Quantifying the Burden of Hospital-Acquired Bloodstream Infection in Children in England by Estimating Excess Length of Hospital Stay and Mortality Using a Multistate Analysis of Linked, Routinely Collected Data

N. Green,[1,4] A. P. Johnson,[1] K. L. Henderson,[1] B. Muller-Pebody,[1] S. Thelwall,[1] J. V. Robotham,[1] M. Sharland,[2] M. Wolkewitz,[3] and S. R. Deeny[1]

[1]Public Health England, London, United Kingdom; [2]Pediatric Infectious Diseases Unit, St George's Hospital, London, United Kingdom; [3]Freiburg Center for Data Analysis and Modeling, Germany; and [4]Department of Infectious Disease Epidemiology, Imperial College London, United Kingdom

Corresponding Author: N. Green, PhD, 61 Colindale Avenue, Colindale, London, NW9 5EQ. E-mail: nathan.green@phe.gov.uk.

Received March 21, 2014; accepted June 14, 2014; electronically published July 22, 2014.

Background. Hospital-acquired bloodstream infection (HA-BSI) is associated with substantial morbidity, mortality, and healthcare costs in all patient populations. Young children have been shown to have a high rate of healthcare-associated infections compared with the adult population. We aimed to quantify the excess mortality and length of stay in pediatric patients from HA-BSI.

Methods. We analyzed data collected retrospectively from a probabilistically linked national database of pediatric (aged 1 month–18 years) in-patients with a microbiologically confirmed HA-BSI in England between January and March 2009. A time-dependent Cox regression model was fit to determine the presence of any effect. Furthermore, a multistate model, adjusted for the time to onset of HA-BSI, was used to compare outcomes in patients with HA-BSI to those without HA-BSI. We further adjusted for patients' characteristics as recorded in hospital admission data.

Results. The dataset comprised 333 605 patients, with 214 cases of HA-BSI. After adjustment for time to HA-BSI and comorbidities, the hazard for discharge (dead or alive) from hospital for patients with HA-BSI was 0.9 times (95% confidence interval [CI], .8–1.1) that of noninfected patients. Excess length of stay associated with all-cause HA-BSI was 1.6 days (95% CI, .2–3.0), although this duration varied by pathogen. Patients with HA-BSI had a 3.6 (95% CI, 1.3–10.4) times higher hazard for in-hospital death than noninfected patients.

Conclusions. Hospital-acquired bloodstream infection increased the length of stay and mortality of pediatric inpatients. The results of this study provide an evidence base to judge the health and economic impact of programs to prevent and control HA-BSI in children.

Key words. length of stay; multistate model; pediatric.

Hospital-acquired bloodstream infection (HA-BSI) is associated with substantial morbidity, mortality, and healthcare costs in all patient populations [1–4]. However, young children and older adults have been shown to have higher rates of healthcare-associated infections (HCAI) than the general population [5–7]. In a recent national point prevalence survey in the UK, the highest prevalence of HCAI (8.2%; 95% CI, 6.6–10.0) was found in children aged between 1 month and 2 years, compared with an overall prevalence of 6.4% (95% CI, 4.6–8.7) [5], with HA-BSI diagnosed in 15% of pediatric HCAI cases. Thus, HA-BSI is an important issue in children in particular. Furthermore, pediatric HCAI is a Europe-wide and global problem. An HCAI point prevalence survey conducted by the European Centre for Disease Prevention and Control found HCAI diagnosed in 15.7% of patients on pediatric intensive care units (ICUs) and 1.8% on general paediatric units [8]. Amongst others, studies from the United States of America, Brazil, Kenya, and Tunisia have similarly highlighted the impact of HA-BSI in children [9–12].

Journal of the Pediatric Infectious Diseases Society, Vol. 4, No. 4, pp. 305–12, 2015. DOI:10.1093/jpids/piu073

Although the incidence and etiology of pediatric HA-BSI has been investigated, the health and economic impacts of such infections is not well described. Two clinically relevant metrics with which to capture these are the number of excess bed days and the mortality attributable to HA-BSI. Previous estimates of pediatric mortality due to HA-BSI in critically ill children ranged from 11% to 18% [3, 4] and excess length of stay (LoS) ranged between 12 and 21.1 days [13–14]. However, the evidence to date regarding the health and economic impact of HA-BSI in pediatric populations may be overestimated due to the methods used to account for potential confounders such as underlying illness or other comorbidities. Appropriate statistical techniques are required to account for the timing and duration of HA-BSI episodes and the competing risks of discharge from hospital alive and in-hospital mortality [15], where patients may experience an event other than the one of interest, which alters the probability of experiencing the event of interest. In recent studies, using more appropriate statistical methods, researchers demonstrated that HA-BSI is expected to increase both LoS and risk of in-hospital mortality [1, 16–18]. However, these studies were exclusively in adults and the findings varied depending on the microorganisms studied.

Robust and pathogen-specific estimates of the additional LoS and excess mortality due to HA-BSI provide an evidence base to assess the potential health and economic impact of hospital interventions [19] and large-scale national programs [20–22] aimed at reducing HCAI.

