

The Increased Length of Hospital Stay and Mortality Associated With Community-Associated Infections in Australia

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Background. An increasing proportion of antibiotic-resistant infections are community acquired. However, the burden of community-associated infections (CAIs) and the resulting impact due to resistance have not been well described.

Methods. We conducted a multisite, retrospective case-cohort study of all acute care hospital admissions across 134 hospitals in Australia. Patients admitted with a positive culture of 1 of 5 organisms of interest, namely *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Enterococcus faecium*, from January 1, 2012, through December 30, 2016, were included. Data linkage was used to link hospital admissions and pathology data. Patients with a bloodstream infection (BSI), urinary tract infection (UTI), or respiratory tract infection (RTI) were included in the analysis. We compared patients with a resistant and drug-sensitive infection and used regression analyses to derive the difference in length of hospital stay (LOS) and mortality estimates associated with resistance.

Results. No statistically significant impact on hospital LOS for patients with resistant CAIs compared with drug-sensitive CAIs was identified. CAI patients with drug-resistant Enterobacteriaceae (*E. coli*, *K. pneumoniae*) BSIs were more likely to die in the hospital than those with drug-sensitive Enterobacteriaceae BSIs (odds ratio [OR], 3.28; 95% CI, 1.40–6.92). CAI patients with drug-resistant *P. aeruginosa* UTIs were more likely to die in the hospital than those with the drug-sensitive counterpart (OR, 2.43; 95% CI, 1.12–4.85).

Conclusions. The burden of CAI in the hospital is significant, and antibiotic resistance is adding to associated mortality.

Keywords. community; antimicrobial resistance; urinary infections; mortality.

Antimicrobial resistance (AMR) is a recognized global public health emergency that poses a fundamental threat to human health, development, and security [1, 2]. Many countries globally, including Australia, have developed national action plans in response to this emerging threat [3]. To adequately evaluate the implementation of Australia's National AMR Strategy, comprehensive information about the incidence of AMR and the associated health impacts is needed. Currently, this type of evidence in Australia is lacking, especially within the community setting [4].

A comprehensive approach to estimating the AMR-attributable impact is emerging, and recent data demonstrate

that the burden of AMR is increasing. A large, multicountry analysis estimated that antibiotic-resistant infections in Europe resulted in 33 110 deaths and 874 541 disability-adjusted life-years (composed of years of life lost due to premature death and due to disability) [5]. This burden is similar to the cumulative burden caused influenza, tuberculosis, and HIV [5]. In Australia, we have quantified the AMR health burden in hospitals and found that bloodstream infections (BSIs) resulted in high morbidity and mortality in patients with an antibiotic-resistant infection. Patients with a third-generation cephalosporin-resistant (3GCR) *K. pneumoniae* BSI stayed in the hospital an extra 4.6 days compared with third-generation cephalosporin-sensitive (3GCS) patients [6]. Similarly, methicillin resistance in *Staphylococcus aureus* BSIs extended hospital stays by an extra 2.9 days, compared with methicillin-sensitive *S. aureus* (MSSA) [6]. Consequently, the health care costs of these infections were higher, compared with corresponding drug-sensitive strains. However, urinary tract infections (UTIs) were the most prevalent (51.5 cases per 100 000 patient-days) and accounted for the greatest proportion of hospital costs, followed by *Pseudomonas aeruginosa* respiratory tract infection (RTI) [6]. An estimated AUS\$33 million are spent annually on

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treating patients with a resistant pathogen of 2 common BSIs, namely ceftriaxone-resistant *Escherichia coli* and methicillin-resistant *Staphylococcus aureus* (MRSA) [7]. Currently, there are no Australian studies that have quantified the AMR-attributable (due to resistant infection only) morbidity and mortality in the community setting.

While many bacterial AMR infections are associated with exposures in hospital environments [5], there is an increasing prevalence of resistance among patients in community settings [8–11] and with commensal pathogens [12]. Infections associated with AMR in community settings include UTIs [13], RTIs [14], and skin infections [15]. Community-acquired AMR is important to global spread, as some of these infections are highly prevalent and are readily transmissible in both health care and community settings [16–18] and can infect animal species [19].

