Clinical and Economic Burden of Bacteraemia Due To Multi-Drug-Resistant Organisms in Korea: A Prospectively Selected Case Control Study

Kyoung-Ho Song  
Seoul National University Bundang Hospital

Chung-Jong Kim  
Ewha Womans University  https://orcid.org/0000-0002-9987-6533

Nam-Kyong Choi  
Ewha Womans University

Jeonghoon Ahn  
Ewha Womans University

Pyoeng Gyun Choe  
Seoul National University Hospital

Wan Beom Park  
Seoul National University Hospital

Nam Joong Kim  
Seoul National University Hospital

Hee Jung Choi  
Ewha Women's University Mokdong Hospital

Ji Yun Bae  
Ewha Women's University Mokdong Hospital

Eu Suk Kim  
Seoul National University Bundang Hospital

Hyunju Lee  
Seoul National University Bundang Hospital

Jeong Su Park  
Seoul National University Bundang Hospital

Younghoe Jung  
Hallym University Sacred Heart Hospital

Seung Soon Lee  
Hallym University Sacred Heart Hospital

Kyung-Hwa Park  
Chonnam National University Hospital

Sook-In Jung  
Chonnam National University Hospital

Yeon-Sook Kim  
Chungnam National University Hospital

Ji-Hwan Bang  
Seoul Metropolitan Boramae Hospital: Seoul National University Seoul Metropolitan Government Boramae Medical Center

Shinwon Lee  
Pusan National University Hospital

Yu Min Kang  
Kangwon National University Hospital

Yee Gyung Kwak  
Inje University Ilsan Paik Hospital

Hong Bin Kim  
https://orcid.org/0000-0001-6262-372X

Research Article

Keywords: Staphylococcus aureus, bacteraemia, VRSA, MRSA, VRE, MRPA, MRAB, CRE, economic burden

Posted Date: December 23rd, 2021
Abstract

Background

Multidrug-resistant organisms (MDROs), including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), multidrug resistant *Acinetobacter baumannii* (MRAB), multidrug resistant *Pseudomonas aeruginosa* (MRPA), and carbapenem-resistant Enterobacteriaceae (CRE) are particularly important public health threats, but their detailed clinical outcomes and socioeconomic burden are adequately addressed.

Methods

We prospectively searched for these MDROs bacteraemia cases with matched controls from 10 hospitals across Korea, in a 6-month period, in 2017. Patients were classified into the MDRO, susceptible organism, and no-infection groups. The corresponding susceptible or no-infection controls had similar principal diagnosis at admission time, major surgery or intervention during hospitalization, age (± 10 years), sex, and within ± 60 days of admission date. We collected detailed clinical information and estimated the total additional direct medical cost of each MDRO bacteraemia case using the multistate model.

Results

Of 486 MDRO bacteraemia cases identified for MRSA, MRAB, MRPA, CRE, and VRE, at 260, 87, 18, 20, and 101, respectively, their 90-day mortality rates (overall, 40.3%) were 30.4%, 63.2%, 16.7%, 55.0%, and 47.5%, respectively. Their additional medical costs (overall, $27,700) were $15,768, $35,682, $39,908, $72,051, and $33,662 (compared to the no-infection group), respectively. Overall, these five MDRO bacteraemia cases occurred in 7,979 patients, caused 3,280 deaths, and cost $294,505,002 (range, $170,627,020 to $416,094,679) socioeconomic loss.

Conclusions

Tremendous clinical and economic burden occurred with MDRO bacteraemia compared with those of antibiotic-susceptible and no-infection groups. Substantial investment and efforts by related government agencies and medical staffs are needed to urgently prevent the increase, spread and expansion of antibiotic-resistant bacteria.

Introduction

Infectious diseases, particularly nosocomial infections, cause tremendous burden, both in the hospital and in society. The burden of antibiotic-resistant infections, in particular multidrug-resistant organisms (MDROs), is more burdensome than that for susceptible pathogens. Therefore, concerns about the economic burden of MDROs are increasing. In 2019, the Centres for Diseases Control and Prevention estimated that, in the United States, more than 2,800,000 people were affected by antibiotic-resistant infections and 35,900 people consequently died.[1] In Spain, the economic burden of carbapenem-resistant Gram-negative bacteria was estimated at 472 million euros.[2] We previously reported the estimated annual incidence of invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infection at 13,000 cases in 2010 in South Korea.[3] We also evaluated the economic burden of nosocomial MRSA bacteraemia at 60 million dollars yearly, in a nationwide study.[4] However, there is a general lack of studies on the clinical and societal burden of major MDROs.

