ORIGINAL ARTICLE

Burden of Bloodstream Infection Caused by Extended-Spectrum β-Lactamase–Producing Enterobacteriaceae Determined Using Multistate Modeling at a Swiss University Hospital and a Nationwide Predictive Model

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OBJECTIVE. To obtain an unbiased estimate of the excess hospital length of stay (LOS) and cost attributable to extended-spectrum β-lactamase (ESBL) positivity in bloodstream infections (BSIs) due to Enterobacteriaceae.

DESIGN. Retrospective cohort study.

SETTING. A 2,200-bed academic medical center in Geneva, Switzerland.

PATIENTS. Patients admitted during 2009.

METHODS. We used multistate modeling and Cox proportional hazards models to determine the excess LOS and adjusted end-of-LOS hazard ratio (HR) for ESBL-positive and ESBL-negative BSI. We estimated economic burden as the product of excess LOS and average bed-day cost. Patient-level accounting data provided a complementary analysis of economic burden. A predictive model was fitted to national surveillance data.

RESULTS. Thirty ESBL-positive and 96 ESBL-negative BSI cases were included. The excess LOS attributable to ESBL-positive and ESBL-negative BSI was 9.4 (95% confidence interval [CI], 0.4–18.4) and 2.6 (95% CI, 0.7–5.9) days, respectively. ESBL positivity was therefore associated with 6.8 excess days and CHF 9,473 per BSI. The adjusted end-of-LOS HRs for ESBL-positive and ESBL-negative BSI were 0.62 (95% CI, 0.43–0.89) and 0.90 (95% CI, 0.74–1.10), respectively. After reimbursement, the average financial loss per acute care episode in ESBL-positive BSI, ESBL-negative BSI, and control cohorts was CHF 48,674, 48,131, and 13,532, respectively. Our predictive model estimated that the nationwide cost of third-generation cephalosporin resistance would increase from CHF 2,084,000 in 2010 to CHF 3,526,000 in 2015.

CONCLUSIONS. This is the first hospital-wide analysis of excess LOS attributable to ESBL positivity determined using multistate modeling to avoid time-dependent bias. These results may inform health-economic evaluations of interventions targeting ESBL control.

Infect Control Hosp Epidemiol 2013;34(2):133-143

The past 2 decades have witnessed a rapid global increase in extended-spectrum β-lactamase (ESBL) production by Enterobacteriaceae causing both healthcare- and community-associated infections.[1,2] ESBLs threaten the utility of commonly used empiric antibiotic therapy and have been associated with both delayed initiation of appropriate antibiotic therapy and excess mortality.[3-6] It is important to gain an accurate appreciation of the economic burden of ESBL-producing bacteria to justify the prioritization of infection control and antibiotic stewardship interventions required to confront this problem.[7]

The excess length of stay (LOS) associated with an infection is the key driver of its cost from the hospital perspective.[7-9] Estimation of this figure, however, is hampered by several methodological challenges.[4,10] An accurate estimation must account for the competing risks of death and increased LOS[5,11] and for time-dependent bias.[12] Failing to explicitly address the timing and onset of infection will always result in an overestimation of the attributable hospital LOS and therefore of cost.[10,13,14] Multistate models account for competing outcomes and time-dependent bias[11,15] and have not been used to evaluate the burden of infection by ESBL-positive organisms outside the intensive care context.[16]

The primary aim of this study was to quantify the economic

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Received July 2, 2012; accepted September 24, 2012; electronically published December 18, 2012.

 0899-823X/2013/3402-0006$15.00. DOI: 10.1086/669086

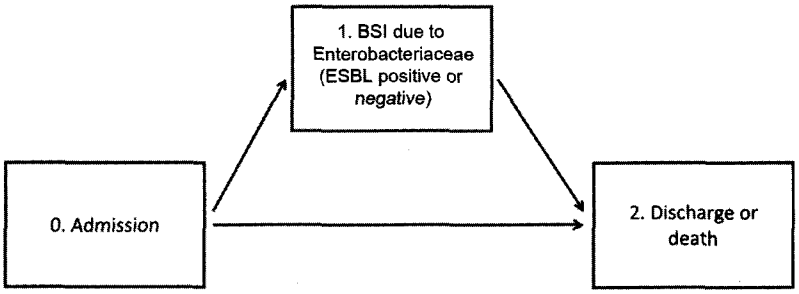

FIGURE 1. Representation of the multistate model adopted for this analysis. Every patient enters the model at state 0 (hospital admission, no bloodstream infection [BSI] detected). Death or final discharge from acute care is modeled by transition into state 2, which can occur with or without transition through state 1 (onset of BSI). ESBL, extended-spectrum β-lactamase.

burden attributable to ESBL production among Enterobacteriaceae by using multistate modeling to estimate excess LOS associated with bloodstream infection (BSI) due to ESBL-positive and ESBL-negative isolates and then to extrapolate the excess cost due to ESBL positivity from the hospital perspective by using the average bed-day cost. The secondary aim was to develop a predictive model for the burden of third-generation cephalosporin resistance among Enterobacteriaceae causing BSIs throughout Switzerland.