Quantifying AMR burden is difficult, as AMR is not a disease but a range of bacteria that lead to different disease outcomes [12]. It is then the presence of resistance to antimicrobial treatment that creates the disease burden [20]. The focus on the severe forms of infections identified in patients admitted to hospitals has limited studies conducted in community settings, resulting in a limited understanding of the true burden of disease. Additionally, capacity for good quality standardized microbiological data [21] linked to clinical outcomes for determination of AMR impact has been limited outside of hospitals and is further exacerbated by limited data sharing and availability [20]. Together, the unique characteristics of AMR and the scarcity of data on community-associated infections (CAIs) have made enumerating the impact of AMR in community settings particularly challenging.

We sought to examine the morbidity and mortality associated with AMR-CAI in an Australian setting.

METHODS

Setting and Study Design

This was a multisite, retrospective study of all acute care hospital admissions in Queensland, Australia, from January 1, 2012, through December 30, 2016. Data were provided by the Queensland Department of Health, Pathology Queensland database, which collects and stores information on antimicrobial susceptibilities for all Queensland public hospitals ($n = 170$). Testing is carried out by 35 laboratories that collect data from local laboratories in a range of settings including rural and metropolitan hospitals. The first clinical isolate from patients with a positive culture and susceptibility profile of 4 organism groups, including Enterobacteriaceae (combined *E. coli* and *K. pneumoniae* infections), *P. aeruginosa*, *S. aureus*, or *E. faecium*, from multiple sites (BSI, UTI, and RTI) was analyzed. Data linkage was used to generate a data set that matched Queensland Hospital Admitted Patients Data Collection [22] with Queensland Department of Health Pathology [23].

Linkage was done by matching the hospital and hospital-level patient identifiers.

Definitions

Community-associated (CA) BSI was defined as a positive blood culture present <48 hours after admission. CA-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 mL in a urine specimen. A consensus definition requires 10^3 organisms per mL to diagnose cystitis and 10^4 per mL for pyelonephritis [24]. CA-RTI was defined as a positive *P. aeruginosa* smear or culture and a count of $>10^4$ colony-forming units per mL 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 CA-BSI [25, 26], CA-UTI [27, 28], and CA-RTI [29].

Antibiotic susceptibility results were provided as European Committee on Antimicrobial Susceptibility Testing interpreted values (resistant, intermediate, and sensitive). 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 8 exposure groups with a total of 5 organisms:

1. 3GC-resistant Enterobacteriaceae (includes *E. coli* and *Klebsiella* spp.)
2. 3GC-sensitive Enterobacteriaceae (includes *E. coli* and *Klebsiella* spp.)
3. Ceftazidime-resistant *P. aeruginosa*
4. Ceftazidime-sensitive *P. aeruginosa*
5. Methicillin-resistant *S. aureus* (MRSA)
6. Methicillin-sensitive *S. aureus* (MSSA)
7. Vancomycin-resistant *E. faecium* (VRE)
8. Vancomycin-sensitive *E. faecium* (VSE)

Statistical Analysis

Gamma regression was used to analyze the potential difference in patients' hospital LOS between those with drug-resistant and drug-sensitive variants of CAI. This difference is presented as the exponentiated coefficient estimate of the resistant indicator covariate. Similarly, logistic regressions were used to estimate the potential difference in the hospital mortality outcome between patients with drug-resistant and drug-sensitive CAIs where the difference is expressed as odds ratios.

In each regression analysis performed, the analysis also adjusted for other potential confounders such as age, sex, year of infection, and Charlson comorbidities.

Differences in both outcomes (hospital LOS and death in hospital) were assessed across all CAI patients by combinations of organism and infection sites, separately. Model residuals were assessed to check for model adequacy and potentially influential observations.

Regression analysis included infection groupings that were clinically significant and had a sufficient number of patients in either the drug-resistant or drug-sensitive group to make the results meaningful with an inclusion criterion of 50 clinical isolates per group.

Patient Consent

Patient consent waiver and full ethical clearance were granted by the Queensland University of Technology Human Research Ethics Committee (HREC1700000232).

