Attributable Length of Stay, Mortality Risk, and Costs of Bacterial Health Care–Associated Infections in Australia: A Retrospective Case-cohort Study

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Background. Unbiased estimates of the health and economic impacts of health care–associated infections (HAIs) are scarce and focus largely on patients with bloodstream infections (BSIs). We sought to estimate the hospital length of stay (LOS), mortality rate, and costs of HAIs and the differential effects on patients with an antimicrobial-resistant infection.

Methods. We conducted a multisite, retrospective case-cohort of all acute-care hospital admissions with a positive culture of 1 of the 5 organisms of interest (Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, or Enterococcus faecium) from 1 January 2012 through 30 December 2016. Data linkage was used to generate a data set of statewide hospital admissions and pathology data. Patients with bloodstream, urinary, or respiratory tract infections were included in the analysis and matched to a sample of uninfected patients. We used multistate survival models to generate LOS, and logistic regression to derive mortality estimates.

Results. We matched 20,390 cases to 75,635 uninfected control patients. The overall incidence of infections due to the 5 studied organisms was 116.9 cases per 100,000 patient days, with E. coli urinary tract infections (UTIs) contributing the largest proportion (51 cases per 100,000 patient days). The impact of a UTI on LOS was moderate across the 5 studied pathogens. Resistance significantly increased LOS for patients with third-generation cephalosporin-resistant K. pneumoniae BSIs (extra 4.6 days) and methicillin-resistant S. aureus BSIs (extra 2.9 days). Consequently, the health-care costs of these infections were higher, compared to corresponding drug-sensitive strains.

Conclusions. The health burden remains highest for BSIs; however, UTIs and respiratory tract infections contributed most to the health-care system expenditure.

Keywords. antimicrobial resistance; length of stay; hospital-associated infections; mortality; cost.

Health care–associated infections (HAIs) are often preventable [1], but continue to pose a significant burden on patients’ health and the economy [2]. On any given day, 1 in 18 patients in a European hospital [3] and 1 in 10 Australian inpatients [4] has a HAI. Impacts of HAI include prolonged hospital stays, readmissions, disability, and increased risk of treatment failure [1, 5–7]. Antimicrobial resistance (AMR) is a recognized global public health emergency that poses a fundamental threat to human health, development, and security [8].

While the burden of HAIs is well described, many studies either do not appropriately adjust for time-dependent bias [9] or focus on bloodstream infections (BSIs) only [6, 10, 11], omitting other highly prevalent HAIs, such as urinary tract infections (UTIs) [12]. Few have focused on a comprehensive assessment of the AMR burden [10, 11, 13]. Hence, the current evidence base for the impact of HAIs is likely to be overestimated, because of time-dependent bias and its effect on hospital length of stay (LOS) estimates [14, 15], or be narrowed in scope. This creates a gap in our ability to assess the health benefits and cost effectiveness that (new) infection control strategies may offer in reducing HAIs and AMR.

The objective of this study was to provide robust estimates of the health burden of 5 bacterial HAIs and the additional impact of AMR, using multistate modeling. We estimated the impacts of Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, and Enterococcus faecium from multiple sites (BSI, UTI, and respiratory tract infections [RTI]) on patient in-hospital stay and mortality. In addition, the economic cost impact of these infections to the Australian
health-care system was estimated, including the additional AMR cost impact.

METHODS

Setting and Study Design
This was a multi-site, retrospective case-cohort study of all acute-care hospital admissions in Queensland, Australia, from 1 January 2012 through 30 December 2016. Patients with a positive culture of 1 of the 5 organisms of interest, including *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, or *E. faecium*, from multiple sites (BSI, UTI, and RTI) were matched with a sample of uninfected patients. Data linkage was used to generate a data set that matched Queensland Hospital Admitted Patients Data Collection [16] with Queensland Department of Health Pathology [17]. Linkage was done by matching the hospital and hospital-level patient identifiers and by ensuring that sample collection dates fell within recorded admission and discharge dates. Up to 3 uninfected patients were matched based on hospital, age group, sex, and separation date.

Definitions
Health care–associated (HA)-BSI was defined as a positive blood culture present >48 hours after admission. HA-UTI was defined as a patient having a urine culture >48 hours after admission with no more than 2 species of organisms identified and a count of >10^5 colony-forming units of bacteria per milliliter in a urine specimen. HA-RTI was defined as a positive *P. aeruginosa* smear or culture and a count of >10^4 colony-forming units per milliliter from lung tissue or pleural fluid present >48 hours after admission. Only the first positive culture per patient was analyzed. These definitions are consistent with published and accepted criteria for defining HA-BSI [18], HA-UTI [12, 18, 19], and HA-RTI [20].