METHODS

Setting and Study Design

The University of Geneva Hospitals (HUG), a 2,200-bed primary and tertiary center, is the only major public hospital in the Swiss canton of Geneva and provides both acute and nonacute care to a population of 450,000 people. We studied 3 parallel cohorts of patients admitted between January 1 and December 31, 2009: (1) those with BSI due to ESBL-positive Enterobacteriaceae, (2) those with BSI due to ESBL-negative Enterobacteriaceae, and (3) those without BSI due to Enterobacteriaceae. This was a retrospective, observational cohort study incorporating data from a prospective hospital-based BSI surveillance system.[17,18] Approval was granted by the Internal Medicine Ethics Committee (HUG 11-022R).

Definitions

An inpatient episode was defined as the period of continuous hospitalization from admission from outside HUG (or birth for newborns) until the last day of acute care (terminated by discharge, transfer, or death) and could include days in acute and nonacute care. Inpatient episodes consisting entirely of nonacute or psychiatric care were excluded. A BSI was defined as culture of any Enterobacteriaceae from at least 1 blood culture bottle and was designated primary or secondary according to Centers for Disease Control and Prevention definitions.[19] The date of infection was defined as the first day the BSI criteria were met. ESBL-positive BSI and ESBL-negative BSI were defined, respectively, as BSI due to ESBL-positive and ESBL-negative Enterobacteriaceae. Inadequate initial antimicrobial therapy was defined as the failure to prescribe an antimicrobial agent that was appropriate for the treatment of BSI and to which the infecting organism was susceptible within 24 hours of the time of the BSI. Healthcare-associated and community-acquired infections were distinguished as defined elsewhere.[20]

Patient Populations and Data Collection

The first cohort consisted of all inpatients with an ESBL-positive BSI during the study period. For each ESBL-positive patient, 3 patients with ESBL-negative BSI from the same ward were selected for inclusion in the second cohort. Multiple episodes of BSI for the same patient were included only if subsequent infections were not considered a relapse or the persistence of a previous episode. Patients were excluded if treatment with curative intent was not undertaken. For all patients with BSI, data on the following potential confounding covariates were collected: age, sex, hospital location at date of infection, healthcare-associated or community-acquired infection, infection site, bacterial species, adequacy of initial antibiotic treatment, intensive care unit (ICU) admission, and comorbid conditions on hospital admission. All ESBL-positive BSIs and all healthcare-associated ESBL-negative BSIs were prospectively included in a hospital-based BSI surveillance system. For patients with non-healthcare-associated ESBL-negative BSI, data were obtained retrospectively from electronic patient records.

The third cohort consisted of all patients with inpatient episodes commencing in 2009 during which a BSI due to Enterobacteriaceae did not occur. Data on age, sex, dates of discharge from acute ward or death, ICU admission, and surgical procedures were extracted retrospectively from electronic hospital records. This method was also used to validate surveillance data for the 2 BSI cohorts.

Three predefined outcomes were examined: in-hospital mortality, excess LOS, and hospitalization costs measured from the hospital perspective. All included patients were observed until discharge or in-hospital death.

TABLE 1. Baseline Characteristics of Patients Experiencing Bloodstream Infections (BSIs) due to Enterobacteriaceae