In South Korea, six MDROs have become nationally-notifiable infectious diseases (NNID) since 2010 with documented prevalence at hospitals through a national sentinel surveillance programme by the Korea Disease Control and Prevention Agency (KDCA). The NNIDs include vancomycin-resistant *S. aureus* (VRSA), methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant Enterococcus (VRE), multidrug-resistant *Pseudomonas aeruginosa* (MRPA), multidrug-resistant *Acinetobacter baumannii* (MRAB), and carbapenem-resistant Enterobacteriaceae (CRE). However, since the KDCA only reported on MDRO incidence when there were blood samples, the severity of the infection and economic burden of MDRO are unknown.[5]

Hence, in this study, we evaluated the clinical outcomes of MDRO infections and estimated the medical costs and socioeconomic burden of MDRO bacteraemia, nationally, in Korea.

Methods

Study design

We prospectively searched for and collected MDRO bacteraemia cases with matched controls from September 2017 to February 2018 using the multistate model of Stewardson et al.[6] Patients were classified into the MDRO (R-group), susceptible organism (S-group), and no (N-group) infection groups. Hospital costs and length of stay (LOS) were compared among the groups.

Setting

The study was performed in 10 secondary or tertiary hospitals selected in South Korea based on the regional distribution of the hospitals (see Supplementary Figure S1).

Participants
We collected bacteraemia cases caused by *S. aureus*, Enterococcus, *A. baumannii*, *P. aeruginosa*, and Enterobacteriaceae. All *S. aureus*, *A. baumannii*, and *P. aeruginosa* bacteraemia cases, regardless of antibiotic susceptibilities. All R-group cases of bacteraemia due to VRE or CRE, selected based on predefined criteria, were collected. The corresponding susceptible or no-infection controls were selected and matched in a 3~5:1 ratio to MDRO cases, based on the following five criteria: similar principal diagnosis at the time of admission, similar major surgery or intervention during the hospitalization, age (± 10 years), sex, and ± 60 days of admission date. For patients that experienced bacterial infection during the same hospital course, the control case was discarded, and another was selected. MDRO bacteraemia cases that developed within 48 h of admission or patients whose duration of admission was over 180 days were excluded from the case-control matching.

Variables

Baseline characteristics, including route of admission, length of hospital stay (LOS), and underlying diseases, were documented, as were data on severity of infection (reported as the sequential organ failure assessment [SOFA] score), portal of bacteraemia, duration of post-bacteraemia hospital stay, and mortality. The hospital costs of each patient were also recorded.

Statistical analyses

**Estimation of additional medical costs related to MRDO bacteraemia**

We estimated the total additional direct medical costs associated with each MDRO bacteraemia, calculated by multiplying the extra cost per patient and the annual number of patients per bacteraemia type, using the KDCA surveillance data.[5] The additional cost per case in the R-group was calculated by subtracting the mean hospital cost of the S-group or N-group from that of the corresponding R-group. The currency exchange rate applied in our calculation was 1,110 Korean won to 1 US dollars.

**Estimation of the number of unexpected mortalities due to MDRO infection, nationwide**

Patients in the R-group were categorised according to age groups with -10 year intervals, to calculate the ratio of patients per age group among the total deaths. The estimated number of deaths due to each type of MDRO bacteraemia nationally was calculated by multiplying the number of MDRO bacteraemia cases in the national surveillance system and the 90-day mortality rate of our data. See web-only Supplementary Tables S1 and S2 for the total number of cases per group.

Using the mortality rate per age group, the estimated total number of deaths in 1 year was calculated per age group. We assumed that the age distribution of patients and the mortality rate obtained from the 10 hospitals and those generated nationwide were similar.

