Journal of Infection and Public Health 12 (2019) 372–379

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Attributable length of stay and cost for pediatric and neonatal central line-associated bloodstream infections in Greece

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ARTICLE INFO

Article history:
Received 11 September 2018
Received in revised form
14 December 2018
Accepted 17 December 2018

Keywords:
CLABSI
Bloodstream infection
Pediatric
Cost
Burden

ABSTRACT

Background and objective: Central line-associated bloodstream infections (CLABSIs) are the most frequent pediatric hospital-acquired infections and are associated with significant morbidity and healthcare costs. The aim of our study was to determine the attributable length of stay (LOS) and cost for CLABSIs in pediatric patients in Greece, for which there is currently a paucity of data.
Methods: A retrospective matched-cohort study was performed in two tertiary pediatric hospitals. Inpatients with a central line in neonatal and pediatric intensive care units, hematology/oncology units, and a bone marrow transplantation unit between June 2012 and June 2015 were eligible. Patients with confirmed CLABSI were enrolled on the day of the event and were matched (1:1) to patients without CLABSI (non-CLABSIs) by hospital, unit, and LOS prior to study enrollment (188 children enrolled, 94 CLABSIs). The primary outcome measure was the attributable LOS and cost. Baseline demographic and clinical characteristics were recorded. Attributable outcomes were calculated as the differences in estimates of outcomes between CLABSIs and non-CLABSIs, after adjustment for propensity score and potential confounders.
Results: There were no differences between the two groups regarding their baseline characteristics. After adjustment for age, gender, matching characteristics, central line management after study enrollment, and propensity score, the mean LOS and cost were 57.5 days and €31,302 in CLABSIs versus 36.6 days and €17,788 in non-CLABSIs. Overall, a CLABSI was associated with a mean (95% CI) adjusted attributable LOS and cost of 21 days (7.3–34.8) and €13,727 (5,758–21,695), respectively. No significant difference was detected in LOS and cost by hospitalization unit.
Conclusions: CLABSIs were found to impose a significant economic burden in Greece, a finding that highlights the importance of implementing CLABSI prevention strategies.

Introduction

Healthcare-associated infections (HAIs) represent the most frequent complication among hospitalized neonates and children worldwide, especially in pediatric and neonatal intensive care units (PICUs and NICUs) and in hematology-oncology units. HAIs result in high morbidity, mortality, and healthcare costs [1–3], and pose a significant threat in Greece. According to the 2011–12 Surveillance Report from the European Centre for Disease Prevention and Control (ECDC), Greece ranked fourth among European countries with respect to rates of HAI, with an HAI prevalence of 9%; this rate was even higher in ICUs (31%) [4]. Moreover, Greece ranked second with respect to rates of bloodstream infections (BSIs), which accounted for 18.9% of all observed HAIs, and in the top three European countries with respect to rates of catheter-related infections (>12% of all HAIs) [4].

Central line-associated bloodstream infections (CLABSIs) are the most common HAIs in critically ill pediatric patients of all age groups, due to the patients' frequent need for central venous catheters (CVCs) [1,2,5,6]. Various studies have demonstrated that most CLABSIs are preventable; in many cases they are even considered "zero events" [3,6–11]. However, CLABSI rates remain far

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https://doi.org/10.1016/j.jiph.2018.12.004

above zero both in adult and pediatric populations in several countries, especially in those with limited resources, including Greece [12–14]. Although limited data are available regarding CLABSI rates in Greek pediatric units, the data that does exist reveal that CLABSI rates range from 1.35 to 14.7/1000 central line days [5,8,15,16].

There is strong evidence demonstrating that CLABSIs are significantly associated with high morbidity and healthcare costs [2,3]. Attributable mortality for CLABSI has been found to range from 12% to 25% worldwide [17,18], while attributable healthcare costs vary by country and healthcare system. Although there is a large body of published evidence regarding the attributable CLABSI outcomes in adult populations [18–21], there is lack of evidence for pediatric populations. A review of the literature shows that the attributable length of stay (LOS) and cost for CLABSIs in pediatric populations range from 19 to 21.2 days and from $55,646 to $69,332, respectively [22,23].