Our aim was to quantify, for the first time, excess LoS and mortality associated with pediatric HA-BSI in children in England, by using a unique dataset comprising national laboratory surveillance and clinical data derived from pediatric in-patient Hospital Episode Statistics (HES) [23].

DATA AND METHODS

Data Collection and Linkage

A case of HA-BSI was defined as the isolation of 1 positive bacterial, clinically relevant blood isolate reported to the national laboratory surveillance database (LabBase2) database that occurred 48 hours or more after admission to hospital. The pediatric HA-BSI cohort used in this study comprised a previously described group of patients in England aged 1 month–18 years, with a positive blood culture between January and March 2009, and in-hospital follow-up to March 2010 [24]. Data on BSI were extracted from the LabBase2 maintained by Public Health England, which stores information on infections voluntarily reported by hospital microbiology laboratories. Patient information was extracted from HES, which contains demographic and clinical data, dates of hospital admission, and discharge for all patients and in-hospital mortality with date of death.

The LabBase2 data were probabilistically linked with HES data [25]. The technique assigned match weights to 1 or more potential matches for those records that could not be assigned "unequivocal matches," and the record with the highest weight was accepted as a match.

A case of HA-BSI was defined as the isolation of clinically significant bacteria from a blood sample taken 2 or more days after admission to hospital (day 0). A comparison group comprised pediatric patients aged 1 month–18 years who were hospitalized between January and March 2009 but with no record of HA-BSI. The large size of this population imposed computational limitations. As a result, in-hospital follow-up of non-HA-BSI patient beyond this period was not feasibly possible so the HA-BSI dataset was administratively censored at March 31, 2010 and the non-HA-BSI at March 31, 2009 (additional details are provided in Appendix, Section I and Appendix Tables 1 and 2). Each hospital admission was assumed to be independent so readmissions were assumed to be different patients.

Clinical criteria were coded using International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes, and surgical procedures were coded according to the Office of Population Censuses and Surveys Classification of Interventions and Procedures (OPCS-4) codes [26–27].

Non-HA-BSI patient records with ICD-10 codes indicating infection may have included previously unmatched true HA-BSI patients. Appendix Tables 5 and 8–10 present results with these patient records removed from the comparison group, such that the remaining dataset did not contain patients with community-acquired infections or other HA infections.

Patients with "Other" or "Unknown" ICD-10 codes were removed because of their nonidentifiability. It was not possible to classify these patients by risk factors or whether they were uninfected with certainty. Patients with head injury or mental health illness codes were also removed because their in-care patient journey contrasted markedly with other patients', commonly recording systematically longer LoS. Appendix Table 3 lists all group codes, and Appendix Figure 1 shows a CONSORT diagram summarizing the construction of the final dataset. Patients with same-day admission and discharge were recorded as having LoS 0.5 days.

Patient Confounders

Age, sex, and comorbidity were selected as baseline confounders. Because a comorbidity index for pediatric

Table 1. Dataset Summary Statistics Including Risk Factor, Comorbidities, and Patient Movements Summary Statistics*

Characteristics	Non-HA-BSI				HA-BSI				All			
	Count	Mean/Median	*P* Value	IQR	Count	Mean/Median	*P* Value	IQR	Count	Mean/Median	*P* Value	IQR
Patient sample size	333 391	–	1.00	–	214	–	< .005	–	333 605	–	1.00	–
Age (years)	–	8/6	–	[1, 14]	–	5/1	–	[0, 8]	–	8/6	–	[1, 14]
LoS (days)	–	1.35/0.5	–	[0.5, 1]	–	56.55/30	–	[10, 66]	–	1.38/0.5	–	[0.5, 1]
Time from admission to infection (days)	–	–	–	–	–	30.40/11.5	–	[3, 36]	–	–	–	–
Deaths	157	–	< .005	–	13	–	.06	–	170	–	< .005	–
Sex (F)	160 928	–	.48	–	104	–	.49	–	161 032	–	.48	–
Comorbidity group												
Cancer	4596	–	.01	–	12	–	.06	–	4608	–	.01	–
Premature birth	632	–	< .005	–	42	–	.2	–	674	–	< .005	–
Congenital disorder	24 912	–	.07	–	72	–	.34	–	24 984	–	.07	–
Surgical	4083	–	.01	–	12	–	.06	–	4095	–	.01	–
In-dwelling catheter	6243	–	.02	–	39	–	.18	–	6282	–	.02	–
Tai comorbidity score [29]	20 717	–	.06	–	65	–	.3	–	20 782	–	.06	–
At least 1	97 007	–	.29	–	164	–	.77	–	97 171	–	.29	–
Type of Admission												
Elective	128 255	–	.38	–	48	–	.22	–	128 303	–	.38	–
Emergency	187 144	–	.56	–	106	–	.5	–	187 250	–	.56	–
Total	315 399	–	.94	–	154	–	.72	–	315 553	–	.94	–
Intensive neonatal care	20	–	< .005	–	8	–	.04	–	28	–	< .005	–
Origin of patient												
Another hospital	2380	–	.01	–	38	–	.18	–	2418	–	.01	–
Residence	318 235	–	.95	–	130	–	.61	–	318 365	–	.95	–
Total	320 615	–	.96	–	168	–	.79	–	320 783	–	.96	–

Abbreviations: HA-BSI, hospital-acquired bloodstream infection; IQR, interquartile range.