Antibiotic susceptibility results were provided as European Committee on Antimicrobial Susceptibility Testing interpreted values (resistant, intermediate, and susceptible). All resistant and intermediate results were regarded as “resistant” for the purpose of phenotype analysis. Third-generation cephalosporin (3GC) resistance was inferred from ceftazidime and ceftriaxone resistance, and methicillin resistance in *S. aureus* was inferred from resistance to flucloxacillin.

There were 10 exposure groups:

1. 3GC-resistant *K. pneumoniae*
2. 3GC-sensitive *K. pneumoniae*
3. 3GC-resistant *E. coli*
4. 3GC-sensitive *E. coli*
5. Cefazidime-resistant *P. aeruginosa*
6. Cefazidime-sensitive *P. aeruginosa*
7. Methicillin-resistant *S. aureus* (MRSA)
8. Methicillin-sensitive *S. aureus* (MSSA)
9. Vancomycin-resistant *E. faecium* (VRE)
10. Vancomycin-sensitive *E. faecium* (VSE)

Statistical Analysis
A multistate survival model was used to estimate the difference in LOS between those with an infection and those without [21] using the etm-package in R [22] and adapting for the case-cohort design [23] of our data. BSIs, UTIs, and RTI for the 5 organisms were the time-varying exposure of interest, and separate analyses were performed for each organism and infection site, referred to subsequently as “infection groupings.” The multistate model has 4 states: uninfected, infected, discharged alive, and died in hospital (Figure 1).

Patients entered the model through the “uninfected” state. Transition between states was determined by transition hazards (α), accounting for both time-dependent and competing risk natures of the events (Supplementary Material). Long hospitalizations were censored at 90 days to remove any long-stay effects [10]. We estimated the excess LOS attributable to resistance by simulating the estimated extra LOS for resistant and susceptible infections from the respective multistate models as separate gamma distributions, and computing the difference. We used 10 000 simulations from each fitted distribution to estimate the excess LOS attributable to resistance.

From logistic regressions, we estimated the effect of HAI on in-hospital death as the death odds ratio (OR), which was appropriate for data sets with small amounts of administrative censoring [24]. The death OR quantifies the association between HAI and hospital mortality risk. Estimates were obtained from 4 regression models, which differed by the level of grouping structure (ie, all *S. aureus* versus MRSA versus *S. aureus* BSI versus MRSA BSI). Death OR estimates of resistant and susceptible

![Figure 1.](https://academic.oup.com/cid/doi/figure/kiaa1228/5895480)
pairs were compared using the estimated marginal means (Supplementary Material, logistical regression). Results are presented as ORs and 95% confidence intervals (CIs). We included potential confounding variables of age, sex, admission year, time from admission to infection, hospital peer-group and remoteness [25], and comorbidities as additional covariates in the logistic regression model. Comorbidities were identified using a validated algorithm based on International Classification of Disease, 10th Revision, Australian Modification (ICD-10-AM) coding [26] and were converted to the Charlson comorbidity index [27].

Cost of Infection

The cost of infection was calculated as a product of the prolongation of LOS associated with infection and a monetary value of a bed day. First, we used an estimate per bed day ($250.40 Australian dollars) [28] reported from a contingent valuation study that elicited a hospital Chief Executive Officer’s “willingness to pay” to release a bed day from some infection-reducing intervention. This is akin to the opportunity costs (and referred to hereafter as “opportunity costs”) of a bed day, and provides a valuation more likely to be used for decision-making under scarce resources. Second, we used the “accounting costs” per bed days, obtained by dividing the total annual hospital budget by the number of bed days supplied during the same period ($2721.8 Australian dollars, estimated by adjusting 2016–17 estimates to 2020 prices) [29]. Cost of resistance was calculated as the additional costs of a resistant infection over the corresponding susceptible infection pairing. Annual costs for the infection groups were calculated by multiplying the cost per infection and the incidence density for each group. Results are presented as the average annual costs over the 5-year period of the data set, with 95% CIs. All costs were converted to 2020 US dollars (USD) using the XE Currency Converter, Live Rates [30].

Ethics

Ethical approval, including consent waiver, was granted by the Queensland University of Technology Human Research Ethics Committee (HREC1700000232).