There is a paucity of data regarding the attributable cost and LOS for CLABSIs in Greece. Considering the high prevalence of HAIs in Greece, along with the current policies that pose cost-containment measures and reallocation of healthcare resources, the need for determination of the cost of CLABSIs is of significant importance [4]. Quantifying excess LOS and cost is essential for assessing the amount of resources and bed-days that might be gained from preventive measures, which can guide decision-making around investments in infection control [24,25]. Although there are some cost estimations for CLABSIs in the literature, as mentioned above, these estimations are not applicable to other countries since the cost depends on the healthcare system and the prices of healthcare resources used for the management of CLABSIs; factors that strongly vary among countries. As such, the aim of our study was to determine the attributable cost and LOS for CLABSIs in the Greek pediatric and neonatal populations, so that we can estimate the economic benefit of the design and implementation of a prevention initiative that is our ultimate goal.

Methods

Study design and population

A retrospective matched-cohort study was performed in two tertiary pediatric hospitals (Agia Sophia and Aglaia Kiriakou) in Athens, Greece. Three NICUs, two PICUs, three hematology/oncology units, and one bone marrow transplantation unit (BMTU) participated in the study. The study period was between June 2012 and June 2015.

The study sample consisted of all children <18 years of age who met the following inclusion criteria: they were hospitalized with at least one central line within two calendar days before study enrollment, and this central line was still in place on either the day of study enrollment or the day before. The central lines followed-up were non-tunneled (including umbilical catheters), tunneled (Hickman catheters or implantable ports), and peripherally inserted central catheters (PICCs). Children with CLABSI hospital admission diagnosis were excluded (community-acquired CLABSIs).

Children that presented with confirmed CLABSI diagnosis during hospitalization were the exposed patients (CLABSIs). CLABSI was defined, according to CDC criteria, as "a laboratory-confirmed bloodstream infection where a central line or umbilical catheter was in place for >2 calendar days on the date of the event and was still in place on the date of the event or the day before, and that this infection was not present on admission or related to infection at another site" [26]. CLABSIs had been previously prospectively recorded by the staff of the Center for Clinical Epidemiology and Outcomes Research (CLEO), as part of an institutional quality-improvement effort for stewardship and prevention. CLABSI tracking by CLEO started in June 2012, and all CLABSIs enrolled in our study had already been tracked.

Children with CLABSIs were enrolled on the day of the event and were matched (1:1) with children without CLABSIs (non-CLABSIs or unexposed) by hospital, hospitalization unit, and LOS prior to study enrollment. More specifically, for every CLABSI that had been enrolled, a non-CLABSI was detected from the same unit using patients' medical records. This non-CLABSI should have been hospitalized at least as long as the CLABSI patient on the day of the CLABSI patient enrollment. After the matching procedure, 94 CLABSIs and 94 non-CLABSIs were enrolled.

Using the LOS prior to study enrollment as a matching factor, we intended to minimize endogenous variables bias, due to reverse causality between the risk of HAIs and LOS (LOS is a risk factor for CLABSI, and CLABSI is a risk factor for higher LOS) [24]. Thus, all patients enrolled in our study had the same potential to present with CLABSI during their hospitalization, with respect to this specific risk factor. Overmatching was avoided, in an effort to minimize selection bias.

The Scientific Councils of both hospitals and the Scientific Directors of each participating unit granted approval for our study. Due to its retrospective and confidential nature, informed consent was waived.

Data collection

Data were collected retrospectively by the same investigator, through the hospital medical records, using a case report form developed to serve the purposes of the present study. Baseline demographic and clinical characteristics, as well as the utilization of healthcare resources that could be attributed to the diagnosis and treatment of a CLABSI or related complications were recorded. These resources included diagnostic tests (laboratory and imaging), medicine (antibiotics, resuscitation medicine, parenteral nutrition solutions, etc.), supportive therapies (dialysis, transfusion, surgery), and medical supplies used to maintain or replace CVCs. Chemotherapeutics were not recorded, as their use was considered irrelevant to the CLABSI.

Main outcomes

The primary outcome measures were the attributable LOS and cost. The attributable LOS was defined as the hospitalization days after the enrollment day, until discharge or death. The attributable cost was determined from hospital perspective, including variable (direct medical) and fixed (hospital overhead, personnel) costs.

Cost estimation

Direct medical costs were calculated using a micro-costing approach. Specifically, the healthcare resources utilized, as collected from patients' medical records, were combined with the corresponding unit costs (see Appendix, Table A.1). All unit costs were in Euros and were inflated to 2017 values.

The costs of diagnostic tests were obtained from the official website of the Greek public sickness fund "E.O.P.Y.Y." [27], and the reimbursement costs for public hospitals were used as a proxy for the actual costs. These costs were then multiplied by the utilized diagnostic units.

