Original Article

The Excess Financial Burden of Multidrug Resistance in Severe Gram-negative Infections in Singaporean Hospitals

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Abstract

Introduction: Multidrug-resistant (MDR) Gram-negative healthcare-associated infections are prevalent in Singaporean hospitals. An accurate assessment of the socioeconomic impact of these infections is necessary in order to facilitate appropriate resource allocation, and to judge the cost-effectiveness of targeted interventions. Materials and Methods: A retrospective cohort study involving inpatients with healthcare-associated Gram-negative bacteraemia at 2 large Singaporean hospitals was conducted to determine the hospitalisation costs attributed to multidrug resistance, and to elucidate factors affecting the financial impact of these infections. Data were obtained from hospital administrative, clinical and financial records, and analysed using a multivariate linear regression model. Results: There were 525 survivors of healthcare-associated Gram-negative bacteraemia in the study cohort, with 224 MDR cases. MDR bacteraemia, concomitant skin and soft tissue infection, higher APACHE II score, ICU stay, and appropriate definitive antibiotic therapy were independently associated with higher total hospitalisation costs, whereas higher Charlson comorbidity index and concomitant urinary tract infection were associated with lower costs. The excess hospitalisation costs attributed to MDR infection was $8638.58. In the study cohort, on average, 62.3% of the excess cost attributed to MDR infection was paid for by government subvention. Conclusion: Multidrug resistance in healthcare-associated Gram-negative bacteraemia is associated with higher financial costs—a significant proportion of which are subsidised by public funding in the form of governmental subvention. More active interventions aimed at controlling antimicrobial resistance are warranted, and the results of our study also provide possible benchmarks against which the cost-effectiveness of such interventions can be assessed.

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Key words: Antimicrobial resistance, Cohort study, Gram-negative bacteraemia, Healthcare costs

Introduction

Healthcare-associated infections (HAIs) are a burden on healthcare systems in both developed as well as developing nations, resulting in prolonged hospitalisation, poor outcomes and increased hospitalisation costs. Between 5% and 15% of acute-care inpatients develop an infection during their admission, and critically ill patients nursed in intensive care units (ICUs) are 5 to 10 times more likely to acquire a HAI than those in general wards.[1,2] Gram-negative bacilli (GNB) collectively cause the majority of HAIs, and have been associated with progressively increasing rates of resistance, including multidrug resistance.[3] In Singapore, a hospital-based surveillance program showed that 21.7% and 27.4% of *Escherichia coli* and *Klebsiella pneumoniae* blood isolates were resistant to third-generation cephalosporins, whereas 12.8% and 50.0% of blood *Pseudomonas aeruginosa* and *Acinetobacter* spp. isolates respectively were resistant to the carbapenems.[4]

Although it remains contentious as to whether multidrug resistance is an independent risk factor for mortality in severe GNB infections,[5-8] it is almost universally accepted that it results in prolonged hospitalisation and higher economic costs compared to similar infections caused by antibiotic-susceptible GNB.[5,6,8,9] An accurate assessment of the socioeconomic impact of multidrug-resistant (MDR)-GNB infections is necessary in order to facilitate appropriate resource allocation to deal with this issue, and to judge the cost-effectiveness of interventions directed against reducing MDR-GNB infections. However, because of

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significant differences in healthcare funding, delivery and costs between countries, it is inadvisable to extrapolate the additional financial impact of multidrug resistance derived from studies conducted in dissimilar healthcare systems.

We had conducted a retrospective cohort study on GNB bloodstream infections to determine the clinical outcomes and hospitalisation costs attributed to multidrug resistance, and to elucidate factors affecting the financial impact of these infections. The results on mortality and duration of hospitalisation have been published elsewhere,[7] but the analysis on hospitalisation costs is presented below.

Materials and Methods

A detailed description of the methodology and conduct of the cohort study has been presented elsewhere.[7] In brief:

Subjects

Consecutive inpatients with first episodes of healthcare-associated Gram-negative bacteraemia were recruited from the 1600-bed Singapore General Hospital and the 1400-bed Tan Tock Seng Hospital between January 2007 and July 2009. Each subject was followed up until the point of discharge.[7] For the analysis of hospitalisation costs, all fatalities were excluded.