RESULTS

Overall, data for 96 025 patients from 134 Queensland hospitals were analyzed. Studied hospitals included facilities located in major cities [31] (n = 18), regional hospitals (n = 74), and rural health-care services (n = 42), with the majority of patient data collected from hospitals in major cities (62.3%). Evaluable data were comprised of 20 390 infected cases with 1 of the 5 organisms of interest, and 75 635 uninfected controls. Patients with UTIs were older than those with BSIs, and females were overrepresented, except for in the S. aureus UTI group, where the proportion of males was high (72%). The average age of the control group was 68 years old (standard deviation [SD], 23), whilst patients classified as cases had a similar overall age of 68 years old (SD, 20), but a smaller proportion of females (59% in cases versus 66% in controls; see Table 1).

The overall incidence of the 5 studied HAIs was 116.8 per 100 000 patient days (Table 1). More HAIs were due to Gram-negative bacteria than to Gram-positive bacteria. UTIs secondary to E. coli were most common, with an incidence of 51.5 cases per 100 000 patient days, whilst BSIs were most frequently due to S. aureus (5.7 cases per 100 000 patient days). The incidence of P. aeruginosa RTI was 11.6 cases per 100 000 patient days. Drug-sensitive strains were more prevalent than drug-resistant strains (Table 1).

All-cause in-hospital mortality was highest in patients with a BSI, compared those with a UTI or RTI. Enterococcus faecium BSIs were associated with the greatest number of deaths, especially in those who were infected with a resistant strain (25.6%, n = 43). The all-cause mortality proportions for patients with E. coli and P. aeruginosa BSIs were 16.7% and 15.8% of patients, respectively.

Infection-attributable Excess Hospital Length of Stay

HA-BSIs resulted in a greater excess LOS in hospital than UTIs or RTIs (Figure 2). Staphylococcus aureus BSIs resulted in an additional 5.3 days (95% CI, 5.2–5.5) in hospital, followed by P. aeruginosa and E. faecium at 3.5 days (95% CI, 3.3–3.7) and 3.4 days (95% CI, 3.2–3.6), respectively (Figure 2A). Patients with a MRSA BSI stayed in hospital for an additional 7.9 days (95% CI, 7.8–8.1), which was 2.9 days (95% CI, 2.7–3.1) longer than MSSA BSI patients. Similarly, patients with a 3GC-resistant K. pneumoniae BSI stayed in hospital for an additional 7.3 days (95% CI, 7.1–7.4), whilst those with drug-sensitive K. pneumoniae had an excess LOS of 2.7 days, resulting in an additional 4.6 days (95% CI, 4.3–4.8) attributable to resistance. There was no additional impact on hospital LOS for patients who had a E. coli infection, either drug-sensitive or drug-resistant (Figure 2). Patients with a vancomycin-sensitive strain of E. faecium BSI stayed in hospital an additional 2.5 days (95% CI, 2.1–2.9) compared with patients with VRE. The same effect was not seen in patients with a urinary E. faecium infection (Figure 2B).

Across all 5 infections, the impact of a UTI on hospital LOS was moderate (Figure 2B). The additional impact on hospital LOS for patients with a drug-resistant infection was more notable in patients with a 3GC-resistant K. pneumoniae UTI, who stayed in hospital an additional 2 days (95% CI, 1.7–2.2) compared to patients infected with a drug-sensitive strain.

Patients with a P. aeruginosa RTI stayed in hospital for an additional 2.8 days (95% CI, 2.7–3.0) compared to uninfected controls (Figure 2C). Ceftazidime-resistant infections resulted in a LOS of 1.5 days, whilst patients with a ceftazidime-sensitive infection stayed in hospital for an estimated 3 days (95% CI, 2.9–3.2).
Infection-attributable Mortality

All BSIs were associated with increased odds of death (Figure 3A). Enterococcus faecium BSI patients were associated with a death OR of 4.5 (95% CI, 2.7–7.3) compared with uninfected patients. This was followed by K. pneumoniae BSI (OR, 3.1; 95% CI, 2.3–4.3) and E. coli BSI (OR, 2.9; 95% CI, 2.3–3.7) patients, who had an additional 3-fold increased risk of death compared to control patients. The death OR was significant only for E. faecium UTI patients (OR, 1.4; 95% CI, 1.1–1.8; Figure 3B) and P. aeruginosa RTI patients (OR, 2.4; 95% CI, 2.0–2.8; Figure 3C). Differences in death ORs between resistant and susceptible infections were not statistically significant, but were most notable in P. aeruginosa (BSI OR, 1.6 [95% CI, 1.6 to 4.2]; UTI OR, 1.6 [95% CI, 1.1 to 4.2]; and RTI OR, 1.6 [95% CI, 0.6 to 2.1]).