Characteristic	Infection			Source		
	Patients with			Patients with		
	ESBL BSI (n = 30)	Non-ESBL BSI (n = 96)	P	HCA BSI (n = 58)	CA BSI (n = 68)	P
Demographics						
Male sex	21 (70.0)	60 (62.5)	.454	36 (62.1)	45 (66.2)	.632
Age, median ± SD, years	62 ± 16	67 ± 19	.364	67 ± 13	63 ± 21	.008
Comorbidities						
Cardiovasular disease	3 (10.0)	17 (17.7)	.400	11 (19.0)	9 (13.2)	.380
COPD	1 (3.3)	4 (4.2)	.999	3 (5.2)	2 (2.9)	.661
Peripheral vascular disease	3 (10.0)	3 (3.1)	.146	4 (6.9)	2 (2.9)	.413
Cerebrovascular disease	8 (26.7)	11 (11.5)	.075	9 (15.5)	10 (14.7)	.899
Renal insufficiency	2 (6.7)	10 (10.4)	.730	6 (10.3)	6 (8.8)	.772
Liver disease	3 (10.0)	14 (14.6)	.761	4 (6.9)	13 (19.1)	.045
Diabetes without end-organ damage	10 (33.3)	9 (9.4)	.003	11 (19.0)	8 (11.8)	.260
Diabetes with end-organ damage	3 (10.0)	4 (4.2)	.356	4 (6.9)	3 (4.4)	.702
HIV	0 (0)	1 (1.0)	.999	0 (0)	1 (1.5)	.999
Cancer	8 (26.7)	33 (34.4)	.432	25 (43.1)	16 (23.5)	.019
Immunosuppression	7 (23.3)	15 (15.6)	.332	14 (24.1)	8 (11.8)	.068
Peptic ulcer disease	2 (6.7)	1 (1.0)	.141	0 (0.0)	3 (4.4)	.249
Connective tissue disease	0 (0)	2 (2.1)	.999	2 (3.5)	0 (0)	.210
No commorbidity	8 (26.7)	28 (29.2)	.999	12 (20.7)	24 (35.3)	.070
Epidemiological category			.358			
Healthcare associated	16 (53.3)	42 (43.8)		...	...	
Community acquired	14 (46.7)	54 (56.2)		...	...	
Ward at BSI onset			.938			<.001
Medicine	7 (23.3)	17 (17.1)		18 (31.0)	6 (8.8)	
Surgery	7 (23.3)	20 (20.8)		21 (36.2)	6 (8.8)	
ICU	1 (3.3)	5 (5.2)		4 (6.9)	2 (2.9)	
Pediatrics	1 (3.3)	2 (2.1)		0 (0)	3 (4.4)	
Rehabilitation/geriatrics	3 (10.0)	7 (7.3)		10 (17.2)	0 (0.0)	
Gynecology/obstetrics	1 (3.3)	4 (4.2)		1 (1.7)	4 (5.9)	
Emergency	10 (33.3)	41 (42.7)		4 (6.9)	47 (69.1)	
Origin of infection						
Primary BSI	10 (33.3)	23 (24.0)	.308	24 (41.4)	9 (13.2)	<.001
Secondary BSI	20 (66.7)	73 (76.0)	.308	34 (58.6)	59 (86.8)	<.001
Bone and joint	0 (0)	1 (1.0)	.999	0 (0)	1 (1.5)	.999
Cardiovascular system	0 (0)	1 (1.0)	.999	0 (0)	1 (1.5)	.999
Gastrointestinal system	2 (6.7)	13 (13.5)	.519	5 (8.6)	10 (14.7)	.293
Pneumonia or LRTI	0 (0)	3 (3.1)	.999	2 (3.5)	1 (1.5)	.594
Reproductive tract	1 (3.3)	1 (1.0)	.421	0 (0)	2 (2.9)	.499
Skin and soft tissue	0 (0)	2 (2.1)	.999	1 (1.7)	1 (1.5)	.999
Surgical site infection	1 (3.3)	3 (3.1)	.999	4 (6.9)	0 (0)	.042
Urinary tract	17 (56.7)	49 (51.0)	.590	22 (37.9)	44 (64.7)	.003
ICU admission	8 (26.7)	21 (21.9)	.586	18 (31.0)	11 (16.2)	.048
Pathogen						
Escherichia coli	25 (83.3)	59 (61.5)	.027	35 (60.3)	49 (72.1)	.164
Klebsiella species	2 (6.7)	18 (18.8)	.155	12 (20.7)	8 (11.8)	.172
Proteus species	0 (0)	4 (4.2)	.572	2 (3.5)	2 (2.9)	.999
Enterobacter species	1 (3.3)	8 (8.3)	.685	5 (8.6)	4 (5.9)	.731
Other Enterobacteriaceae	2 (6.7)	7 (7.3)	.999	4 (6.9)	5 (7.4)	.999
ESBL production	...	...		16 (27.6)	14 (20.6)	.358
Inadequate initial antimicrobial therapy	14 (46.7)	24 (25.0)	.024	18 (31.0)	20 (29.4)	.843

NOTE. Data are no. (%), unless otherwise indicated. CA, community acquired; COPD, chronic obstructive pulmonary disease; ESBL, extended-spectrum β-lactamase; HCA, healthcare associated; HIV, human immunodeficiency virus; ICU, intensive care unit; LOS, length of stay; LRTI, lower respiratory tract infection; SD, standard deviation.