Data

Demographical, clinical and microbiological variables were collected from inpatient clinical, administrative and laboratory records. Multidrug resistance (MDR) was defined as resistance to all antimicrobial agents tested in 3 or more antibiotic classes.[10] Severity of illness was scored using the Acute Physiology and Chronic Health Evaluation, version II (APACHE II), with variables taken at the day of positive cultures,[11] while the Charlson comorbidity index was used as an aggregate measure for prognosticating subjects' comorbidities.[12] Other concomitant sites of infection were classified according to the National Healthcare Safety Network definitions.[13]

The primary outcome was total hospitalisation costs, incorporating cost for drugs, laboratory and medical tests, ICU stay if applicable, as well as any other procedures. All costs are reported in Singapore dollars, and were obtained from each hospital's Finance department along with individual inpatient subventions for subjects eligible for Ministry of Health (MOH) subsidisation (hospital B1, B2 and C classes).[14]

Statistical Methods

For determination of covariates associated with total hospitalisation costs, we performed linear regression, with a multivariate model based on significant covariates identified on univariate analysis using the likelihood ratio test, with probability of removal set at 0.05. Data were analysed on a natural logarithmic scale as exploratory analyses revealed that the residuals from the models were not normally distributed. To calculate excess hospitalisation costs between MDR and non-MDR cases after adjustment for confounders, we used the following formula: ($e^{0.61}$ x 10,181.47) – 10,181.47, where 0.61 is the adjusted coefficient from the multivariate model, and $10,181.47 is the baseline hospitalisation cost for the non-MDR group. Comparative analyses were performed between non-MDR and MDR groups with the χ^2 test or Fisher's test (for dichotomous variables) and Mann-Whitney U test (for continuous variables).

Intercooled Stata 10.2 (StataCorp, Texas, USA) was used for all statistical calculations, and level of significance set at 5%.

Ethics

The study was approved by the ethics review boards of both institutions (Reference: E/08/193).

Definitions

We considered bacteraemia to be healthcare-associated if it fulfilled previously published criteria for nosocomial or healthcare-associated bacteraemia, namely, positive blood culture obtained from patients who have:[15]

- Been hospitalised for 48 hours or longer without evidence of infection on admission, OR
- Been hospitalised in an acute care hospital for 2 or more days in the 90 days preceding the bacteraemia, OR
- Attended a hospital or haemodialysis clinic in the 30 days preceding bacteraemia, OR
- Received intravenous therapy or specialised wound/nursing care at home in the 30 days preceding bacteraemia.

Results

There were 525 survivors of healthcare-associated Gram-negative bacteraemia in the study cohort, of whom 224 had MDR bacteraemia, with the demographical and clinical variables as well as outcomes shown in Table 1. No pan-resistant bacteria were cultured. Median total hospitalisation costs for subjects with MDR bacteraemia were just above twice that of those with non-MDR bacteraemia. Median subsidies were $6186.00 (IQR: $2915.00 – $14,830.00) for

Table 1. Descriptive Characteristics of Healthcare-associated Gram-negative Bacteraemia Survivors, Segregated by Multidrug Resistance

Characteristic	Non-MDR* bacteraemia (n = 301)	MDR* bacteraemia (n = 224)	*P* value
Hospital (%)			
• Singapore General Hospital	151 (50.2)	106 (47.3)	0.519
• Tan Tock Seng Hospital	150 (49.8)	118 (52.7)	
Hospital class (%)			
• A	11 (3.6)	9 (4.0)	
• B1	21 (7.0)	16 (7.1)	0.046
• B2	124 (41.2)	66 (29.5)	
• C	145 (48.2)	133 (59.4)	
Median age, years (IQR*)	66 (55 – 77)	67 (52 – 76)	0.446
Male gender (%)	140 (46.5)	121 (54.0)	0.089
Ethnicity (%)			
• Chinese	235 (78.1)	159 (71.3)	0.212
• Malay	30 (10.0)	31 (13.9)	
• Indian	31 (10.3)	25 (11.2)	
Discipline (%)			
• Medical	199 (66.1)	143 (64.1)	0.637
• Surgical	102 (33.9)	80 (35.9)	
Bacteraemia within 48 hours of hospitalisation (%)	154 (51.2)	77 (34.4)	<0.001
Median length of stay prior to bacteraemia, days (IQR*)	2 (0 – 10)	8 (1 – 18)	<0.001
Median APACHE II score (IQR*)	8 (5 – 12)	11 (7 – 15)	<0.001
Median Charlson index (IQR*)	7 (5 – 9)	7 (4 – 10)	0.592
ICU* stay prior to bacteraemia (%)	8 (2.7)	16 (7.1)	0.015
Organism (%)			
• *A. baumannii*	23 (7.6)	25 (11.2)	
• *Enterobacter spp.*	0 (0.0)	49 (21.9)	
• *Escherichia coli*	119 (39.5)	58 (25.9)	<0.001
• *Klebsiella pneumoniae*	63 (20.9)	54 (24.1)	
• *Proteus mirabilis*	25 (8.3)	10 (4.5)	
• *P. aeruginosa*	71 (23.6)	28 (12.5)	
Polymicrobial bacteraemia (%)	52 (17.3)	39 (17.5)	0.949
Other sites of infection (%)[17]			
• Bone & joint infection	1 (0.3)	5 (2.2)	0.088
• Catheter-related	31 (10.3)	31 (13.8)	0.214
• Intra-abdominal infection	37 (12.3)	30 (13.4)	0.709
• Pneumonia	37 (12.3)	27 (12.1)	0.934
• Skin & soft tissue infection	27 (9.0)	33 (14.7)	0.040
• Urinary tract infection	116 (38.5)	72 (32.1)	0.131