The cost of medical supplies used for CVC management was obtained by the official website "Observe Net" of the National Medical Supplies' Committee [28], which provides unit costs for Greek public hospitals. These costs were then multiplied by the utilized units.

Medication cost was calculated by multiplying the daily dose of each medicine by the medication days for each patient, and then by the medicine price per recorded unit (gram, ml, etc.). The hospital price of medicines was calculated on the grounds of the ex-factory prices, as extracted from the drug price bulletin issued by the Ministry of Health on 19.07.2017, after applying the necessary discounts and rebates provided in the relevant legislation [29].

Costs of dialysis and transfusion were obtained from previously published studies performed in Greece [30,31], and were inflated to 2017 values. Due to lack of analytical cost from public pediatric hospitals, the costs of surgical interventions were obtained from large private pediatric hospitals, which use analytical accounting techniques. In order to reflect production costs only, their profits were deducted from the cost of each surgery, by applying relevant profit margins.

Hospitalization cost was calculated by combining the LOS with a cost per diem. The cost per diem was calculated on the grounds of the hospital overhead cost and personnel cost. These were obtained from data provided by the Greek Ministry of Health, based on the annual expenditure reports of the two hospitals, and were divided by the total annual hospitalization days.

Statistical analyses

Descriptive statistics between CLABSIs and non-CLABSIs are presented as absolute (n) and relative frequencies (%) for categorical variables and median (25th–75th percentile) for continuous not-normally distributed variables. Cost and LOS data are presented as means and 95% Confidence Intervals. These 95% CIs were obtained from 1000 non-parametric bootstrapped resamples, using the 95% percentile bootstrap CI method (i.e. 2.5% and 97.5% percentiles of the bootstrap distribution), since cost and LOS data are truncated at zero and they do not follow normal distributions. Patients with missing data on LOS and cost were not included in the statistical analysis.

Univariate conditional logistic regression was conducted to identify factors significantly associated with CLABSI, indicating that matching in the three selected factors did not lead to balance of other potential confounders. Mann–Whitney U or Kruskal–Wallis H test was used to assess the association with categorical variables and LOS/cost, as appropriate, and Spearman's ρ to assess the association between continuous characteristics and LOS/cost.

Univariate generalized linear mixed models were used to estimate the impact of CLABSI on cost and LOS. More specifically, a gamma distribution with a log link function was applied to determine the impact of CLABSI on the total cost and a negative binomial distribution to estimate its impact on LOS. Matching between CLABSI and non-CLABSI cases was taken into account by introducing a random effect for the matching identifier. To estimate the impact of CLABSI on cost and LOS after controlling for potential confounders, a multivariate generalized linear mixed model was conducted with CLABSI indicator as the main predictor. Age, gender, hospital, hospitalization unit, LOS prior to study enrolment, central line management after study enrollment and propensity score were also included in this model. The propensity score for predicting the risk of acquiring a CLABSI was derived, to account for the clinical severity of patients, using conditional logistic regression. CLABSI (yes/no) was the dependent variable, and CVC placement in surgery room, presence of stomy in the 48 hours prior to study enrollment, presence of neutropenia and transfusion of blood products in the 14 days prior to study enrollment, LOS in ICU, and length of catheter stay (LOCS) prior to study enrollment were the independent variables. The variables used to calculate the propensity score were those found to be significantly associated with either CLABSI (exposure) or outcome (LOS or cost) at a univariate level.

A probability value of 5% was considered as statistically significant. All statistical calculations were performed using STATA software (version 8, 2003, STATA Corp, College Station, TX, USA).

A sample size of 90 CLABSIs and 90 non-CLABSIS was found to be required in order to detect a true difference in means of log transformed cost between CLABSIs and non-CLABSIs of 0.5 units (i.e. 10 vs. 9.5) with a pooled standard deviation of 1.2, a power of 80%, and a level of significance 5%. These estimations for mean and standard deviation were obtained from the already collected data by our organization during a pilot study.

Results

Baseline characteristics

Baseline characteristics of CLABSI and non-CLABSI children are presented in Table 1. As observed, no differences were found between the two groups regarding age, gender, clinical condition, and presence of recorded factors stating severity of illness in the last 48 hours or 14 days prior to study enrollment. However, it was found that longer LOCS prior to study enrollment by one day was associated with statistically significantly higher probability of experiencing CLABSI by 3% (OR 1.03, 95% CI 1.01–1.05). In addition, patients who had been transfused with blood products in the 14 days prior to study enrollment had almost 2.5 times the probability of experiencing CLABSI compared to those who hadn't been transfused (OR 2.44, 95% CI 1.13–5.31, Table 1).