**Estimation of additional socioeconomic costs of MRDO bacteraemia**

The socioeconomic burden included: 1) the cost of caregiving, calculated by multiplying the daily cost of hired caregivers ($59.10 [65,000 Korean won], obtained from the caregiver association and the excess LOS; 2) the productivity loss due to unexpected death, calculated from the number of deaths associated with MDRO bacteraemia and the annual wages reported by the Ministry of Labour in Korea (Labour Statistics of Korea, Ministry of Labour 2017; available from http://wage.go.kr/index.jsp). The productivity loss due to the unexpected death of a given patient was the sum of the annual wages up to the time that patient would have reached 65 years of age, if he or she had not died. The annual discount rate was considered as 5%. Only patients aged < 65 years, the mandatory retirement age for almost all professions, were included in the calculation of productivity loss.

**Sensitivity analyses**

Three different models were built. We set a basic model and two other modified models (each using either the lower or the upper limits of values). In this analysis, we calculated the economic burden by changing the caregiver employment rate, the patient employment rate, and the discount rate. Sensitivity analyses were performed to assess the impact of changing variables.

**Ethical review**

This study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB no. B-1804-463-105) and also the IRBs of each participating hospital. Informed consent was waived by each IRB.

**Results**

**Clinical characteristics**

During the 6-month study period, a total of 547 cases of *S. aureus* (260, 141, 141, 20, and 101 cases of MRSA, *A. baumannii* [MRAB, n=87], *P. aeruginosa* [MRPA, n=18], CRE, and VRE bacteraemia, respectively) occurred in the 10 hospitals. The flows of case and control selection are shown in Figure 1.

The rate of infection acquired while in an intensive care unit was lowest for MRSA (16.5%) and highest for MRAB (58.6%) bacteraemia. Although the median LOS was longest for CRE (53 days) the median post-bacteraemia LOS was longest for MRPA (33 days). The in-hospital mortality rates, highest for CRE (65.0%), were 62.1% and 49.5% for MRAB and VRE bacteraemia, respectively, and lowest for MRPA (16.7%) and MRSA (28.1%) bacteraemia. The 90-day mortality rate was higher in MDRO than in susceptible bacteraemia patients for *S. aureus* and *A. baumannii* infection. Baseline characteristics and
clinical outcomes are shown in Table 1. See web-only Supplementary Tables S1 and S2 for the mortality rates by age groups. Survival curves are shown in Figure 2.