RESULTS

Overall, data for 21 268 patients from the 134 hospitals were analyzed, which included facilities located in major cities, regional hospitals, and rural health care services.

Of the total 21 268 patients infected with any 1 of the 5 clinically important CAIs, 1079 patient infections were due to drug-resistant bacteria (Table 1).

Females were over-represented across the UTI grouping, caused by Enterobacteriaceae (3GC-resistant, 69% female; 3GC-sensitive, 79% female) and *E. faecium* (VRE, 74% female; VSE, 68% female), but not *S. aureus* or *P. aeruginosa*, where the ratio of female to male was more equal (Table 1).

The most common CAI in our analysis was 3GC-sensitive Enterobacteriaceae (87.5/100 000), largely due to a high incidence of urinary infections (79.2/100 000) within this grouping. Across all groups, drug-sensitive strains were more prevalent than drug-resistant strains. More CAIs were due to gram-negative (Enterobacteriaceae and *P. aeruginosa*) compared with gram-positive infection (*S. aureus*, *E. faecium*) (Table 1).

The most common comorbidity in our study population was chronic obstructive pulmonary disease (COPD; data not shown). In our analysis, 8.5% of patients presenting to the hospital with a community-associated drug-resistant infection, compared with 4.7% of patients with a drug-sensitive infection, had COPD as the principal diagnosis. The largest impact was in patients with a *P. aeruginosa* infection, where almost a third (27.5%, n = 82) of patients with a drug-resistant *P. aeruginosa* infection and 19.9% (n = 698) with a drug-sensitive *P. aeruginosa* infection had COPD. Other notable comorbidities that patients with a community-associated infection presented with in hospital were congestive heart failure (2.7% of all

Table 1. Patient Characteristics for the Study Population, Queensland 2012–2016

			No.	Female, %	Age (SD), y	Died in Hospital, No. (%)	LOS, Median (IQR), d	Incidence/100 000
<i>S. aureus</i>	All	R	215	32.6	58.8 (26.8)	16 (7.4)	13 (6–25)	1.2
		S	1300	34.9	59.7 (24.0)	104 (8.0)	13 (6–26)	7.5
	BSI	R	135	32.6	52.3 (25.8)	9 (6.7)	18 (10–32)	0.8
		S	882	31.7	58.8 (23.7)	81 (9.2)	17 (9–32)	5.1
	UTI	R	80	32.5	69.8 (24.9)	7 (8.8)	6.5 (4–12.3)	0.5
		S	418	41.6	61.6 (24.7)	23 (5.5)	6 (3–12)	2.4
<i>E. faecium</i>	All	R	77	71.4	71.9 (16.1)	4 (5.2)	7 (4–11)	0.4
		S	121	62.8	71.4 (20.6)	6 (5.0)	7 (4–13)	0.7
	BSI	R	3	0.0	78.0 (1.7)	0 (0.0)	11 (8.5–11)	0.0
		S	20	35.0	62.2 (25.2)	0 (0.0)	13 (7.8–17.3)	0.1
	UTI	R	74	74.3	71.7 (16.3)	4 (5.4)	6.5 (4–10.7)	0.4
		S	101	68.3	73.2 (19.1)	6 (5.9)	7 (4–11)	0.6
Enterobacteriaceae	All	R	489	65.8	68.1 (22.8)	27 (5.5)	6 (4–11)	2.8
		S	15 267	76.4	67.0 (24.1)	507 (3.3)	5 (3–9)	87.5
	BSI	R	63	42.9	71.2 (15.9)	9 (14.3)	8 (6–12.5)	0.4
		S	1446	51.7	66.4 (21.4)	66 (4.6)	7 (4–10)	8.3
	UTI	R	426	69.2	67.7 (23.6)	18 (4.2)	6 (3–11)	2.4
		S	13821	79.0	67.1 (24.3)	441 (3.2)	5 (3–9)	79.2
<i>P. aeruginosa</i>	All	R	298	39.6	66.5 (20.5)	17 (5.7)	8 (4–13)	1.7
		S	3501	44.8	70.5 (20.0)	189 (5.4)	6 (4–12)	20.1
	BSI	R	7	42.9	67.4 (26.9)	0 (0.0)	9 (4–12.5)	0.0
		S	147	25.9	70.4 (18.1)	12 (8.2)	8 (5–18.8)	0.8
	UTI	R	95	36.8	77.5 (13.5)	11 (11.6)	6 (3–12.5)	0.5
		S	1722	48.4	73.3 (20.4)	75 (4.4)	6 (3–11)	9.9
	Resp	R	196	40.8	61.1 (21.0)	6 (3.1)	9 (4–13)	1.1
		S	1632	42.8	67.6 (19.3)	102 (6.3)	7 (4–12)	9.4