Table 1. (con't) Descriptive Characteristics of Healthcare-associated Gram-negative Bacteraemia Survivors, Segregated by Multidrug Resistance

Characteristic	Non-MDR* bacteraemia (n = 301)	MDR* bacteraemia (n = 224)	*P* value
Appropriate antibiotic therapy (%)			
• Empirical	243 (80.7)	65 (29.0)	<0.001
• Definitive	300 (99.7)	211 (94.2)	<0.001
Total hospitalisation cost, SGD (IQR)	10,181.47 (5,552.29 – 23,279.82)	22,651.24 (11,046.84 – 48,782.93)	<0.001

*MDR: multidrug-resistant; IQR: interquartile range; ICU: intensive care unit

290 subjects with non-MDR bacteraemia and $13,780.00 (IQR: $5888.00 to $28,400.00) for 215 subjects with MDR bacteraemia (*P* <0.001).

The results of univariate analysis for association of subject characteristics with hospitalisation costs are shown in Table 2, while significant covariates found in the final multivariable model are displayed in Table 3.

On multivariate analysis, MDR bacteraemia, concomitant skin and soft tissue infection (SSTI), higher APACHE II score, ICU stay before bacteraemia, and appropriate definitive antibiotic therapy were independently associated with higher total hospitalisation costs. Those who had been prescribed appropriate empirical antibiotic therapy were likely to have incurred a lower cost on univariate analysis, but this variable was insignificant on multivariate analysis. Higher Charlson comorbidity index and concomitant urinary tract infection (UTI) were associated with lower total hospitalisation costs.

The excess hospitalisation costs attributed to MDR infection was 45.7 % of the baseline, which amounted to $8638.58. In the study cohort, on average, 62.3% of the excess cost attributed to MDR infection was paid for by government subvention.

Discussion

In our study, the excess total hospitalisation cost attributed to multidrug resistance was significant and high in subjects with Gram-negative bacteraemia. This is in line with other published reports. Maudlin and co-workers[9] conducted a single-centre retrospective cohort study on 662 patients in South Carolina and reported that the additional hospitalisation cost attributable to antibiotic resistance in various GNB was 29.3%. Cosgrove and co-workers[16] studied a cohort of 477 patients with third-generation cephalosporin-susceptible or resistant *Enterobacter* spp. They found that emergence of resistance had an average

Table 2. Univariate Analysis of the Impact of Cohort Characteristics on Hospitalisation costs in Bacteremia Survivors

Characteristic	Hospitalisation cost		
	Coefficient*	95% CI	*P* value
Hospital			
• Singapore General Hospital	0.00	-	-
• Tan Tock Seng Hospital	0.16	– 0.03 to 0.36	0.102
Hospital Class			
• A	0.00	-	-
• B1	– 0.42	– 1.06 to 0.22	0.198
• B2	– 0.63	– 1.18 to 0.08	0.025
• C	– 0.48	– 1.03 to 0.06	0.080
Age	– 0.02	– 0.02 to – 0.01	<0.001
Male gender	0.21	0.01 to 0.40	0.037
Ethnicity			
• Chinese (reference)	0.00	-	-
• Malay	0.04	– 0.27 to 0.35	0.793
• Indian	– 0.20	– 0.52 to 0.12	0.220
Surgical discipline	0.13	– 0.07 to 0.34	0.206
APACHE II score	0.06	0.04 to 0.07	<0.001
Charlson comorbidity index	– 0.05	– 0.08 to – 0.03	<0.001
ICU* stay	1.61	1.13 to 2.09	<0.001
Polymicrobial bacteraemia	0.08	– 0.18 to 0.34	0.549
Organism type:			
• *Acinetobacter baumannii* (reference)	0.000	-	-
• *Enterobacter* spp.	– 0.42	– 0.86 to 0.02	0.063
• *Escherichia coli*	– 0.77	–1.13 to – 0.42	<0.001
• *Klebsiella pneumoniae*	– 0.19	– 0.57 to 0.18	0.306
• *Proteus mirabilis*	– 0.93	–1.42 to – 0.44	<0.001
• *Pseudomonas aeruginosa*	– 0.36	– 0.74 to 0.03	0.068
MDR† bacteraemia	0.71	0.52 to 0.90	<0.001
Other sites of infection[17]			
• Catheter-related	0.61	0.31 to 0.92	<0.001
• Intra-abdominal infection	– 0.25	– 0.54 to 0.04	0.092
• Pneumonia	0.26	– 0.04 to 0.56	0.085
• Skin & soft tissue infection	0.53	0.22 to 0.84	0.001
• Urinary tract infection	– 0.63	– 0.82 to – 0.43	<0.001
Appropriate antibiotic therapy			
• Empirical	– 0.28	– 0.48 to – 0.09	0.005
• Definitive	0.64	0.04 to 1.25	0.037