|                      | S. aureus | A. baumannii | P. aeruginosa | Enterobacteriaceae | Enterococcus |
|----------------------|-----------|--------------|---------------|---------------------|--------------|
|                      | MRSA n=260| MSSA n=287    | MRAB n=87     | Non-MDR ABA n=54    | MRPA n=18    |
|                      | p-value   | p-value      | p-value       | p-value             | p-value      |
|                      |           |              |               |                     | N=20         | N=101        |
| Age (years)          | 65.7 (21.2)| 62.0 (21.8)  | 64.9 (18.2)   | 54.1 (18.1)         | 68.8 (14.7)  |
|                      | 40 (12-68) | 4 (2-6)      | 119 (43)      | 0.784               | 67.1 (14.4)  |
|                      |            |              |               |                     | 0.640        |
|                      | 0.640      | 0.628        | 54.1 (18.1)   |                     | 0.640        |
| Sex (male)           | 156 (60.6%)| 165 (57.5%)  | 55 (63.2%)    | 32 (59.3%)          | 11 (61.1%)   |
|                      | 4 (2-6)    | 0.638        |               |                     | 78 (63.4%)   |
|                      |            |              |               |                     | 0.850        |
|                      | 9 (45.0%)  | 57 (56.4%)   |               |                     |              |
| Location             |           |              |               |                     |              |
| Ward                 | 98 (37.7%) | 99 (34.5%)   | 22 (25.3%)    | 32 (59.3%)          | 7 (38.9%)    |
|                      | 0.005      |              | <0.001        |                     | 63 (51.2%)   |
|                      |            |              |               |                     | 0.018        |
|                      |            |              |               |                     | 10 (50.0%)   |
|                      |            |              |               |                     | 65 (64.4%)   |
| Intensive care unit  | 43 (16.5%) | 23 (8.0%)    | 51 (58.6%)    | 9 (16.7%)           | 8 (44.4%)    |
|                      | 0.255      |              |               |                     | 20 (16.3%)   |
|                      |            |              |               |                     | 9 (45.0%)    |
|                      |            |              |               |                     | 27 (26.7%)   |
| Emergency room       | 119 (45.8%)| 164 (57.1%)  | 14 (16.1%)    | 12 (22.2%)          | 3 (16.7%)    |
|                      | 0.393      |              |               |                     | 40 (32.5%)   |
|                      |            |              |               |                     | 1 (5.0%)     |
|                      |            |              |               |                     | 9 (8.9%)     |
| Out-patient clinic   | 0          | 1 (0.3%)     | 0             | 1 (1.9%)            | 0            |
|                      |            |              |               |                     | 0            |
| Length of stay (median, IQR) | 28 (12-51) | 19 (10-35)  | 27 (13-52)    | 19 (9-41)          | 40 (28-90)   |
|                      | 0.001      |              | 0.101         |                     | <0.001       |
|                      |            |              |               |                     | 53 (22-95)   |
|                      |            |              |               |                     | 43 (26-75)   |
| Post bacteraemia LOS (median, IQR) | 17 (7-38)  | 16 (8-29)   | 7 (1-22)      | 11 (7-20)          | 33 (19-61)   |
|                      | 0.255      |              | 0.166         |                     | <0.001       |
|                      |            |              |               |                     | 27 (9-32)    |
|                      |            |              |               |                     | 25 (12-68)   |
| SOFA score (median, IQR) | 4 (1-8)    | 3 (1-6)     | 8 (5-13)      | 3 (1-7)            | 5 (3-8)      |
|                      | 0.003      |              | <0.001        |                     | 4 (2-6)      |
|                      |            |              |               |                     | 0.408        |
|                      |            |              |               |                     | 7 (4-13)     |
|                      |            |              |               |                     | 4 (2-6)      |
| Mortality            |           |              |               |                     |              |
| In hospital          | 73 (28.1%) | 57 (19.9%)   | 54 (62.1%)    | 13 (24.1%)          | 3 (16.7%)    |
|                      | 0.024      |              | <0.001        |                     | 32 (26.0%)   |
|                      |            |              |               |                     | 0.391        |
|                      |            |              |               |                     | 13 (65.0%)   |
|                      |            |              |               |                     | 50 (49.5%)   |
| 7 days               | 30 (11.5%) | 26 (9.1%)    | 40 (46.0%)    | 9 (16.7%)           | 1 (5.6%)     |
|                      | 0.628      |              | 0.001         |                     | 19 (15.4%)   |
|                      |            |              |               |                     | 0.369        |
|                      |            |              |               |                     | 5 (25.0%)    |
|                      |            |              |               |                     | 18 (17.9%)   |
| 30 days              | 68 (26.2%) | 52 (18.1%)   | 49 (56.3%)    | 12 (22.2%)          | 1 (5.6%)     |
|                      | 0.023      |              | <0.001        |                     | 29 (23.6%)   |
|                      |            |              |               |                     | 0.069        |
|                      |            |              |               |                     | 9 (45.0%)    |
|                      |            |              |               |                     | 40 (39.6%)   |
| 90 days              | 79 (30.4%) | 57 (19.9%)   | 55 (63.2%)    | 13 (24.1%)          | 3 (16.7%)    |
|                      | 0.017      |              | <0.001        |                     | 40 (32.5%)   |
|                      |            |              |               |                     | 0.368        |
|                      |            |              |               |                     | 11 (55.0%)   |
|                      |            |              |               |                     | 48 (47.5%)   |

Note. MRSA; methicillin resistant S. aureus; MSSA; methicillin susceptible S. aureus; MRAB; multidrug resistant A. baumannii; MDR; multidrug resistant, ABA; A. baumannii, MRPA; multidrug resistant P. aeruginosa, PAE; P. aeruginosa, CRE; carbapenem resistant Enterobacteriaceae, VRE; vancomycin resistant Enterococcus, LOS; length of stay, SOFA; Sequential Organ Failure Assessment

Additional hospital costs and LOS, MDRO versus infection with susceptible organisms