Factors associated with LOS and cost

Mean LOS (95% CI) was 55.2 days (44.8–66.5) for CLABSIs and 39.7 days (31.4–49.6) for non-CLABSIs, and thus significantly longer in CLABSI patients ($p = 0.008$, Table 2). A variability in LOS was observed across the several hospitalization units (mean LOS ranged from 27.2 days in the BMTU to 63.7 days in NICUs, $p = 0.008$), while LOS was also significantly associated with CVC placement in the surgical room ($p = 0.05$) and presence of severe neutropenia in the 14 days prior to study enrollment ($p = 0.043$) or stomy in the 48 hours prior to study enrollment ($p = 0.005$). LOS was not correlated with any other patient characteristic, as shown in Table 2. Furthermore, LOS was correlated with LOS prior to study enrollment and LOS in ICU prior to study enrollment, but not with LOCS prior to study enrollment (Spearman $\rho = 0.201$, $p = 0.005$, Spearman $\rho = 0.218$, $p = 0.002$ and Spearman $\rho = 0.101$, $p = 0.169$ respectively).

Mean total cost (95% CI) was significantly higher for CLABSIs, reaching at €29,985 (24,227–36,618) compared with that of €19,241 (15,333–23,898) for non-CLABSIs ($p = 0.001$, Table 3). Cost was associated with CVC placement in the surgical room ($p = 0.036$) and also with presence of stomy in the 48 hours prior to study enrollment ($p = 0.019$), but with no other patient characteristics, as shown in Table 3. In addition, cost was correlated with LOS, LOS in ICU, and LOCS prior to study enrollment (Spearman $\rho = 0.201$, $p = 0.005$, Spearman $\rho = 0.169$, $p = 0.02$ and Spearman $\rho = 0.144$, $p = 0.048$ respectively).

With regard to factors after study enrollment, LOS and cost were significantly associated with central line management (both $p < 0.001$, Tables 2 and 3).

Estimated adjusted attributable LOS and cost

After adjustment for age, gender, matching characteristics, CVC outcomes after study enrollment, and propensity score, the mean LOS and cost were 57.5 days and €31,302 in CLABSIs versus 36.6 days and €17,788 in non-CLABSIs, respectively. Overall, CLABSI was associated with a mean (95% CI) adjusted attributable LOS and cost of 21 days (7.3–34.8) and €13,727 (5,758–21,695),

Table 1
Baseline characteristics of patients with and without CLABSI.

Patient characteristics	CLABSI (n = 94)	Non-CLABSI (n = 94)	OR (95% CI)[b]
Age (median years, 25th–75th per.)	1.39 (0.26–6.87)	2.55 (0.16–7.21)	0.96 (0.89–1.05)
Gender (n, %)			
Male	57 (60.64)	58 (61.7)	0.91 (0.39–2.14)
Female	37 (39.36)	36 (38.3)	
Clinical classification (n, %)			
Perinatal condition, congenital/chromosomal abnormality	30 (31.91)	34 (36.17)	ref.
Neoplasm	41 (43.62)	43 (45.74)	0.74 (0.16–3.44)
Other	23 (24.47)	17 (18.09)	1.6 (0.49–5.2)
Length of CVC stay (median days, 25th–75th per.)[a]	15.5 (8–33)	11 (4–20)	1.03 (1.01–1.05)
Catheter type (n, %)			
Tunneled CVC	62 (65.96)	62 (65.96)	1 (0.35–2.85)
Non-tunneled CVC	32 (34.04)	32 (34.04)	
Presence in the last 48 h (n, %)[a]			
ICU hospitalization	54 (57.45)	55 (58.51)	–
Inotropes	13 (13.83)	14 (14.89)	0.92 (0.4–2.08)
Mechanical ventilation	32 (34.04)	30 (31.91)	1.2 (0.52–2.78)
Levin	54 (57.45)	48 (51.06)	2.5 (0.78–7.97)
Foley catheter	30 (31.91)	29 (30.85)	1.17 (0.39–3.47)
Stomy	10 (10.64)	17 (18.09)	0.42 (0.15–1.18)
Presence in the last 14 days (n, %)[a]			
Severe neutropenia	36 (38.3)	32 (34.04)	1.57 (0.61–4.05)
Steroids	43 (45.74)	40 (42.55)	1.2 (0.6–2.38)
Parenteral nutrition	47 (50)	43 (45.74)	1.36 (0.63–2.97)
Transfusion of blood products	79 (84.04)	66 (70.21)	2.44 (1.13–5.31)
Surgery	18 (19.15)	20 (21.28)	0.87 (0.41–1.82)
Antibiotics	90 (95.74)	88 (93.62)	1.5 (0.42–5.32)
Immunosuppression	42 (44.68)	37 (39.36)	2 (0.68–5.85)
Normal nutrition	83 (88.3)	84 (89.36)	0.88 (0.32–2.41)
Multiple CVCs (>1)	23 (24.47)	16 (17.02)	1.88 (0.79–4.42)