*For count data, subset size is given; for continuous values, mean/median is given. Note that a patient can be in more than 1 risk factor group.

Table 2. Cox Model Cause-Specific Hazard Regression for Alternative Outcomes by Organism Group, With 95% CI and Expected Excess LoS*

Organism/Outcome	Hazard Ratio for Time to Discharge While Alive (95% CI)		Hazard Ratio for Time to In-Hospital Death (95% CI)		Hazard Ratio for Time to Death or Discharge (95% CI)		Excess LoS (95% CI)
	Time-Adjusted	Fully-Adjusted	Time-Adjusted	Fully-Adjusted	Time-Adjusted	Fully-Adjusted	
All	0.90 (0.79, 1.04)	0.89 (0.75, 1.05)	5.10 (2.20, 11.76)†	3.63 (1.26, 10.43)†	0.95 (0.82, 1.09)	0.93 (0.78, 1.10)	1.57 (0.20, 2.95)†
Gram-positive	0.88 (0.76, 1.02)	0.84 (0.70, 1.00)	3.42 (1.29, 9.08)†	2.34 (0.67, 8.13)	0.90 (0.79, 1.05)	0.86 (0.72, 1.03)	2.35 (−0.22, 4.92)
Gram-negative	0.76 (0.52, 1.10)	0.83 (0.56, 1.22)	12.55 (3.75, 42.38)†	4.35 (0.73, 25.70)	0.90 (0.61, 1.31)	0.99 (0.66, 1.49)	3.81 (−3.71, 11.32)
CoNS	0.78 (0.62, 0.99)†	0.73 (0.54, 1.00)	0.36 (0.09, 1.39)	0.14 (0.02, 0.94)	0.77 (0.61, 0.98)†	0.72 (0.53, 0.98)†	6.94 (−2.71, 16.58)
Escherichia coli	0.88 (0.60, 1.29)	0.64 (0.37, 1.11)	7.85 (0.92, 66.47)	6.42 (0.36, 114.12)	0.95 (0.65, 1.38)	0.70 (0.42, 1.18)	−3.09 (−5.4, −0.77)†
Enterobacter spp.	0.82 (0.49, 1.38)	0.76 (0.36, 1.60)	16.12 (2.48, 105.60)†	5.99 (0.38, 95.60)	1.01 (0.55, 1.84)	0.94 (0.42, 2.13)	9.45 (−6.04, 24.93)
Enterococcus spp.	0.79 (0.51, 1.22)	0.84 (0.54, 1.32)	7.39 (2.14, 25.33)†	3.22 (0.68, 15.30)	0.88 (0.58, 1.33)	0.95 (0.63, 1.44)	5.62 (−3.31, 14.54)
Klebsiella spp.	0.66 (0.34, 1.31)	0.83 (0.42, 1.62)	8.85 (2.03, 38.33)†	2.59 (0.33, 19.96)	0.84 (0.44, 1.59)	1.07 (0.56, 2.05)	11.31 (−16.32, 38.95)
Nonpyogenic streptococci	1.27 (0.90, 1.81)	1.25 (0.80, 1.92)	8.67 (1.16, 65.6)†	6.42 (0.51, 81.37)	1.36 (0.95, 1.96)	1.32 (0.85, 2.07)	−3.64 (−5.34, −1.94)†
Staphylococcus aureus	0.72 (0.55, 0.92)†	0.7 (0.52, 0.92)†	5.37 (0.96, 30.02)	6.3 (0.98, 40.56)	0.76 (0.59, 0.98)†	0.74 (0.55, 0.99)†	0.89 (−3.68, 5.46)
Other (Gram-positive)	1.19 (0.67, 2.08)	1.07 (0.64, 1.81)	N/A	N/A	1.17 (0.67, 2.06)	1.06 (0.63, 1.78)	−2.61 (−3.90, −1.31)†
Other (Gram-negative)	0.52 (0.33, 0.82)†	0.41 (0.26, 0.65)†	2.51 (0.32, 19.64)	0.99 (0.07, 13.80)	0.55 (0.35, 0.86)†	0.43 (0.28, 0.68)†	14.86 (−6.40, 36.11)

Abbreviations: CI, confidence intervals; CoNS, coagulase-negative staphylococci; LoS, length of stay.

*Note that an individual patient may belong to multiple groups.

†Statistically significant value.

patients equivalent to the Charlson index for adult patients [28–29] does not currently exist, we determined relevant clinical groupings associated with high morbidity informed by the published literature [30, 31]. The clinical groups were cancer, premature birth, congenital disorder, surgical procedure, presence of an indwelling catheter, and the pediatric morbidity score developed by Tai et al [30]. A patient was assigned to 1 or more of these groups using their ICD-10 and OPCS-4 codes. Table 1 presents the characteristics of HA-BSI and non-HA-BSI patients, whereas Appendix Table 4 presents a table of the characteristics of non-HA-BSI patients with a stay ≥2 days.