TABLE 2. Excess Length of Stay (LOS) and Hazard Ratios (HRs) for End of LOS Associated with Bloodstream Infection (BSI) due to Extended-Spectrum β-Lactamase (ESBL)–Positive and ESBL-Negative Enterobacteriaceae

		HR (95% CI)	
	Excess LOS (95% CI), days	Univariate	Adjusted[a]
ESBL-positive BSI (compared with no BSI)	9.4 (0.4–18.4)[b]	0.52 (0.36–0.76)	0.62 (0.43–0.89)
ESBL-negative BSI (compared with no BSI)	2.6 (−0.7 to 5.9)[c]	0.75 (0.62–0.92)	0.90 (0.74–1.10)

NOTE. CI, confidence interval.

[a] Adjusted for age, sex, intensive care unit admission, and surgery.

[b] In total, 30 ESBL-positive BSIs versus 96 ESBL-negative BSIs (censored at time of infection) and 42,476 patients without BSI due to Enterobacteriaceae.

[c] In total, 96 ESBL-negative BSIs versus 30 ESBL-positive BSIs (censored at time of infection) and 42,476 patients without BSI due to Enterobacteriaceae.

Microbiological Testing

During the study period, blood culture specimens were inoculated into BACTEC Aerobic Plus/F and Lytic Anaerobic/F vials and then incubated and monitored with the BACTEC 9240 system (BD Diagnostic Systems). Microorganisms were identified using standard laboratory procedures. Antimicrobial susceptibilities and ESBL status were determined by the disk diffusion method, in accordance with Clinical and Laboratory Standards Institute guidelines.[21] ESBL confirmation was performed using a combination of 4 disks: cefotaxime versus cefotaxime/clavulanate and ceftazidime versus ceftazidime/clavulanate. Isolates were declared ESBL positive whenever the inhibition zone around the disk containing clavulanate was at least 5 mm larger than that of the disk containing the same cephalosporin but without clavulanate.

Excess LOS Estimation

A multistate model approach was used to estimate the excess LOS due to ESBL-positive BSI and ESBL-negative BSI, with excess LOS attributable to ESBL positivity then computed as the difference between the outputs of these 2 analyses. The occurrence of BSI was the time-dependent exposure, while final discharge from acute care (or in-hospital death) was the study end point (Figure 1). Patients with ESBL-negative BSI were administratively censored from the date of their infection when assessing LOS due to ESBL-positive BSI.[15] Likewise, patients with ESBL-positive BSI were censored at infection onset when assessing LOS due to ESBL-negative BSI. Nonparametric estimation of transition probabilities was performed using the Aalen-Johansen estimator to provide the matrix of transition probabilities, as described elsewhere.[11,15,22] The mean difference in LOS (in days) was computed for each day as the difference between the predicted LOS given the intermediate state ("onset of BSI") being reached or not reached on that day. The overall change in LOS was then computed as an average of these quantities, weighted by the time to BSI among infected patients. Standard errors and confidence intervals (CIs) were derived by 500 bootstrap resampling runs.[15]

To compare the instantaneous risk of the 2 BSI cohorts reaching the end point (discharge from acute care or death), the end-of-LOS hazards over the course of time were calculated. End-of-LOS hazard was defined as the number of discharged patients (dead or alive) on a given day divided by the number of patients still hospitalized at the beginning of that day. The Nelson-Aalen estimator was used to describe the cumulative transition hazards over the course of time.[23] To assess the independent effect of ESBL-positive and ESBL-negative BSI on LOS, they were evaluated as time-dependent covariates using Cox proportional hazards models to estimate the end-of-LOS hazard ratio (HR). Variables for adjustment included age, sex, ICU admission, and surgery during the current hospitalization.

LOS analysis was performed using R, version 2.10.1 (R Development Core Team), an open-source language for statistical computing and graphics. All other analyses were performed using Stata, version 11 (StataCorp).

Cost Estimation

Total cost accounting charges were divided by the number of bed-days in acute and nonacute care to obtain an average cost of a hospital bed-day in 2009, excluding psychiatry. The excess cost due to ESBL positivity from the hospital perspective was estimated as the product of this average bed-day cost and the excess LOS attributed to ESBL positivity during the study period.[7] Costs were computed in 2009 Swiss francs (CHF).

