetobacter loffii	1	
Pseudomonas aeruginosa	2	
Klebsiella pneumoniae	1	
Gram-positive	3	
Streptococcus mitis	1	
Staphylococcus coagulase negativa	1	
Staphylococcus aureus	1	
Fungi	1	
Yeast		
Candida spp	1	
Non Yeast	0	

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