Procedure

We compared outcomes between patients with HA-BSI on a given day with patients without HA-BSI on that day. These were time-dependent nested samples of patients in contrast to a single, time-independent, case-control patient stratification. In the all-cause HA-BSI analysis, the earliest infection time of any HA-BSI for a given patient-stay was retained and subsequent HA-BSI data discarded. Likewise, when analyzing a particular pathogen, the earliest relevant infection time was retained and others discarded. This selection was irrespective of the presence of prior or subsequent infection with a different organism.

The comparison was carried out for patients with HA-BSI due to the following groups of microorganisms: coagulase-negative staphylococci (CoNS), *Enterococcus* spp, *Staphylococcus aureus*, *Escherichia coli*, pyogenic streptococci, *Enterobacter* spp., and *Klebsiella* spp., all Gram-negative HA-BSI and all Gram-positive HA-BSI. For example, when HA-BSI was defined as *S aureus* HA-BSI, we compared the clinical outcome of patients with *S aureus* HA-BSI with patients who have no record of an HA-BSI.

Patient outcomes of interest were in-hospital death and excess LoS. These were analyzed for the dataset endpoints of (1) hospital discharge while alive, or (2) in-hospital death, and the time in days at which these occurred relative to a patient's admission date. This distinction was necessary because patients with HA-BSI who died while in hospital may have had a reduced LoS, whereas a prolonged LoS might be seen for patients who were discharged alive. We performed separate statistical tests to determine the presence of an effect on LoS due to HA-BSI for patients with either in-hospital death or discharged while alive as the outcome. Furthermore, an overall excess LoS estimate was calculated by combining these 2 into a single outcome.

Statistical Analysis

Multistate Model. We constructed a multistate model with 3 states; 0 = "Admission, no BSI"; 1 = "HA-BSI"; and

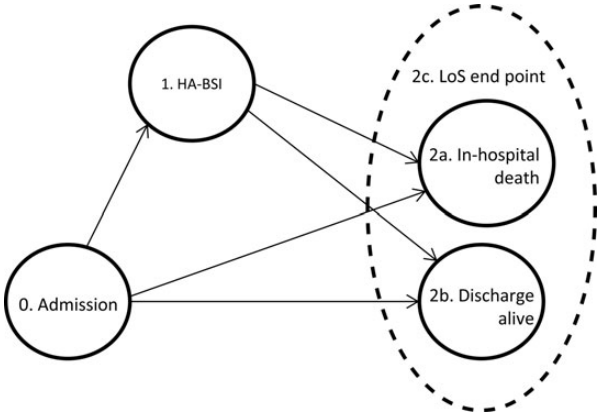

Figure 1. Schematic diagram of multistate model with 4 states. Each patient enters the model at state 0 (hospital admission no hospital-acquired bloodstream infection detected) and may move between states with defined daily probabilities (each arrow representing a possible transition). At each time-point, each patient occupies 1 of the states.

2 = "Discharge". State 2 consisted of 2 competing endpoints 2a = "Discharged alive" and 2b = "In-hospital death". Hospital-acquired bloodstream infection was considered an intermediate, discrete state between admission and discharge while alive or in-hospital death states (Figure 1). If a patient entered the HA-BSI state, they were considered infected until they were discharged from hospital alive or died. Uninfected patients were those that remained in the state Admission, no HA-BSI until discharged alive or death. Thus, each model had 3 states, in which time-varying hazards determined between-state transitions, with probabilities estimated using the Aalen-Johansen estimator [32].

The competing endpoints (discharged alive and death in-hospital) were combined as a single state to give a measure of the overall excess LoS related to HA-BSI, which accounted for the time dependency of the infection [33]. The mean difference in LoS between HA-BSI and non-HA-BSI patients was calculated for each day from admission to the end-state. Overall excess LoS was then calculated as the average excess LoS across all days, weighted relative to the frequency of transitions to HA-BSI, discharge alive or in-hospital death on each day [34]. This method produced a time-adjusted estimate of excess LoS due to HA-BSI in days, either in aggregate or for infections caused by particular pathogens. This estimate could not be further adjusted for confounders. Standard errors were estimated using bootstrap sampling and confidence intervals (CIs) were calculated assuming approximate normality.

Cox Regression. The risk of in-hospital death or discharge while alive was modeled with a time-dependent regression model, assuming Cox proportional hazards, with HA-BSI treated as a time-dependent risk factor. Because the number of deaths in the dataset was very small relative to the number of patients discharged while alive, a cause-specific hazard approach was used in which the times of occurrence of competing risks were represented by censored times. The model structure adjusted for time to HA-BSI, by using the times between HA-BSI and discharge rather than simply the times between admission and discharge. Other confounders were explicitly adjusted for by a multivariate analysis with the assumption that patient characteristics at admission remained unaltered throughout a patient's stay.

Comparisons of hazard ratios (HRs) for the time-adjusted and "fully-adjusted" (ie, with all identified confounders) models were carried out. This allowed for the assessment of the possible influence of identified comorbidities on excess LoS estimates.