CI, confidence interval.
[a] Prior to study enrollment.
[b] Odds Ratios (OR, 95%CI) were calculated by Conditional Logistic Regression, having taken performed matching into account.

respectively (Table 4). No significant difference was detected in attributable LOS and cost by hospitalization unit (Table 4).

In addition, after performing subgroup analysis in survivors (72 CLABSIs versus 85 non-CLABSIs), CLABSI was found to increase LOS and cost in a similar manner (Table 5), even when performing the analysis among matched pairs of our sample in which both members survived (67 pairs in total).

Discussion

In our study, our initial hypothesis that CLABSI imposes a significant burden on the Greek hospitals in terms of LOS and cost was confirmed. We found that attributable LOS and cost for CLABSIs in Greek pediatric and neonatal population is 21 days and €13,727, respectively. As far as we know, this is the first study aiming to quantify the attributable LOS and cost for CLABSI in Greece and our results indicate that prevention initiatives should be implemented and they could potentially lead to cost savings. The need for prevention is further highlighted by the high mean pediatric CLABSI rate of 4.41 infections per 1000 central line-days that is reported in the literature (6.02 in NICUs, 6.09 in PICUs, and 2.78 per 1000 central line-days in Hematology-Oncology Units) [16].

A review of the literature shows that the attributable LOS for CLABSIs ranges from 11.5 days in adult ICUs and PICUs to 37.82 days in NICUs worldwide [12,13,22,23,32–34]. This variability in LOS within several studies is mainly due to differences in study design, population, setting, confounders taken into account, and in general the type of analysis performed.

With regard to attributable LOS, our results are aligned with those of two pediatric studies conducted in the US that also used propensity score analysis. In the first study, the mean attributable LOS between matched CLABSIs and non-CLABSIs was found to be 19 days in a general mixed pediatric population of the Nationwide Inpatient Sample databases [22], while in the second one LOS was found to be 21.2 days in a pediatric hematology/oncology population [23]. Propensity score analysis, in general, allows for more accurate comparisons of attributable LOS and cost between CLABSIs and non-CLABSIs and it is therefore used in relevant cost estimation studies.

In the literature, it is also noted that higher LOS is observed in low-income versus high-income countries, because of missing timeliness of diagnostic procedures and slower setting of proper antibiotic administration [35].

With respect to cost, although significant data have been published for adults [18–21], there is lack of evidence for pediatric populations. The two aforementioned studies from the US calculated mean attributable cost for pediatric CLABSIs, with the first reporting a cost of $55,646 [22], and the second one reporting a cost of $69,332 in the pediatric hematology/oncology population [23]. Other studies worldwide have calculated costs using different definitions of BSI (not the CDC CLABSI definition), and as such the results of these studies are not comparable with ours [1,36].

With regard to cost estimations, there are many factors that could explain the differences observed among studies. The perspective of analysis (hospital, societal, etc.), the costing methodology (i.e. micro-costing methods or not) [24], the year of costing, the differences in clinical practice patterns and healthcare financing among countries are some of these factors. For example, in high-income countries novel medical technologies are used, which may account for overwhelming hospitalization costs, as opposed to the low-income countries where such technologies may not be available.

Quantifying the attributable cost for CLABSIs in the Greek pediatric population makes it possible for our team to proceed to

Table 2
Factors associated with length of stay (LOS): bivariate analysis.