As shown in Table 2, the mean LOS difference was 1.0 day between the R-group and S-group, and the mean difference in hospital cost was $1,089 for S. aureus bacteraemia; these were longest and highest in the R-group for Enterobacteriaceae, respectively. Compared to the S-group, R-group cases caused 2.3 additional days of hospital stay and $7,507 additional hospital costs for A. baumannii bacteraemia.
Table 2
Differences in costs and lengths of hospital stay between patients with multidrug-resistant and corresponding susceptible organisms’ bacteraemia

| Organisms | S. aureus | A. baumannii | P. aeruginosa | Enterobacteriaceae | Enterococcus |
|-----------|-----------|--------------|---------------|-------------------|-------------|
| Group     | MRSA      | MSSA         | MRAB          | Non-MDR ABA       | MRPA        | Non-MDR PAE | CRE         | Susceptible Enterobacteriaceae | VRE | Susceptible Enterococcus |
|           | (n=163)   | (n=163)      | (n=27)        | (n=27)            | (n=13)      | (n=13)      | (n=13)      | (n=27)                                | (n=72) | (n=27)                     |
| LOS (d)   | 29.8 (± 30.2) | 28.8 (± 31.1) | 30.2 (± 29.1) | 27.9 (± 24.0)     | 41.6 (± 20.9) | 27.3 (± 28.6) | 55.4 (± 43.8) | 21.3 (± 14.0)                          | 48.2 (± 35.1) | 41.3 (± 29.3)               |
| LOS difference (d) | 1.0 (± 38.1) | 2.3 (± 26.8) | 14.3 (± 28.1) | 34.1 (± 48.2)     | 6.8 (± 47.9) | 33,365            |
| Hospital cost ($) | 16,386 (± 17,320) | 15,297 (± 24,918) | 24,452 (± 24,918) | 16,946 (± 16,515) | 26,168 (± 14,944) | 17,447 (± 14,320) | 73,248 (± 63,761) | 14,998 (± 15,053)          | 47,779 (± 47,430) | 35,850 (± 35,900)           |
| Hospital cost difference ($) | 1,089 (± 23,240) | 7,507 (± 16,110) | 8,721 (± 16,304) | 58,250 (± 68,426) | 144,144 (± 57,934) |

Note. MRSA; methicillin resistant S. aureus, MSSA; methicillin susceptible S. aureus, MRAB; multidrug resistant A. baumannii, MDR; multidrug resistant, ABA; A. baumannii, MRPA; multidrug resistant P. aeruginosa, PAE; P. aeruginosa, CRE; carbapenem resistant Enterobacteriaceae, VRE; vancomycin resistant Enterococcus, LOS; length of stay

Additional Hospital Costs And Los, Mdro Versus No Infection

As shown in Table 3, the mean LOS difference between the R-group and N-group was 24 days, and the mean difference in hospital cost was $15,768 for S. aureus bacteraemia; these were longest and highest in the R-group for Enterobacteriaceae, respectively. Compared to the N-group, the R-group was associated with 24 additional days of hospital stay and $35,682 additional hospital costs for A. baumannii bacteraemia.

Table 3
Differences in costs and length of hospital stay differences between patients with multidrug resistant organisms’ bacteraemia and no infection

| Organisms | S. aureus | A. baumannii | P. aeruginosa | Enterobacteriaceae | Enterococcus |
|-----------|-----------|--------------|---------------|-------------------|-------------|
| Group     | MRSA      | Non-infection control (n=113) | MRAB | Non-infection control (n=56) | MRPA | Non-infection control (n=5) | CRE | Non-infection control (n=9) | VRE | Non-infection control (n=74) |
| LOS (d)   | 43.1 (± 34.7) | 18.9 (± 14.7) | 39.3 (± 35.9) | 15.3 (± 16.6) | 56.2 (± 29.1) | 14.4 (± 5.7) | 69.6 (± 44.5) | 19.0 (± 14.2) | 46.4 (± 34.2) | 18.8 (± 14.7) |
| LOS difference (d) | 24.2 (± 33.8) | 24.4 (± 38.1) | 41.8 (± 30.9) | 50.5 (± 41.9) | 50.5 (± 41.9) | 50.5 (± 41.9) | 50.5 (± 41.9) | 50.5 (± 41.9) | 50.5 (± 41.9) | 50.5 (± 41.9) |
| Hospital cost ($) | 26,508 (± 29,197) | 10,740 (± 10,017) | 46,178 (± 9,788) | 10,570 (± 9,788) | 49,335 (± 45,871) | 9,426 (± 4,689) | 86,082 (± 62,469) | 14,031 (± 12,571) | 45,334 (± 45,809) | 11,616 (± 11,670) |
| Hospital cost difference ($) | 15,768 (± 27,877) | 35,682 (± 35,082) | 39,908 (± 41,840) | 72,051 (± 58,489) | 33,662 (± 42,144) |