All computation was carried out using the statistical software R version 3.0.0. The R-packages msm and etm (available at http://cran.r-project.org) were used to estimate excess LoS and standard errors [32, 35].

RESULTS

The dataset contained data on 333 605 patients, of which 214 (0.06%) were identified as developing HA-BSI between January and March 2009 (Table 1). Among 62 676 patients admitted for at least 2 days, 0.34% acquired an HA-BSI [24] (see Appendix Table 6 for details). Table 1 presents summary statistics for admitted patients. The average age of HA-BSI cases was lower than for non-HA-BSI patients (HA-BSI median 1 year, non-HA-BSI median 6 years). A higher proportion of HA-BSI patients were members of at least 1 comorbidity group (HA-BSI 77%, non-HA-BSI 29%).

The overall crude median LoS for all patients was less than 1 day (interquartile range [IQR], .5–1.0), representing patients with same-day admission and discharge, and 30 days (IQR, 10.0–66.0) for patients with an HA-BSI (Table 1). For patients with an HA-BSI, the median time to infection was 11.5 days (IQR, 3.0–35.8). The distributions of time to infection, discharge, and death for patients with HA-BSI are shown in Figure 2. The median time to infection ranged from 7 days (IQR, 2.0–23.0) for patients with an *S aureus* HA-BSI to 41 days (IQR, 13.2–65) for patients with a *Klebsiella* spp. HA-BSI. In Figure 2, the relatively large, light gray regions indicate that a significant proportion of an HA-BSI patient's hospital stay is spent uninfected so a crude analysis, using a static sample stratification in either infected or noninfected cases, would clearly result in an overestimate of the excess LoS attributable to HA-BSI.

The crude in-hospital mortality was 13 of 214 (61 per 1000) for patients with HA-BSI and 157 of 333 391