*The regression coefficient was analysed on the natural logarithmic scale and generally positive values indicate a positive association between hospitalisation costs and each covariate.

†MDR: multidrug-resistant; ICU: intensive care unit

Table 3. Significant Covariates on Multivariable Analysis with Total Hospitalisation Cost as the Outcome

Characteristic	Hospitalisation cost		
	Coefficient*	95% CI	*P* value
MDR† bacteremia	0.61	0.42 to 0.81	<0.001
Higher APACHE II score	0.04	0.02 to 0.05	<0.001
Higher Charlson comorbidity index	– 0.05	– 0.07 to – 0.02	<0.001
Intensive care unit stay	0.94	0.50 to 1.38	<0.001
Other sites of infection			
• Skin and soft tissue infection	0.31	0.04 to 0.58	0.024
• Urinary tract infection	– 0.41	– 0.59 to – 0.22	<0.001
Appropriate definitive therapy	0.83	0.31 to 1.36	0.002

*The regression coefficient was analysed on the natural logarithmic scale and generally positive values indicate a positive association between hospitalisation costs and each covariate.

†MDR: multidrug-resistant

attributable hospital charge of USD29,379.00. However, it is difficult to compare absolute results across studies because the of the heterogeneity of financial calculations and differences in statistical distributions.[17] As mentioned earlier, such results also cannot be extrapolated to different healthcare systems.

Specific to the Singapore healthcare system, public funding (i.e. government subvention) accounted for a substantial percentage of the overall excess costs attributable to multidrug resistance. Given that there are more than 700 MDR-Gram-negative bacteraemia cases each year in Singaporean public hospitals,[18] the majority of which occur in subsidised patients, the overall cost to the system and public funds is not small. Within the study period, however, there was no significant year-on-year increase in the hospitalisation costs of the subjects (data not shown).

Higher APACHE II score and ICU stay before bacteremia were associated with higher hospitalisation costs in our subjects. This is similar to results in other studies.[9] Appropriate definitive antibiotic therapy resulted in higher costs likely because of the need for expensive broad-spectrum antibiotics, particularly for MDR bacteraemia. Because of the significant proportion of infected burns patients in our cohort, SSTIs were an independent risk factor for higher hospitalisation costs. Healthcare-associated UTIs among our subjects were associated with lower hospitalisation costs, a finding that is consistent with a comprehensive review that included 70 studies related to the cost of various infections, concluding that nosocomial UTIs have the lowest attributable cost whereas nosocomial

bloodstream infections have the highest attributable cost.[19]

There was a significantly lower proportion of MDR-GNB among subjects with bacteraemia within 48 hours of hospitalisation. This is likely because despite the association with healthcare, the subjects may still be infected by less resistant bacteria from the community, and this had been highlighted in the original article describing the criteria that were used in this study.[15] *Enterobacter* spp. and *A. baumannii* were more likely to be MDR, while the converse was true for *E. coli* and *P. aeruginosa*. This reflects previously described trends in antimicrobial resistance locally,[4,18] whereas *Enterobacter* spp., with their intrinsic production of *amp*C beta-lactamase, quite easily meets the criteria for multidrug resistance.

Our study is limited in that hospitalisation costs were not separated into pre- and post-diagnosis of the infection. However, the increased cost of managing an infection may start before the diagnosis of infection, which makes it difficult to separate pre- and post-treatment costs. Furthermore, assigning attributable costs to each episode of infection would render the analysis too subjective. The current study involved 2 institutions, and the findings may not be generalisable to other institutions. Finally, we pooled infections rather than examined the effect on single organisms. The results could be biased if antibiotic resistance occurred in more highly virulent organisms.

Conclusion

In addition to prolonged hospitalisation, multidrug resistance in Gram-negative bacteraemia is associated with higher financial costs for individual patients. In the local context, a significant proportion of these costs are disbursed from public funding in the form of governmental subvention. This adds further weight to arguments for more active interventions aimed at controlling antimicrobial resistance. The results of our study also provide possible benchmarks against which the cost-effectiveness of these interventions can be assessed.

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