Note. MRSA; methicillin resistant S. aureus, MRAB; multidrug resistant A. baumannii, MDR; multidrug resistant, ABA; A. baumannii, MRPA; multidrug resistant P. aeruginosa, PAE; P. aeruginosa, CRE; carbapenem resistant Enterobacteriaceae, VRE; vancomycin resistant Enterococcus, LOS; length of stay

Cost of caregiver and productivity loss due to unexpected death

The additional cost of caregiving in the R-group due to extended LOS compared to the N-group was $1,405 for S. aureus and A. baumannii; $2,401 for P. aeruginosa; $2,928 for Enterobacteriaceae, and $1,581 for Enterococcus bacteraemia.

The estimated number of deaths that occurred nationwide was 3,280 cases, which included 1,237, 882, 36, 254, and 871 for MRSA, MRAB, MRPA, CRE, and VRE bacteraemia, respectively. See web-only Supplementary Tables S1 and S2 for the estimated number of deaths per age group. The estimated productivity loss due to unexpected death was $14,811,599; $22,613,346; $1,121,030; $11,284,929; and $14,579,883 for MRSA, MRAB, MRPA, CRE, and VRE bacteraemia, respectively.

Total Burden Of Mdro Infection And Sensitivity Analyses
The total socioeconomic burden of MDRO infection, estimated as the total additional medical cost, cost of hiring a caregiver, and the sum of productivity loss due to unexpected death, was $294,505,002 (Table 4). In sensitivity analyses, in the standard model (Model 1), the economic burden was $81,847,359; $73,406,391; $10,082,672; $45,175,327; and $77,765,842 for MRSA, MRAB, MRPA, CRE, and VRE bacteraemia, respectively, with a total burden of MDRO bacteraemia of $288,277,591. The total burden of MDRO bacteraemia ranged from $170,627,020 to $416,094,679. The economic burden on both ends of the limit is shown in Table 5.

Table 4
Results of socioeconomic burden estimation of five multidrug-resistant organisms’ bacteraemia

| Values                                      | MRSA   | MRAB   | MRPA   | CRE   | VRE   |
|---------------------------------------------|--------|--------|--------|-------|-------|
| Number of cases in 2017 (N)                 | 4,070  | 1,396  | 218    | 461   | 1,834 |
| Hospital cost differences (C) ($)           | 15,768 | 35,682 | 39,908 | 72,051| 33,662|
| LOS differences (L) (d)                     | 24     | 24     | 41     | 50    | 27    |
| 90 days mortality rate                      | 30.4%  | 63.2%  | 16.7%  | 55.0% | 47.5% |
| Total hospital cost (NXC) ($)               | 64,175,760 | 49,812,072 | 8,699,944 | 33,215,511 | 61,736,108 |
| Excess Cost of caregiver use* ($) (L X 65,000/1110) | 1405.4 | 1405.4 | 2400.9 | 2927.9 | 1581.1 |
| Total cost of excess caregiver use ($) (LX65000/1110XN) | 5,720,000 | 1,961,946 | 523,396 | 1,349,775 | 2,899,703 |
| Estimated Number of deaths in 1 year        | 1,237  | 882    | 36     | 254   | 871   |
| Productivity loss due to mortality* ($)     | 14,811,599 | 22,613,346 | 1,121,030 | 11,284,929 | 14,579,883 |
| Total socioeconomic burden ($)              | 84,707,359 | 74,387,364 | 10,344,370 | 45,850,215 | 79,215,694 |

Sum of the socioeconomic burden of MDROs ($) 294,505,002

Note. MRSA; methicillin resistant *S. aureus*, MRAB; multidrug resistant *A. baumannii*, MRPA; multidrug resistant *P. aeruginosa*, CRE; carbapenem resistant Enterobacteriaceae, VRE; vancomycin resistant Enterococcus

* caregiver hire rate: 100%
* annual discount rate: 5%, employment rate of patients 25%
Discussion

Few studies have estimated the burden of infections due to MDROs at the national level. In this study, we estimated the nationwide disease burden of bacteraemia caused by major MDROs, taking into consideration the direct medical cost and socioeconomic burden. MDRO bacteraemia caused additional medical costs of up to $15,768–$72,051 per patient compared to the control group, and $1,089–$58,250 compared to the group with infections due to susceptible organisms of the same bacterial species. In addition, the total economic burden of MDRO bacteraemia was $294,505,002; with an estimated 3,280(1.1%) of 285,534 deaths in South Korea in 2017.[7]