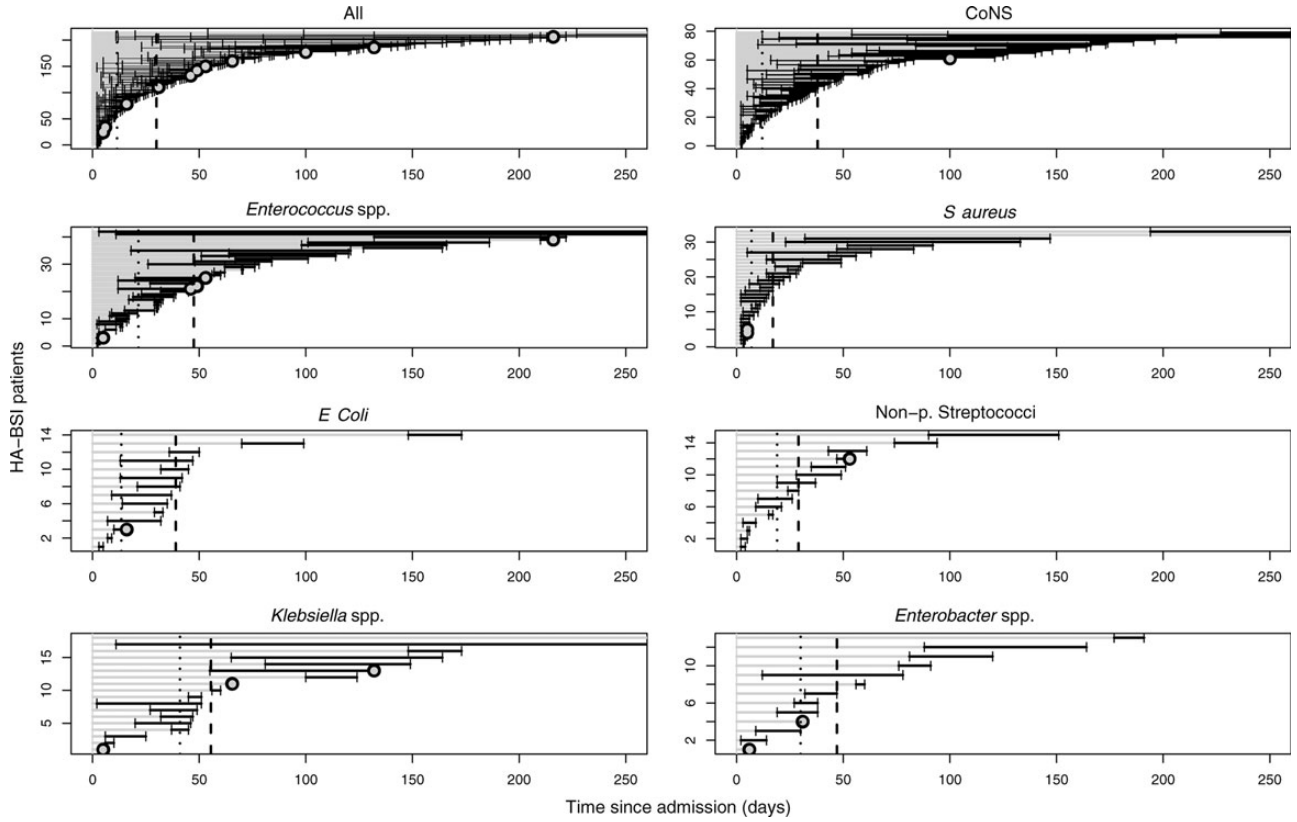

Figure 2. Schematic of patient events for those with all-cause hospital-acquired bloodstream infection (HA-BSI) and other pathogen types under investigation coagulase-negative staphylococci (CoNS), *Enterococcus* spp., *Staphylococcus aureus* (*S aureus*), *Escherichia coli* (*E coli*), nonpyogenic (Non-p.) streptococci, *Klebsiella* spp., and *Enterobacter* spp. Each line represents a patient; a light gray line indicates the pre-HA-BSI period, and the black line indicates the length of stay (LoS) after BSI. At the right limit of each line, a black vertical tick mark represents a discharge from hospital while alive and a light gray circle represents an in-hospital death. The vertical lines represent the median discharge time for noninfected patients with LoS $\geq$ 2 days (solid), the median in-hospital infection time (dotted), and the crude median discharge time for HA-BSI patients not accounting for time to infection (dashed).

(0.5 per 1000) for non-HA-BSI patients, giving a risk ratio of 129.0 (95% CI, 110.6–150.5).

Risk of Death, Discharge, and Excess LoS Associated With HA-BSI

Clinical outcomes for patients with HA-BSI are presented in Table 2. Hazard ratios for time to discharge (alive or due to death) were calculated adjusting only for time to HA-BSI ("time-adjusted") and adjusting for additional confounders (age, sex, cancer, premature birth, congenital disorder, surgical, in-dwelling catheter, and Tai morbidity score) (fully-adjusted). Cases in which an HR and upper limit of the associated 95% CI were < 1, HA-BSI was associated with an increased LoS. In contrast, cases in which an HR and lower limit of the associated 95% CI were > 1, HA-BSI was associated with a decreased LoS.

For the all-cause HA-BSI, on each day, infected patients had a lower chance of being discharged (alive or due to death), with an HR of 0.95 (95% CI, .82–1.09) after adjusting for time to onset of infection only (Table 2). In the fully-adjusted model, the HR was 0.93 (95% CI, .78–1.1). In contrast to considering the relative chances on each day, the chance of leaving hospital (dead or whilst alive) for HA-BSI or non-HA-BSI patients can be compared over all days. There was a 52% chance of a HA-BSI patient leaving hospital before a non-HA-BSI patient. Compare this against the 50% chance if there is no difference between the patients, corresponding to a HR of 1.0. [36].

Equivalent results were found, in terms of the effects due to HA-BSI, when the analysis was repeated for the bacterial species or groups considered, with the exception of *Klebsiella* spp. nonpyogenic streptococci and Other Gram-positive bacteria (none of which were statistically significant). However, only *S aureus*, CoNS, and Other Gram-negative bacteria were statistically significant when fully adjusted.

For the all-cause HA-BSI, on each day, infected patients had a higher chance of in-hospital death than noninfected patients with an HR of 3.63 (95% CI, 1.26–10.43) when fully-adjusted. This conclusion held true for all bacteria with the exception of CoNS (HR, 0.14; 95% CI, 0.02–0.94), which is not meaningful because of only a single associated death. However, the specific rates varied between

organisms, with statistically significant increased rate of deaths for all-cause HA-BSI only, likely due to the relatively small number of in-hospital deaths.

In the time-adjusted model, the excess LoS associated with all-cause HA-BSI was 1.57 days (95% CI, 0.20, 2.95) (Table 2). However, this time period varied by pathogen. Infection with any Gram-positive bacteria was associated with an excess LoS of 2.35 days (95% CI, –.22 to 4.92); for CoNS specifically, the excess LoS was 6.94 days (95% CI, –2.71 to 16.58). Variation was also seen within Gram-negative infections, ranging from –3.09 days (95% CI, –5.40 to 0.77) for *E coli* to 11.31 days (95% CI, –16.32 to 38.95) for *Klebsiella* spp. The negative estimates were due, in particular, to a small sample of patients who were infected soon after admission and were discharged soon after (see Figure 2).

DISCUSSION

In this study, we found that the instantaneous rate for in-hospital death from all-cause HA-BSI was nearly 4 times that of non-HA-BSI patients (HR, 3.63). The instantaneous rate of discharge from hospital (dead or alive) was approximately one tenth lower in patients with HA-BSI (HR, 0.93). In turn, the excess LoS associated with all-cause HA-BSI was estimated to be over a day and a half. Although many of the excess LoS estimates for patients infected with particular pathogens were not statistically significant due to small sample sizes, the results are consistent with an association between increased LoS and in-hospital mortality due to HA-BSI.

To our knowledge, there are few studies specifically estimating excess LoS due to HA-BSI in children. Where studies do exist, excess LoS estimates were greater than those here [13, 37]. Such studies may have overestimated the impact of HA-BSI on LoS because they failed to adopt appropriate modeling approaches to address important time-dependent biases [38].