A concurrent patient-level cost analysis was performed. In 2009, HUG used a microcosting system that identified and aggregated the variable- and fixed-cost components of patient activities, hospital services, and products according to the date of service.[24,25] Each acute care episode was assigned a diagnosis-related group (DRG) according to the Swiss adaptation of the All Patient DRG system based on *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* diagnostic codes,[26] *Classification Suisse des Interventions Chirurgicales (CHOP)* intervention codes,[27] and administrative data. Each DRG had an assigned "cost weighting," a factor by which the base rate (approximately CHF 12,000 for HUG in 2009) was multiplied to calculate the

TABLE 3. Nested Patient-Level Analysis of Costing and Coding Data for the Acute Care Stay of Patients with Extended-Spectrum β-Lactamase (ESBL)–Positive Bloodstream Infection (BSI), Patients with ESBL-Negative BSI, and Patients Matched with the ESBL-Positive Cohort on the Basis of Age, Sex, and Diagnosis-Related Group

	ESBL-positive BSI (n = 26)	ESBL-negative BSI (n = 83)	P[a]	Matched cohort (n = 49)	P[a]
Episode-level data					
Age, median (IQR), years	62 (47–70)	68 (49–78)	.069	64 (48–69)	
Male sex, no. (%)	19 (73.1)	53 (63.9)	.480	36 (73.5)	
LOS, median (IQR), days	18.5 (14–38)	14 (7–27)	.048	10 (5–20)	.006
Patient cost, median (IQR), CHF	38,175 (19,231–75,759)	31,322 (15,311–61,152)	.402	24,576 (14,309–47,264)	.136
Case mix index[b]	2.47	2.20	.879	2.68	.743
Aggregate cohort data					
Total cost, CHF	2,035,455	6,187,937		2,240,540	
Case mix[c]	64.16	182.754		131.453	
Cost incurred per cost weight point, CHF	31,725	33,859		17,044	

NOTE. IQR, interquartile range; LOS, length of stay.

[a] Testing the null hypothesis that there is no difference compared with the ESBL-positive BSI cohort.

[b] Average cost weight points for episodes in cohort.

[c] Sum of cost weight points for all episodes in cohort.

amount potentially billable for that acute care episode.[28] For each patient in acute care at the time of BSI detection, we extracted the individual, itemized costs and the cost weighting of their acute care stay. We also selected an alternate comparator group by matching each ESBL-positive patient with 2 patients from the non-BSI cohort on the basis of sex, age, and identical DRG. The case mix (sum of cost weights) and case mix index (average cost weight) for each cohort was calculated. Two measures were used to compare the economic burden of each cohort from the hospital perspective: (1) the difference between costs incurred and the potentially billable amount and (2) the costs incurred per cost weight unit.

Predictive Model

On the basis of data from 2004–2010 published by Anresis.ch, the Swiss center for surveillance of antibiotic resistance, we used linear regression to fit a predictive model for the burden of BSI due to third-generation cephalosporin-resistant *Escherichia coli* and *Klebsiella pneumoniae* throughout Switzerland.[29] After extrapolating available data nationally, we used this model to estimate the number of BSIs due to these isolates from 2011 to 2015. This figure was then multiplied by our estimate of the excess LOS attributable to ESBL positivity to derive the national burden of resistance from the hospital perspective. The average cost of a bed-day in Switzerland was estimated from Swiss Federal Office of Statistics reports for 2010 by dividing the total charges for hospital care by the total number of bed-days, after excluding psychiatric care.[30] This model incorporates 3 main assumptions: (1) that the excess LOS attributable to ESBL positivity among Enterobacteriaceae in our institution was equivalent to that of third-generation cephalosporin resistance among *E. coli* and *K. pneumoniae* throughout Switzerland, (2) that the number of BSIs due to these 2 bacteria each year will remain constant, and (3) that diagnostic testing and empiric antibiotic treatment remain constant.

RESULTS

Thirty-nine patients with ESBL-positive BSI and 113 patients with ESBL-negative BSI were initially included. After excluding episodes without acute care admission and 1 patient treated without curative intent, 30 ESBL-positive and 96 ESBL-negative inpatient episodes remained. These involved 124 patients, with 2 patients included twice. The median age was 68 (interquartile range [IQR], 55–78) years, 81 (64%) were male, and 68 (54%) of the infections were community acquired. The proportion of infections that were healthcare associated was similar for ESBL-negative and ESBL-positive infections (P = .36). Notably, 47% of patients with ESBL-positive BSI received inappropriate initial antibiotic treatment, compared with 25% of those with ESBL-negative BSI (P = .024). In each group, 3 patients never received appropriate antibiotic treatment. For those who did, the median delay from BSI until appropriate antibiotic therapy was 15 (IQR, 3–43) and 11 (IQR, 4–23) hours for ESBL-positive and ESBL-negative BSI, respectively (P = .186). Characteristics of patients with BSI are shown in Table 1. The non-BSI cohort consisted of 42,476 patients; their median age was 49 (IQR, 27–71) years, and 19,455 (45%) were male.