Patient characteristics	LOS (mean days, 95% CI)[b]	p-value
CLABSI diagnosis		
CLABSI	55.2 (44.8–66.5)	0.008
Non-CLABSI	39.7 (31.4–49.6)	
Age group		
Infants (<1 year)	52.4 (41.8–64)	0.107
Children (≥1 year)	43.7 (34.8–53.6)	
Gender		
Male	49.7 (40.2–60.3)	0.486
Female	43.9 (33.7–54.9)	
Hospitalization unit		
PICU	43.8 (31.2–57.6)	0.008
NICU	63.7 (48.4–79.7)	
Hematology–Oncology Unit	54.8 (35.9–74.3)	
BMTU	27.2 (21.6–32.7)	
Clinical classification		
Perinatal condition, congenital/chromosomal abnormality	52.8 (41–67.8)	0.517
Neoplasm	44.4 (35–55.1)	
Other	44.9 (30–63.3)	
Catheter placement		
In surgical room	52.7 (43.8–62.3)	0.05
Other than surgical room	35.7 (26.9–47.2)	
Levin in the last 48 h[a]		
Yes	55.8 (45–67.5)	0.088
No	37.6 (30.6–45)	
Stomy in the last 48 h[a]		
Yes	82.8 (57.7–114.4)	0.005
No	41.5 (35.7–48)	
Multiple CVCs in the last 14 days[a]		
1	49.6 (41.5–58)	0.119
>1	39 (26.2–52.6)	
Transfusion of blood products in the last 14 days[a]		
Yes	46.2 (38.4–54.7)	0.453
No	51.4 (36.2–67.2)	
Severe neutropenia in the last 14 days[a]		
Yes	35.2 (27.5–42.9)	0.043
No	54.4 (44.7–64.8)	
CVC outcomes after study enrollment		
CVC still in place	37.5 (28.3–48)	<0.001
CVC removal	39.4 (26.7–53.8)	
CVC replacement	60.4 (49.3–73.4)	

LOS, Length of hospital stay after study enrollment; CI, Confidence interval.
[a] prior to study enrollment.
[b] LOS means and 95% CIs are obtained from 1000 non parametric bootstrapped resamples, using the 95% percentile bootstrap CI method (i.e. 2.5% and 97.5% percentiles of the bootstrap distribution), since LOS data are truncated at zero and they do not follow normal distributions.

Table 3
Factors associated with cost: bivariate analysis.

Patient characteristics	cost (mean €, 95% CI)[b]	p-value
CLABSI diagnosis		
CLABSI	29,985 (24,227–36,618)	0.001
Non-CLABSI	19,241 (15,333–23,898)	
Age group		
Infants (<1 year)	24,974 (19,892–30,765)	0.537
Children (≥1 year)	24,293 (19,271–29,932)	
Gender		
Male	26,026 (21,027–31,755)	0.337
Female	22,333 (17,107–27,905)	
Hospitalization unit		
PICU	22,837 (16,409–30,063)	0.11
NICU	29,403 (22,350–36,979)	
Hematology–Oncology Unit	30,236 (19,708–42,164)	
BMTU	16,599 (13,023–20,169)	
Clinical classification		
Perinatal condition, congenital/chromosomal abnormality	24,619 (19,211–31,319)	0.786
Neoplasm	25,634 (20,162–32,177)	
Other	22,267 (15,309–31,206)	
Catheter placement		
In surgical room	27,574 (22,934–33,003)	0.036
Other than surgical room	17,935 (13,665–23,074)	
Levin in the last 48 h[a]		
Yes	27,250 (21,953–33,758)	0.279
No	21,454 (17,247–26,807)	
Stomy in the last 48 h[a]		
Yes	38,461 (25,586–52,994)	0.019
No	22,243 (18,792–25,934)	
Multiple CVCs in the last 14 days[a]		
1	25,590 (21,406–30,297)	0.13
>1	20,638 (14,339–28,559)	
Transfusion of blood products in the last 14 days[a]		
Yes	24,695 (20,343–29,046)	0.814
No	24,215 (17,580–31,260)	
Severe neutropenia in the last 14 days[a]		
Yes	20,332 (16,060–25,089)	0.215
No	27,014 (21,985–32,939)	
CVC outcomes after study enrollment		
CVC still in place	20,392 (15,500–26,009)	<0.001
CVC removal	17,986 (12,556–24,051)	
CVC replacement	31,016 (25,152–37,409)	