Lambert et al [1] adopted a multistate modeling approach, but they restricted their analysis to an adult ICU population. This study estimated an excess LoS due to HA-BSI of 1.1 days for antibiotic-susceptible organisms and 2.5 days for resistant organisms. In our findings, the excess LoS due to HA-BSI (with antibiotic susceptible and resistant organisms) was 1.57 days, which suggests a similar impact of HA-BSI in the pediatric population. Lambert et al [1] found that the excess daily risk of in-hospital death due to HA-BSI was 3.1 (95% CI, 2.7–3.6) for drug-susceptible organisms and 3.6 (95% CI, 3.0–4.4) for drug-resistant organisms, which is comparable to our findings. Although the trend in the species-specific analyzes in our study suggests a greater impact of HA-BSI on mortality, for some species, the small number of deaths meant that the results were not statistically significant.

This study used a larger cohort than previous studies [1, 13, 37], allowing a meaningful comparison between organisms and LoS estimates that are relevant across the pediatric population. However, in contrast to prospective studies, the dataset used here comprised routinely generated data collected on a voluntary basis through a national surveillance scheme and a heterogeneous patient case-mix [39]. Although Cox regression adjusts for clinical comorbidities, the multistate model only provides time-adjusted results. Stratifying the dataset to analyze the impact of comorbidities resulted in a significant loss of power due to diminished sample sizes (presented in Appendix Figures 2 and 3). Thus, although excess LoS estimates are more easily interpretable for clinicians, for health economists and policymakers HRs can be considered to be a more robust statistic.

The rare but important issue of multiple infections was beyond the scope of this research and too rare in our dataset to analyze robustly, but it would be interesting for future research if a larger dataset were available.

Coagulase-negative staphylococci were the most frequently isolated causative organisms in our dataset and have been highlighted as an important hospital pathogen [40]. Although the reporting guidelines indicate that only clinically significant infections should be reported, we cannot be certain that none of the CoNS were contaminants.

CONCLUSIONS

Our results provide robust estimates of the clinical consequences of HA-BSI in children. This provides an evidence base for researchers and policymakers to evaluate the health and economic impact of interventions to prevent HA-BSI in children and reinforces the clinical need for improved infection prevention and control.

Acknowledgments

We thank Mehdi Minaji for dataset linkage.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Lambert ML, Suetens C, Savey A, et al. Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. Lancet Infect Dis **2011**; 11:30–8.