In-Hospital Mortality

Six patients (20%) with ESBL-positive BSI and 10 patients (10%) with ESBL-negative BSI died (P = .17). When adjusted for baseline characteristics (sex, age, healthcare or community attribution, and department at time of BSI were re-

TABLE 4. Studies Examining the Excess Length of Stay (LOS) and Cost Associated with Extended-Spectrum β-Lactamase (ESBL) Production (or Third-Generation Cephalosporin Resistance [3GCR]) in Bloodstream Infections (BSIs)

	Methods				Effects attributed to resistance	
Study	Design, setting, study period, country	Infection, bacteria, resistance	No. resistant; no. susceptible	Time dependence	Excess LOS[a]	Excess cost
Lautenbach et al[38]	Matched case-control study[b] 725-bed academic tertiary center Jun 1997–May 1998 USA	All infections *E. coli, K. pneumoniae* ESBL	33; 66	Not addressed	Median LOS 1.23 times greater for cases than for controls after adjustment (95% CI, 0.81–1.87); $P = .34$	1.71 times higher for cases after adjustment (95% CI, 1.01–2.88); $P = .04$
Blot et al[39]	Retrospective cohort Single-center ICU Jan 1992–Dec 2000 Belgium	Nosocomial BSI Gram-negative bacteria Ceftazidime[c]	120; 208	Not addressed	Median LOS after BSI: 11 (IQR, 5–20) vs 10 (IQR, 3–19); $P = .321$	NA
Schwaber et al[3]	Retrospective cohort 1,200-bed academic tertiary center Jan 2000–Dec 2003 Israel	BSI *E. coli, Klebsiella* spp., *Proteus* spp. ESBL	99; 99	Partially accounted for[d]	Multiplicative effect: 1.56; $P < .001$	Multiplicative effect: 1.57; $P < .003$
Melzer and Petersen[5]	Prospective cohort Single center Jun 2003–Nov 2005 UK	BSI *E. coli* ESBL	46; 308	Not addressed	Median LOS: 9 vs 12; $P = .111$	NA
Mauldin et al[13]	Retrospective cohort Single center Jan 2000–Jun 2008 USA	HAI Gram-negative bacteria Nonsusceptible to quinolones, piperacillin, carbapenems, or extended-spectrum cephalosporins	193; 469	Not addressed	Additional 23.8% after adjustment (IQR, 11.0%–36.6%); $P = .0003$.	Additional 29.3% after adjustment (IQR, 16.2–42.4); $P < .0001$.

Tumbarello et al[35]	Retrospective cohort 1,600-bed academic hospital Jan 2006–Dec 2006 Italy	BSI *E. coli* ESBL	37; 97	Not addressed	Mean ± SD: 20 ± 17 vs 13 ± 9; $P = .02$	€5,026 attributable to ESBL
Yang et al[40]	Retrospective cohort 2,000-bed medical center Jan 2006–Jun 2008 Taiwan	Community-onset bacteremic UTIs *E. coli, K. pneumoniae* ESBL	12; 46	Not addressed	Mean ± SD: 16.3 ± 9.3 vs 7.9 ± 5.2; $P = .010$	USD 615.1 ± 423.5 vs 252.8 ± 269.2; $P = .014$[e]
de Kraker et al[36]	Prospective parallel matched cohort 13 tertiary care centers Jul 2007–Jun 2008 13 European countries	BSI *E. coli* 3GCR	111; 1,110	Partially accounted for[f]	Adjusted extra LOS: 5.0 days (95% CI, 0.4–10.2)	NA
Lambert et al[16]	Prospective cohort study 537 ICUs Jan 2005–Dec 2008 10 European countries	BSI *E. coli* 3GCR	42; 218	Accounted for	Adjusted end-of-LOS HR: 1.09 (95% CI, 0.76–1.58)	NA
This study	Retrospective cohort study 2,200-bed university hospital Jan 2009–Dec 2009 Switzerland	BSI Enterobacteriaceae ESBL	30; 96	Accounted for	Adjusted end-of-LOS HR: 0.62 (95% CI, 0.43–0.89) Extra LOS: 6.8 days	CHF 9,473

NOTE. CI, confidence interval; HAI, healthcare-associated infection; ICU, intensive care unit; IQR, interquartile range; NA, not assessed; SD, standard deviation; UTI, urinary tract infection.

[a] Univariate comparison of LOS in days after BSI onset (resistant vs susceptible), unless otherwise stated. When multivariable analysis was performed, only the adjusted result is presented.

[b] Matched by infecting organism, anatomic site of infection, and date of isolation.

[c] Resistance among *Pseudomonas* species was defined by resistance to one of piperacillin, ciprofloxacin, ceftazidime, or imipenem.

[d] Outcomes adjusted for LOS prior to bacteremia.

[e] Cost of antibiotic therapy only.