CI, Confidence interval.
[a] Prior to study enrollment.
[b] Cost means and 95% CIs are obtained from 1000 non parametric bootstrapped resamples, using the 95% percentile bootstrap CI method (i.e. 2.5% and 97.5% percentiles of the bootstrap distribution), since cost data are truncated at zero and they do not follow normal distributions.

the next step of designing and implementing an appropriate prevention intervention. A variety of successful preventive strategies are already thoroughly described in the literature, that mainly include medical staff education around sterile and timely placement, maintenance and removal of central lines, especially through the creation of bundles and checklists, formation of "central line" teams by infection specialists, checking compliance with hand hygiene measures, as well as maintaining infection surveillance and control [3,9,10]. A multifactorial action plan includes all of these aspects and should be tested for cost-effectiveness, specifically in low-income countries.

The main limitation of our study is that it has been conducted in two Greek pediatric tertiary hospitals, reducing the generalizability of our results to other populations, clinical settings, and countries. However, given that our study was conducted in the two pediatric

Table 4
Estimated adjusted LOS and cost by CLABSI.

Variable	CLABSI (n = 94)	Non-CLABSI (n = 94)	Difference	95% CI
LOS, days[a]				
Overall	57.5	36.6	21	7.3–34.8
By unit				
PICU	52.1	33.2	19.1	5.7–32.6
NICU	75	47.8	27.8	8.7–46.9
Hematology–Oncology Unit	69.8	44.5	24.8	6.8–42.9
BMTU	34	21.7	12.4	4.1–20.8
Cost, €[a]				
Overall	31,302	17,788	13,727	5,758–21,695
By unit				
PICU	29,828	16,951	13,159	4,642–21,677
NICU	36,582	20,788	16,275	6,194–26,357
Hematology–Oncology Unit	38,503	21,881	16,442	5,646–27,238
BMTU	21,166	12,028	9,272	3,661–14,883

CI, Confidence interval; LOS, Length of hospital stay after study enrollment.
[a] LOS and cost are adjusted for age, gender, hospital, hospitalization unit, LOS prior to study enrollment, CVC outcomes after study enrollment and for propensity score. Propensity score variables include catheter placement, presence of stomy the last 48 h prior to study enrollment, presence of neutropenia and transfusion of blood products the last 14 days prior to study enrollment, LOS in ICU and length of catheter stay prior to study enrollment.

Table 5
Estimated adjusted LOS and cost by CLABSI among survivals.

Variable	CLABSI (n = 72)	Non-CLABSI (n = 85)	Difference	95% CI
LOS, days[a]				
Overall	54	34.8	19.1	7.2–31
By unit				
PICU	45.5	29.3	16	5.2–26.7
NICU	77.2	49.8	28	9.2–46.9
Hematology–Oncology Unit	64.5	41.6	22.2	6.9–37.6
BMTU	31.7	20.5	11.1	4–18.1
Cost, €[a]				
Overall	29,729	17,570	12,111	4,584–19,638
By unit				
PICU	26,962	15,935	10,943	3,414–18,471
NICU	36,572	21,614	15,414	4,902–25,925
Hematology–Oncology Unit	36,739	21,713	14,576	4,750–24,401
BMTU	20,246	11,966	8,103	2,995–13,211

CI, Confidence interval; LOS, Length of hospital stay after study enrollment.
[a] LOS and cost are adjusted for age, gender, hospital, hospitalization unit, LOS prior to study enrollment, CVC outcomes after study enrollment and for propensity score. Propensity score variables include catheter placement, presence of stomy the last 48 h prior to study enrollment, presence of neutropenia and transfusion of blood products the last 14 days prior to study enrollment, LOS in ICU and length of catheter stay prior to study enrollment.

hospitals that are reference centers for the pediatric population in Greece, our results could be generalized in Greece. In addition, the retrospective nature of this study may have resulted in data inconsistencies. Given the fact that medical records in Greece are still written by hand and not electronic, together with the significant work overload experienced by Greek physicians, it is possible that some information may have been mis-recorded. Furthermore, regarding cost estimation, we were unable to account for medicines like antipyretics/analgesics; parenteral fluids; and consumables such as gauzes and syringes, as these resources are not routinely recorded in patients' medical records in the Greek hospitals.

With regard to study design, we were unable to overcome the limitation of our 1:1 matching procedure. Finding more than one non-CLABSIs with the same LOS prior to study enrollment with that of the CLABSI on the date of the CLABSI's enrollment was impossible. Finally, there may be unobserved confounding factors that are not considered and as such influenced the magnitude of our findings. This is a common limitation that is difficult to fully avoid.