Infection-attributable Cost

Staphylococcus aureus BSIs were associated with the highest cost. Opportunity costs were estimated as USD $909.1 (SD, $97.6) per infection, and hospital accounting costs were USD $9877.8 (SD, $999.8; Table 2).

Hospitalization of patients with a resistant infection was associated with higher costs than patients with a drug-sensitive strain across the 5 infections, except for patients with VRE bacteremia and ceftazidime-resistant P. aeruginosa RTI (Table 2). Opportunity costs attributable to hospital LOS were lower in VRE BSI patients (USD $318) compared with VSE BSI patients (USD $760) and in patients with a P. aeruginosa RTI (Table 2). For all remaining infections, resistance-attributable costs were higher or comparable to those in patients with drug-sensitive infections. We estimate an additional USD $753.5 (SD, 147.9)
per 3GC-resistant *K. pneumoniae* BSI; USD $503.2 (SD, 172.9) per MRSA BSI; and USD $342.6 (SD, 123.1) per ceftazidime-resistant *P. aeruginosa* BSI. UTIs were associated with increased bed-day costs for all organisms, but the increases were notably smaller than the corresponding BSI costs. The accounting costs for each of the organisms are presented in Table 2.

Averaged over the 5-year study period, the annual costs estimated using accounting estimates of bed-day costs and incidences were highest for *P. aeruginosa* RTI (USD $2,056,492; 95% CI, $1,658,763–2,489,062; Figure 4C) and *S. aureus* BSI (USD $1,973,594; 95% CI, $1,600,910–2,375,414; Figure 4A), compared to uninfected patients. This was followed by *E. coli* UTI, with an estimated annual opportunity cost of USD $1,699,756 per year (95% CI, $1,191,226–2,323,857; Figure 4B) that was over 3-fold higher than the corresponding BSI cost (USD $510,507; 95% CI, $408,993–622,654; Figure 4A). In contrast, *S. aureus* BSI costs (USD $1,973,594) were 7 times the annual *S. aureus* UTI costs (USD $277,655; Figure 4B). For the 5 organisms, the annual HA-UTI cost was USD $3.7 million and the annual HA-BSI cost was USD $3.4 million. The annual cost of HA-RTI, which includes only *P. aeruginosa*, was USD $2.1 million (Figure 4C). The combined accounting costs of patients with BSI, UTI, and RTI drug-sensitive infections were higher than the corresponding drug-resistant costs, and amounted to USD $7.8 million per year (USD $7,762,293) and USD $1.6 million per year (USD $1,614,496), respectively.

**DISCUSSION**

We provide a comprehensive estimate of the impact of antibiotic-sensitive and -resistant bacterial HAIs in Australia. Our study expands upon the literature by more fully adjusting estimates of morbidity (excess LOS) and mortality in patients with drug-resistant UTIs and *P. aeruginosa* RTI. We used data linkage to identify 20,469 patients infected with 1 of 5 clinically significant organisms; of these, 1,693 patients’ infections were due to antibiotic-resistant bacteria. The combined (BSI, UTI, and RTI) antibiotic-resistant infections accounted for 717 extra days of hospital stay annually; suggested total annual costs were
USD $130 297 when opportunity cost estimates for bed days were used, and USD $1.6 million when accounting costs were used. Our results are comparable with the limited available international data [10, 32–34], indicating that both resistant and susceptible bacterial infections cause substantial health and economic burdens. Susceptible infections were more prevalent than resistant infections, and therefore contributed proportionally to health and economic burden.

Current estimates of the resistance-attributable morbidity are available for Enterobacteriaceae [10]; *P. aeruginosa* [35], *E. faecium* [36], and *S. aureus* [9, 10, 35] BSIs; and RTIs [35] caused by *P. aeruginosa* and *S. aureus*. Adjusting for patient age, sex, and admission year, we demonstrated that resistance was an important contributor to increasing hospital LOS. Patients with 3GC-resistant *K. pneumoniae* BSIs and MRSA BSIs stayed in hospital for an additional 4.4 days and 2.9 days, respectively, when compared to patients with drug-sensitive infections. This is comparable to other reported fully-adjusted LOS estimates for *K. pneumoniae* (4.9 days) and MRSA (2.5 days) [10]. We provide the first report of fully adjusted estimates of morbidity and mortality for *P. aeruginosa* infections, as previous studies used methods that partially adjusted for time-dependent bias [35]. We show that patients infected with ceftazidime-resistant *P. aeruginosa* BSIs stayed in hospital an extra 1.7 days and had a higher death OR (OR, 3.9 versus 2.5, respectively), compared to patients with a drug-sensitive strain. Interestingly, the hospital LOS in patients with a ceftazidime-resistant *P. aeruginosa* RTI was shorter than that in patients with a drug-sensitive strain, which may be attributable to the competing influence of higher odds of death in this patient population.