Few studies have estimated the burden of infectious diseases caused by antibiotic-resistant bacteria. Our group previously estimated the burden of nosocomial S. aureus bacteraemia, and reported that 2,946 nosocomial MRSA bacteraemia occurred in 2011, amounting to $60,375,506.[4] Laura et al.[8] reported that nosocomial VRE infections resulted in significantly higher costs than vancomycin-sensitive enterococci (VSE) infections ($37,971 vs $23,025, respectively). In addition, the attributable cost per case of VRE was €13,157 and the mortality rate of patients with VRE infection was expected to increase to 33.3%. According to Chea et al., each case of VRE bacteraemia resulted in an additional medical cost of 28,872 Australian dollars and an increase of 72,051 per patient compared to the control group, and

Previous studies on the nationwide burden of disease have mainly focused on chronic diseases such as chronic obstructive pulmonary disease,[15] diabetes mellitus,[16, 17] and dementia.[18] These studies assessed the changes in quality of life due to diseases. On the contrary, our study focused on acute diseases that are associated with higher mortality and morbidity during relatively short-term follow up periods. In our study, the 90-day disease mortality rates were between 16.7% and > 60%. Therefore, when estimating the economic burden, we focused on the LOS and unexpected mortality, rather than the long-term change in quality of life. Infections with MDRO are mostly nosocomial. Therefore, consumption of additional medical resources, prolonged hospital stays, and deaths are unexpected, unpredictable, and unfavorable, but in many cases are preventable with proper investment of resources.

Table 5
Sensitivity analyses for socioeconomic burden estimation of five multidrug-resistant organisms’ bacteraemia

| Values                                                                 | MRSA     | MRAB     | MRPA     | CRE       | VRE       |
|-----------------------------------------------------------------------|----------|----------|----------|-----------|-----------|
| Model 1; Standard model. Hire of caregiver: 50%, annual discount rate 5%, employment rate of patients 25% |          |          |          |           |           |
| Mean hospital cost differences ($)                                     | 15,768   | 35,682   | 39,908   | 72,051    | 33,662    |
| Total additional hospital cost ($)                                     | 64,175,760| 49,812,072| 8,699,944| 33,215,511| 61,736,108|
| Total cost of excess caregiver use ($)                                 | 2,860,000| 980,973  | 261,698  | 674,887   | 1,449,851 |
| Productivity loss due to mortality ($)                                 | 14,811,599| 22,613,346| 1,121,030| 11,284,929| 14,579,883|
| Total socioeconomic burden ($)                                         | 81,847,359| 73,406,391| 10,082,672| 45,175,327| 77,765,842|

Model 2; lower end model. Hire of caregiver: 25%, annual discount rate 7%, employment rate of patients 15%

| Values                                                                 | MRSA     | MRAB     | MRPA     | CRE       | VRE       |
|-----------------------------------------------------------------------|----------|----------|----------|-----------|-----------|
| 95% lower limit of mean hospital cost differences (C) ($)              | 10,572   | 26,287   | -12,043  | 27,093    | 23,898    |
| Total additional hospital cost ($)                                     | 43,028,040| 36,696,652| -2,625,374| 12,489,873| 43,828,932|
| Total cost of excess caregiver use ($)                                 | 1,430,000| 490,486  | 130,849  | 337,443   | 724,926   |
| Productivity loss due to mortality ($)                                 | 7,989,640| 11,942,500| 556,942  | 5,845,378 | 7,760,733 |
| Total socioeconomic burden ($)                                         | 52,447,680| 49,129,638| -1,937,583| 18,672,694| 52,314,591|

Model 3; upper end model. Hire of caregiver: 75%, annual discount rate 3%, employment rate of patients 35%

| Values                                                                 | MRSA     | MRAB     | MRPA     | CRE       | VRE       |
|-----------------------------------------------------------------------|----------|----------|----------|-----------|-----------|
| 95% upper limit of mean hospital cost differences (C) ($)              | 20,964   | 45,077   | 91,860   | 117,010   | 43,426    |
| Total additional hospital cost ($)                                     | 85,323,480| 62,927,492| 20,025,480| 53,941,610| 79,643,284|
| Total cost of excess caregiver use ($)                                 | 4,290,000| 1,471,459| 392,547  | 1,012,331 | 2,174,777 |
| Productivity loss due to mortality ($)                                 | 23,399,641| 37,080,110| 1,947,344| 23,745,907| 18,719,216|
| Total socioeconomic burden ($)                                         | 113,013,121| 101,479,061| 22,365,371| 78,699,848| 100,537,277|