Conclusions

The attributable LOS and cost of 21 days and €13,727 in the Greek pediatric and neonatal population, as estimated in our study, in combination with the high CLABSI rate observed in the same population, indicate that CLABSIs impose a significant economic burden in Greece [16]. As such, investments in interventions aiming to prevent CLABSIs are required to reduce this burden. Further research should focus on determining the appropriate prevention strategy that would be applicable and cost-effective in our country.

Funding sources

This study was part of the PhD thesis of the physician K.S., financed through a scholarship by the General Secretariat for Research and Technology (GSRT) and the Hellenic Foundation for Research and Innovation (HFRI).

Conflict of interest

None declared.

Ethical approval

Not required.

Appendix A

Table A.1
Cost estimation: a micro-costing approach.

Resource utilization	unit cost per category (€)	Source
Direct medical costs		
Diagnostic tests cost, laboratory		
Complete blood count	€2.88	Based on official website of the Greek public sickness fund
Inflammatory markers (CRP, PCT, ESR)	€23.65	
Culture and antibiogram	€11.85	
Coagulation profile	€39.43	
Basic Metabolic Panel	€42.82	
Serum total protein and levels	€10.44	
Lipid profile	€16.87	
Serum Antibiotic levels	€9.51	
Thyroid panel	€44.92	
Serum amylase	€2.26	
Serum LDH	€3.43	
Diagnostic tests cost, imaging		
X-Rays	€4.05	Based on official website of the Greek public sickness fund
Skull X- Rays	€2.44	
Ultrasound imaging	€8.28	
Abdominal Ultrasound	€20.9	
Renal Ultrasound	€14.59	
Doppler Ultrasound	€8.28	
Triplex Ultrasound	€52.82	
Doppler echocardiography	€70	
CT scan	€71.11	
MRI	€236.95	
PET scan	€560	
Medical supplies for central line management		
Hickman catheter	€65.87	Based on official website "Observe Net" of the National Medical Supplies' Committee
Non tunneled central venous catheter	€17.6	
Umbilical catheter	€4.58	
Peripheral venous catheter	€0.57	
Medication cost		
Antibiotics, average cost	€35.73/gram	Based on daily doses multiplied by duration of therapy per patient and on price bulletin issued by the Ministry of Health (19.07.2017)
Antifungal medicine, average cost	€1772.13/gram	
Antiviral medicine, average cost	€12.47/gram	
Resuscitation medicine, average cost	€11.03/gram	
Corticosteroids, average cost	€42.3/gram	
Parenteral therapy, average cost	€8.23/lt	
Dialysis cost	€242.63	Based on a previously published study performed in Greece
Transfusion cost	€131.74	Based on a previously published study performed in Greece
Surgery cost (operational + narcosis cost)		
Tracheostomy	€447.89	Based on the pricing list of Greek pediatric private hospitals
Gastrostomy	€558.48	
<lang=ËN-US¨ Ileostomy	€886.46	
Ileostomy closure	€952.68	
Esophageal dilation	€287.48	
Esophageal stenosis surgery	€980.03	
Duodenal atresia's surgery	€886.46	
Adhesions' surgery	€705.66	
Duodenal necrosis' surgery	€886.46	
Inguinal hernia surgery	€482.73	
Hepatectomy	€1164.31	
Jejunostomy	€886.46	
Brain tumor ablation	€1457.58	
Laminectomy	€960.04	
Intracranial drainage	€980.03	
CSF drainage	€400.69	
CSF drainage removal	€400.69	
VP shunt	€657.96	
Cardiac catheterization	€796.86	
Permanent pacemaker insertion	€771.57	
External pacemaker placement	€441.49	
Retinal laser	€389.98	
Overhead hospital cost per diem		
"Agia Sophia" hospital	€199.51	Based on annual expenditure reports of the two hospitals, obtained by the Greek Ministry of Health
"Aglaia Kiriakou" hospital	€291.05	
Personnel cost per diem		
"Agia Sophia" hospital	€191.98	Based on annual expenditure reports of the two hospitals, obtained by the Greek Ministry of Health
"Aglaia Kiriakou" hospital	€170.40	
Hospitalization cost per diem		
"Agia Sophia" hospital	€391.49	Calculated by adding overhead hospital and personnel cost per diem
"Aglaia Kiriakou" hospital	€461.45	

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