Due to the low number of patients (Table 1), we excluded the *E. faecium* BSI and *P. aeruginosa* BSI infection groups from the regression analyses (Table 2).

Abbreviations: BSI, bloodstream infection; IQR, interquartile range; LOS, length of stay; R, drug-resistant; Res, respiratory tract infection; S, drug-sensitive; UTI, urinary tract infection.

drug-resistant infections and 2.6% of all drug-sensitive infections, followed by acute myocardial infarct: 1.5% drug-resistant and 2.3% drug-sensitive).

AMR-Attributable Excess Length of Hospital Stay and Mortality

The combined 1079 antibiotic-resistant infections resulted in 12 138 hospital days of hospital stay annually compared with susceptible infections, which resulted in 191 834 hospital days.

None of the LOS analyses showed a statistical difference between drug-resistant and drug-sensitive infection groupings (Table 2). However, CAI patients with drug-resistant Enterobacteriaceae BSIs were more likely to die in the hospital than those with drug-sensitive Enterobacteriaceae BSIs (odds ratio [OR], 3.28; 95% CI, 1.40–6.92). CAI patients with resistant *P. aeruginosa* UTIs were more likely to die in the hospital than those with the drug-sensitive counterpart (OR, 2.43; 95% CI, 1.12–4.85).

DISCUSSION

This study provides comprehensive estimates of the impact of drug-resistant and drug-sensitive community-associated infections caused by gram-positive and gram-negative bacteria in Australian hospitals. This study expands on work previously published by Lee et al. describing the burden due to resistant hospital-associated infections [6]. This study demonstrates that CAI drug-resistant infections contributed 36.5% (n = 1079) of the total burden of AMR in hospitalized patients (n = 2953; 1079 + 1874 [6]). Although no association was identified with hospital length of hospital stay for patients who acquired AMR in the community, patients with 3GC-resistant Enterobacteriaceae BSIs and ceftazidime-resistant *P. aeruginosa* UTIs were at increased risk of dying. Drug-sensitive infections were more prevalent than drug-resistant infection and thereby contributed proportionally to the health burden.

We found no statistical difference in hospital stay due to AMR-CAI, with a previous systematic review reporting similar findings, with approximately half of the included studies showing that patients infected with a resistant infection did not have a significant extra LOS compared with patients with

a susceptible infection [30]. However, as with much of the evidence to date, most of these studies are reporting on the burden from hospital-acquired infections. Longer hospital stay estimates were found to be associated with CAI in a US study [31], leading to higher direct hospital costs in Canada specifically for *Staphylococcus aureus* bacteremia [32]. AMR can lead to additional burden even in the absence of infection onset and in patients who are colonized with a multidrug-resistant bacterium that they acquired in the community [33]. These patients are asymptomatic carriers who incur a considerable financial burden that is not well defined [33]; hence while there was no difference in LOS, these infections may be creating additional burden to the health care system.

We found increased mortality to be associated with community-associated 3GC-resistant Enterobacteriaceae BSIs and ceftazidime-resistant *P. aeruginosa* UTIs. This is consistent with previous research, with a large-scale study in Europe estimating that 36.5% of patients with a resistant infection that was not associated with health care exposure led to 9134 attributable deaths per 100 000 population [5]. Drug-sensitive community-associated infections were more prevalent, ranging from 0 to 87.5 per 100 000 patient-days, compared with CAI-AMR infections, which ranged from 0 to 2.8 per 100 000 patient-days. Surveillance data from Australia have previously identified this pattern [8, 11]. Although the precise prevalence depends on the type of infection and antibiotic, for the majority of strains and antibiotics, drug-sensitive strains remain highly prevalent. The most recent reports identify general stable patterns of resistance in Australia, but resistance in patients with community-acquired Enterobacteriaceae has increased [8, 13].