[f] Patients with BSI were matched for LOS before BSI with controls without BSI.

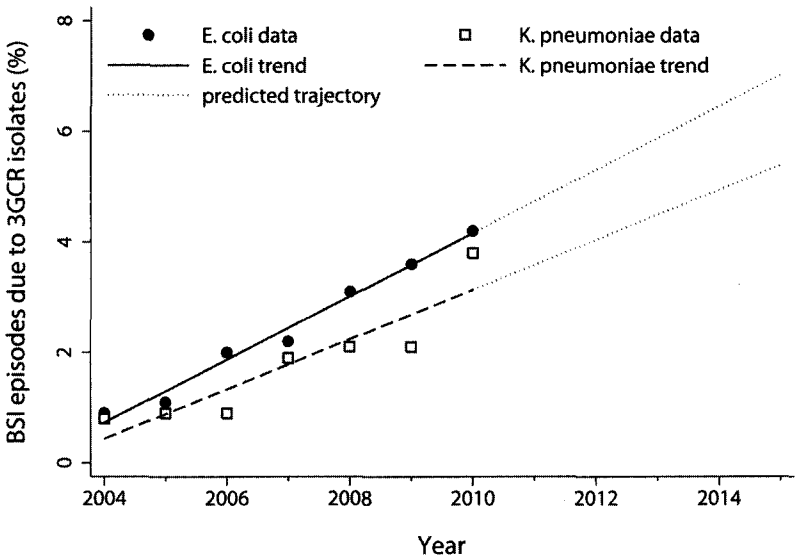

FIGURE 2. Trends in the estimated number of bloodstream infections (BSIs) due to third-generation cephalosporin-resistant (3GCR) *Escherichia coli* and *Klebsiella pneumoniae* in Switzerland. Extrapolated from Anresis.ch data for 2004–2010, with future trajectories for 2011–2015 based on linear regression analysis.

tained), the independent effect of ESBL production on inpatient mortality was not significant (odds ratio, 2.8 [95% CI, 0.7–11.5]; $P = .15$).

LOS

The median total LOS for patients with ESBL-positive BSI and ESBL-negative BSI was 22.5 (IQR, 14–61) and 14.5 (IQR, 7–32.5) days, respectively ($P = .04$). The results of multistate modeling for excess LOS are presented in Table 2. Compared with negative controls, BSI due to Enterobacteriaceae was associated with an excess LOS whether due to ESBL-positive or ESBL-negative isolates. BSI due to ESBL-negative bacteria did not significantly decrease the hazard of discharge after adjustment for confounding (HR, 0.90 [95% CI, 0.74–1.10]). However, ESBL positivity was associated with 6.8 days of excess LOS compared with ESBL-negative BSI and a significantly reduced hazard of discharge (HR, 0.62 [95% CI, 0.43–0.89]).

Cost

The estimated cost for provision of an occupied bed-day in 2009 was CHF 1,391 on average for all acute care and non–acute care beds. This means that ESBL positivity leads to an excess cost of CHF 9,473 per BSI due to Enterobacteriaceae. For the 30 patients with ESBL-positive BSI in 2009, this amounts to a total burden of CHF 284,190 from the hospital perspective.

For patient-level cost analysis, 26 and 83 patients were included from the ESBL-positive and ESBL-negative cohorts, respectively. In addition, 51 patients from the non-BSI cohort were matched with the ESBL-positive patients on the basis of age, sex, and DRG. The costs, case mix index, and cost per cost weight for these cohorts are presented in Table 3. The average loss, calculated as the difference between costs incurred in the provision of care and the amount potentially billable from health insurance companies per acute care episode for patients in the ESBL-positive BSI, ESBL-negative BSI, and control cohorts, was CHF 48,674, 48,131, and 13,532, respectively. The cost incurred per cost weight point for the ESBL-positive BSI, ESBL-negative BSI, and DRG-matched groups were CHF 31,725, 33,859, and 17,044, respectively, demonstrating that both BSI cohorts represent resource-intensive subgroups from a hospital accounting perspective. As a benchmark, the average cost incurred per cost weight point for public patients admitted to HUG in 2009 was CHF 12,708.[31]

Predictive Model

Both visual inspection and the coefficients of determination (R^2) supported application of a linear regression model: 98% and 83% of the variation in the number of BSIs due to third-generation cephalosporin-resistant *E. coli* and *K. pneumoniae*, respectively, could be explained by the year alone during the period 2004–2010 (Figure 2). For *E. coli* and *K. pneumoniae*, the regression coefficients were 0.57 and 0.45, respectively. This model estimated that the proportion of third-generation cephalosporin-resistant isolates causing BSI would increase from 4.0% in 2010 to 6.7% in 2015. During the same period, the number of bed-days attributable to third-generation cephalosporin resistance nationally would increase from 1,300 in 2010 to 2,200 in 2015, equivalent to an accounting cost increase from CHF 2,084,000 to 3,526,000.