2. Elward AM, Hollenbeak CS, Warren DK, Fraser VJ. Attributable cost of nosocomial primary bloodstream infection in pediatric intensive care unit patients. Pediatrics **2005**; 115:868–72.
3. Armenian SH, Singh J, Arrieta AC. Risk factors for mortality resulting from bloodstream infections in a pediatric intensive care unit. Pediatr Infect Dis J **2005**; 24:309–14.
4. Gray J, Gossain S, Morris K. Three-year survey of bacteremia and fungemia in a pediatric intensive care unit. Pediatr Infect Dis J **2001**; 20:416–21.
5. Health Protection Agency. English National Point Prevalence Survey on Healthcare-associated Infections and Antimicrobial Use 2011: Preliminary data. Health Protection Agency, London, **2012**; 1–139.
6. Edwards JR, Peterson KD, Mu Y, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008. Am J Infect Control **2009**; 37:783–805.
7. Laupland KB, Gregson DB, Vanderkooi OG, et al. The changing burden of pediatric bloodstream infections in Calgary, Canada, 2000-2006. Pediatr Infect Dis J **2009**; 28:114–7.
8. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011–2012. **2012**. Available at: http://www.ecdc.europa.eu/en/publications/publications/healthcare-associated-infections-antimicrobial-use-pps.pdf. Accessed 14 July 2014.
9. Wisplinghoff H, Seifert H, Tallent SM, et al. Nosocomial bloodstream infections in pediatric patients in United States hospitals: epidemiology, clinical features and susceptibilities. Pediatr Infect Dis J **2003**; 22:686–91.
10. Pereira CA, Marra AR, Camargo LF, et al. Nosocomial bloodstream infections in Brazilian pediatric patients: microbiology, epidemiology, and clinical features. PLoS One. **2013**; 8:e68144.
11. Aiken AM, Mturi N, Njuguna P, et al. Risk and causes of paediatric hospital-acquired bacteraemia in Kilifi District Hospital, Kenya: a prospective cohort study. Lancet **2011**; 378: 2021–7.
12. Ben Jaballah N, Bouziri A, Mnif K, et al. Epidemiology of hospital-acquired bloodstream infections in a Tunisian pediatric intensive care unit: a 2-year prospective study. Am J Infect Control **2007**; 35:613–8.
13. Biwersi C, Hepping N, Bode U, et al. Bloodstream infections in a German paediatric oncology unit: prolongation of inpatient treatment and additional costs. Int J Hyg Environ Health **2009**; 212: 541–6.
14. Slonim AD, Kurtines HC, Sprague BM, Singh N. The costs associated with nosocomial bloodstream infections in the pediatric intensive care unit. Pediatr Crit Care Med **2001**; 2:170–4.
15. Beyersmann J, Wolkewitz M, Schumacher M. The impact of time-dependent bias in proportional hazards modelling. Stat Med **2008**; 27:6439–54.
16. Wolkewitz M, Vonberg RP, Grundmann H, et al. Risk factors for the development of nosocomial pneumonia and mortality on intensive care units: application of competing risks models. Crit Care **2008**; 12:R44.
17. Wolkewitz M, Frank U, Philips G, Schumacher M, Davey PG. Mortality associated with in-hospital bacteraemia caused by Staphylococcus aureus: a multistate analysis with follow-up beyond hospital discharge. J Antimicrob Chemother **2011**; 66:381–6.
18. Barnett AG, Beyersmann J, Allignol A, et al. The time-dependent bias and its effect on extra length of stay due to nosocomial infection. Value Health **2011**; 14:381–6.
19. Milstone AM, Elward A, Song X, et al. Daily chlorhexidine bathing to reduce bacteraemia in critically ill children: a multicentre, cluster-randomised, crossover trial. Lancet **2013**; 381:1099–106.
20. Coia JE, Duckworth GJ, Edwards DI, et al. Guidelines for the control and prevention of methicillin-resistant *Staphylococcus aureus* (MRSA) in healthcare facilities. J Hosp Infect **2006**; 63 (Suppl 1):S1–44.
21. Fuller C, Robotham J, Savage J, et al. The National One Week Prevalence Audit of MRSA Screening, Department of Health, January 2013. Available at: http://www.ucl.ac.uk/medicine/documents/doh-now-report-2013.
22. Clemens TL. Ready steady go. J Bone Miner Res **2008**; 23:973.
23. Health and Social Care Information Centre. Hospital Episode Statistics : Admitted Patient Care 2011–12, Summary Report. Hospital Episode Statistics **2012**; 1–30.
24. Blackburn RM, Henderson KL, Minaji M, et al. Exploring the epidemiology of hospital-acquired bloodstream infections in children in England (January 2009–March 2010) by linkage of National Hospital Admissions and Microbiological Databases. J Ped Infect Dis **2012**; 1:1–9.
25. Harron K, Goldstein H, Wade A, et al. Linkage, evaluation and analysis of national electronic healthcare data: application to providing enhanced blood-stream infection surveillance in paediatric intensive care. PLoS One **2013**; 8:e85278.
26. World Health Organization. International Statistical Classification of Diseases and Related Health Problems-10th Revision. World Health Organization. **2010**.
27. NHS Connecting for Health. OPCS Classification of Interventions and Procedures Version 4.6 (April 2011) – 2 Volume Pack. TSO (The Stationary Office). **2011**.
28. Nuttall M, van der Meulen J, Emberton M. Charlson scores based on ICD-10 administrative data were valid in assessing comorbidity in patients undergoing urological cancer surgery. J Clin Epidemiol **2006**; 59:265–73.
29. Sundararajan V, Henderson T, Perry C, et al. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol **2004**; 57:1288–94.
30. Tai D, Dick P, To T, Wright JG. Development of pediatric comorbidity prediction model. Arch Pediatr Adolesc Med **2006**; 160: 293–9.
31. Patrick SW, Schumacher RE, Davis MM. Method of mortality risk adjustment in the NICU: a 20-year review. Pediatrics **2013**; 131 (Suppl 1):S68–74.
32. Allignol A, Schumacher M, Beyersmann J. Empirical transition matrix of multi-state models: the etm package. J Stat Softw **2011**; 38:1–15.
33. De Angelis G, Allignol A, Murthy A, et al. Multistate modelling to estimate the excess length of stay associated with methicillin-resistant *Staphylococcus aureus* colonisation and infection in surgical patients. J Hosp Infect **2011**; 78:86–91.
34. Schulgen G, Schumacher M. Estimation of prolongation of hospital stay attributable to nosocomial infections: new approaches based on multistate models. Lifetime Data Anal **1996**; 2:219–40.
35. Jackson CH. Multi-state models for panel data: The msm package for R. J Stat Softw **2011**; 38:1–29.
36. Spiegelhalter DJ. Can we say whether a drug would have enabled someone to live longer? Sadly not. Understanding Uncertainty. Available at: http://understandinguncertainty.org/node/759. Accessed 10 August 2013.
37. Aiken AM, Mturi N, Njuguna P, et al. Risk and causes of paediatric hospital-acquired bacteraemia in Kilifi District Hospital, Kenya: a prospective cohort study. Lancet **2011**; 378:2021–7.
38. Beyersmann J, Gastmeier P, Wolkewitz M, Schumacher M. An easy mathematical proof showed that time-dependent bias inevitably leads to biased effect estimation. J Clin Epidemiol **2008**; 61:1216–21.
39. Henderson KL, Johnson AP, Muller-Pebody B, et al. The changing aetiology of paediatric bacteraemia in England and Wales, 1998–2007. J Med Microbiol **2010**; 59 (Pt 2):213–9.
40. Garcia P, Benitez R, Lam M, et al. Coagulase-negative staphylococci: clinical, microbiological and molecular features to predict true bacteraemia. J Med Microbiol **2004**; 53:67–72.