Previous work in Australia has shown that AMR is increasing in patients harboring uropathogens in community settings [10, 13]. These studies are equivalent to the current study, which identified high incidence of community-associated 3GC-resistant Enterobacteriaceae UTIs (2.8 per 100 000 patient-days) and a statistically significant risk of dying in the hospital with this AMR-CAI. Owing to the high prevalence of UTIs, community-associated 3GC-resistant Enterobacteriaceae UTIs are a major contributor to antibiotic use in Australia [8]. Without effective

Table 2. AMR Attributable Length of Hospital Stay and Mortality for Community-Associated Infections by Infection Site, Queensland 2012–2016

	Infection Site	LOS Multiplier for Resistant Infections [95% CI]	Mortality, Odds Ratio [95% CI]
MRSA vs MSSA	BSI	0.97 [0.83–1.14]	0.79 [0.34–1.63]
	UTI	0.88 [0.68–1.17]	1.25 [0.43–3.27]
VRE vs VSE	UTI	0.94 [0.72–1.23]	1.16 [0.2–5.77]
3GCR vs 3GCS Enterobacteriaceae	BSI	1.18 [0.91–1.57]	3.28 [1.4–6.92]
	UTI	1.08 [0.95–1.24]	1.31 [0.77–2.09]
Ceftazidime-resistant vs susceptible <i>P. aeruginosa</i>	UTI	1.05 [0.78–1.47]	2.43 [1.12–4.85]
	Respiratory	1.03 [0.9–1.19]	0.6 [0.23–1.3]

Bold indicates statistical significance.

Abbreviations: 3GCR, third-generation resistant; 3GCS, third-generation sensitive; BSI, bloodstream infection; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; VRE, vancomycin-resistant *E. faecium*; VSE, vancomycin-sensitive *E. faecium*; UTI, urinary tract infection.

antibiotics active against common uropathogens, many urological procedures will carry excessive risk [34], unavoidable escalation of treatment and hospitalization due to co-resistance to other oral agents (eg, fluoroquinolones and sulphonamides) [35], and extra health care costs [36]. Repurposing old antibiotics to treat common uropathogens may be a useful approach to reduce antimicrobial selective pressure [37]. However, increasing failure of standard empirical treatment for UTIs is foreseeable, and it is likely that many more patients will require microbiology testing before starting antibiotics, not only for individual patient management [37] but also for surveillance data to inform local guidelines [13].

The strength of this study is the utilization of a large statewide pathology data set, with data from both regional and urban settings. The database provides information for all public hospitals in the state and uses a single reliable testing methodology for included specimens. The study is limited by the fact that the list of included infections is not comprehensive of infection, with inclusion of only 5 common and clinically important infections. As only the principal diagnosis codes (ICD-10) were available, each patient in our study was assigned at most 1 comorbidity. This may not accurately reflect the comorbidity associated with infection, but for the purpose of our analysis we used these principal comorbidities as confounders with the potential to influence our outcome measures. Death from an infection with drug-resistant bacteria is the result of many factors that are related to the pathogen, patient, and treatment, in particular if therapy is delayed. We did not adjust our models for co-infections, appropriateness of antibiotic therapy, prior health care contact, or type of care, as these measures were not made available in the administrative data sets used in the study. However, in the future, studies should consider these factors within the context of AMR evolution and spread.

Overall, we determined that the burden of infections acquired in the community is significant, and AMR is likely causing increased mortality for Enterobacteriaceae and *P. aeruginosa*. These findings help to address the currently limited data available in relation to community AMR burden in Australia. They provide further guidance for clinical management of patients with drug-resistant infections identified in the community and help to bridge the gap between hospital-based stewardship activities and community-based programs, which are urgently needed [38].

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Data availability. Data can be made available upon request.

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