DISCUSSION

In patients experiencing BSI due to Enterobacteriaceae, we found that ESBL production is associated with a significant excess LOS and, hence, economic burden from the hospital perspective. To our knowledge, this is the first study to employ multistate modeling in the estimation of excess LOS attributable to ESBL production outside the ICU setting. The strength of this approach is that it accounts for time dependency and competing outcomes. In contrast, neither adjustment for time to infection as baseline covariate or matching for time to infection can adequately account for time-dependent bias while still including all eligible patients.[7,12]

There are several possible explanations why antimicrobial resistance could be associated with increased LOS.[32] The first is inadequate controlling for confounding covariates intrinsic to either the patient, such as severity of illness and comorbid conditions, or the infecting agent, such as the presence of a hypervirulent ESBL-positive clone.[33] The second is treatment related, such as delay of appropriate antimicrobial therapy,[6,34] increased treatment toxicity (such as renal impairment secondary to aminoglycosides), need for surgery, or lack of an active oral agent to facilitate early discharge with outpatient completion of antibiotic therapy. In our study, patients with ESBL-positive BSI were less likely to receive appropriate antibiotic treatment within 24 hours (Table 1).

The key features and results of recent studies reporting the excess LOS and cost associated with ESBL-production or third-generation cephalosporin resistance among Enterobacteriaceae are listed in Table 4. In a single-center retrospective study, Tumbarello et al[35] found that ESBL production in *E. coli* causing BSI was associated with an excess LOS of 7 days and a cost of €5,026 (CHF 7,634 in 2009). De Kraker et al[36] performed a multicenter prospective matched cohort study involving 13 European hospitals and estimated an excess LOS of 5 days attributable to third-generation cephalosporin resistance in BSIs caused by *E. coli*. While both are otherwise robust studies, we would contend that neither the direct comparison of post-BSI-onset LOS between ESBL and non-ESBL BSI used by the former study or the matching and adjustment used by the latter adequately account for time-dependent bias. Regardless, the estimates of excess LOS attributable to ESBL-producing bacteria in those studies are close to ours (Table 4). Interestingly, data from the latter study were used to inform a recent estimate of the cost of BSI due to ESBL-positive *E. coli* in Europe as €18.1 million.[37]

This study has several limitations. First, the single-center setting limits external validity. Generalizability would be sensitive, for example, to local variation in empiric antibiotic therapy for sepsis and frequency of inadequate initial antimicrobial therapy. Second, we did not take into account infections other than BSI. This increased the specificity of true infection among included patients but underestimated the total burden of infections caused by ESBL-positive Enterobacteriaceae. Third, we estimated the economic burden of ESBL production as the product of the excess LOS attributed to ESBL positivity and the average accounting cost of a bed-day, including fixed and variable costs.[7] This standard technique does not account for the fact that fixed costs cannot be regained by the hospital in the short term and may therefore provide an overestimate of the economic burden of resistance.[7,8] In contrast, episodes of readmission were not examined and costs from patient and community perspectives were not considered, thereby underestimating the total burden.

In summary, this study found that ESBL positivity conferred a significant health and economic burden among patients with BSI caused by Enterobacteriaceae. Future research should test the generalizability of this result and advance the techniques used to estimate the opportunity cost of antimicrobial resistance. Regardless, this study provides useful information for those seeking financial support for interventions to reduce the dissemination of ESBL-positive Enterobacteriaceae.

ACKNOWLEDGMENTS

We gratefully acknowledge the contribution to this study by Marie-Noelle Chraïti and members of the Infection Control Program, University of Geneva Hospitals. This work was performed during the PhD of A.S. at the Department of Medicine, University of Melbourne.

Financial support. This investigator-initiated project was supported by Pfizer. The sponsor did not interfere with study design, analysis, and publication of the results. A.S., C.F., G.D.A., J.S., and S.H. received funding from the European Commission (FP7-HEALTH-2009-SINGLE STAGE-SATURN contract 241796, MOSAR network contract LSHP-CT-2007-037941, and R-Gnosis contract 282512).

Potential conflicts of interest. S.H. reports that he has received consultant and speaker honoraria from bioMérieux, Da Volterra, and Destiny Pharma. J.S. reports that he is chief medical advisor for bioMérieux. All other authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

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Presented in part: 22nd European Congress of Clinical Microbiology and Infectious Diseases; London, United Kingdom; March 31–April 3, 2012 (Abstract P-1863).

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