Infections acquired in a hospital, whether they are resistant or susceptible, increase the LOS, and more than likely also impact the disease severity and likelihood of survival. However, quantifying the LOS in hospital and any changes to the risk of mortality in these patients is challenging, because the exposure (infection) is a time-dependent variable. Hence, the longer a patient stays in a hospital, the higher their risk of acquiring an infection. Modeling the infection time during a patient’s hospital...
| Table 2. Estimated Bed-day Costs |
|---------------------------------|
|                                | Opportunity cost, mean (SD) | Accounting cost, mean (SD) |
|                                | Per infection               |                              |
|                                | R                            | S                            | R-S<sup>a</sup>       |
|                                |                              |                              |                       |
| Bloodstream infections         |                              |                              |                       |
| S. aureus                      | 909.1 (97.6)                 | 1347.7 (144.4)               | 844.6 (91.1)          | 503.2 (172.9)          |
| E. faecium                     | 573.9 (88.4)                 | 318.0 (36.0)                 | 670.3 (83.1)          | −442.3 (90.8)          |
| E. coli                        | 399.7 (45.7)                 | 403.6 (43.8)                 | 401.0 (44.6)          | 2.7 (82.7)             |
| K. pneumoniae                  | 526.3 (57.4)                 | 1250.1 (137.3)               | 496.5 (53.9)          | 753.5 (1479)           |
| P. aeruginosa                  | 571.9 (82.3)                 | 898.5 (106.4)                | 559.5 (60.7)          | 342.6 (123.1)          |
|                              |                              |                              |                       |                       |
| Urinary infections             |                              |                              |                       |                       |
| S. aureus                      | 257.4 (30.5)                 | 415.8 (52.3)                 | 235.3 (27.8)          | 180.5 (59.6)           |
| E. faecium                     | 184.1 (23.3)                 | 244.9 (29.7)                 | 152.3 (20.3)          | 92.6 (28.6)            |
| E. coli                        | 875.1 (15.1)                 | 173.8 (22.5)                 | 90.6 (15.2)           | 83.2 (27.3)            |
| K. pneumoniae                  | 54.9 (13.1)                  | 418.6 (54.3)                 | 36.7 (12.5)           | 381.5 (55.7)           |
| P. aeruginosa                  | 145.8 (20.0)                 | 348.7 (39.6)                 | 139.1 (19.1)          | 209.5 (44.4)           |
|                              |                              |                              |                       |                       |
| Respiratory infections         |                              |                              |                       |                       |
| P. aeruginosa                  | 486.4 (53.5)                 | 412.4 (46.1)                 | 498.5 (54.6)          | −86.4 (71.6)           |
|                              |                              |                              |                       |                       |
|                              |                              |                              |                       |                       |

Data are represented as opportunity and accounting costs associated with health care–associated infections in Queensland (2012–2016). Abbreviations: E. coli, Escherichia coli; E. faecium, Enterococcus faecium; K. pneumoniae, Klebsiella pneumoniae; P. aeruginosa, Pseudomonas aeruginosa; R, resistant; S, sensitive; S. aureus, Staphylococcus aureus; SD, standard deviation. *Cost of resistance calculated as the difference in cost between a resistant and sensitive infection.
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...and this is the method we employed [14]. As such, the cost estimates provided are likely to be an underestimate of the true economic burden of HAIs. This is due to the challenge of attributing the change in mortality observed in the data solely to HAI, which is a likely oversimplification of the hospitalized patients’ conditions, particularly for those with only a UTI.

We demonstrate the health and economic burdens attributable to a range of antibiotic-susceptible and -resistant HAIs in Australian health-care facilities. The health burden remains highest for BSIs; however, UTIs and RTIs contributed most to the health-care system expenditure.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Figure 4. Infection-attributable annual costs for health care–associated infections in the (A) bloodstream, (B) urinary tract, and (C) respiratory tract, Queensland, 2012–2016. Abbreviations: 3GC, third-generation cephalosporin; CI, confidence interval; E. coli, Escherichia coli; E. faecium, Enterococcus faecium; K. pneumoniae, Klebsiella pneumonia; MRSA, methicillin-resistant S. aureus; MSSA, methicillin-sensitive S. aureus; P. aeruginosa, Pseudomonas aeruginosa; S. aureus, Staphylococcus aureus; USD, United States dollar; VRE, vancomycin-resistant E. faecium; VSE, vancomycin-sensitive E. faecium.
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