Note. MRSA; methicillin resistant S. aureus, MRAB; multidrug resistant A. baumannii, MRPA; multidrug resistant P. aeruginosa, CRE; carbapenem resistant Enterobacteriaceae, VRE; vancomycin resistant Enterococcus
We estimated nationwide trends based on data from 10 sample hospitals. This naturally led to uncertainty in the results. In South Korea, the status of major MDRO infections has been documented via a national surveillance program since 2010. Hence, we attempted to reduce estimation errors by using a national data. We used data from 10 study hospitals to assess the differences in medical expenses between patients and controls, in the LOS, and mortality rates by age; and subsequently, estimated the nationwide impact based on national surveillance data. Sensitivity analyses were also conducted to improve our results.

This study had some limitations. First, some medical costs, such as productivity loss due to the extension of the hospitalization period, loss of work ability, and others factors such as social burden due to deterioration of quality of life from illnesses, were not considered in the analyses. Although these are important components of indirect medical costs, it is difficult to calculate these costs with only the additional information obtained through socioeconomic status and patient questionnaires. In addition, in patients with acute infections, these indirect medical expenses accounted for a relatively small portion of the total expenses. Second, we used a multistate model with a case-case-control design. We selected control with susceptible organism infection and those without infection but with similar major clinical factors of MDRO infection cases, to calculate the differences in the LOS and cost, between the two groups. However, in the process of selecting possible similar control groups of patients, some patients were not selected in the control groups and were excluded from analyses.

Conclusions

In conclusion, five types of MDRO bacteraemia infected 7,979 patients, with 3,280 deaths, and caused $294,505,002 of socioeconomic burden, ranging from $170,627,020 to $416,094,679 dollars. Proper investigation and investment of infection control measures should be introduced to immediately decrease the burden of MDRO infections.

Abbreviations

MDROs: Multidrug-resistant organisms; MRSA: methicillin-resistant Staphylococcus aureus; VRE: vancomycin-resistant enterococci; MRAB: multidrug resistant Acinetobacter baumannii; MRPA: multidrug resistant Pseudomonas aeruginosa; CRE: carbapenem-resistant Enterobacteriaceae; NNID: nationally-notifiable infectious diseases; KDCA: Korea Disease Control and Prevention Agency; VRSA: vancomycin-resistant S. aureus; LOS: length of stay; SOFA: sequential organ failure assessment; IRB: Institutional Review Board; VSE: vancomycin-sensitive enterococci

Declarations

Ethics approval

This study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB no. B-1804-463-105) and also the IRBs of each participating hospital. Informed consent was waived by each IRB.

Consent for publication

Not applicable

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

This work was supported by the Research Program funded by the Korea Disease Control and Prevention Agency (2017E280301).

Author's Contributions

KHS, JA, HBK formulated the research question, NKC Conceived and designed the analysis JA directed the study’s methodological implementation and helped revise the manuscript, CJK, PGC, WBP, NJK, HJC, JYB, ESK, JS, SSL, KHP, SIJ, YSK, JHB, SL, YMK, YGK collected the data, CJK, NKC performed analysis, CJK,KHS conducted the data analysis and drafted the manuscript, all authors critically revised the manuscript, and approved the final version of the manuscript

Acknowledgement

none

References
1. Centers for Diseases control and prevention: Antibiotic Resistance Threats in the United States. Atlanta, GA: U.S. Department of Health and Human Services; 2019.

2. Canton R, Huarte R, Morata L, Trillo-Mata JL, Munoz R, Gonzalez J, Tort M, Badia X: Determining the burden of infectious diseases caused by carbapenem-resistant gram-negative bacteria in Spain. Enferm Infecc Microbiol Clin (Engl Ed). 2021;39(4):179–83.

3. Song KH, Kim ES, Sin HY, Park KH, Jung SI, Yoon N, Kim DM, Lee CS, Jang HC, Park Y et al: Characteristics of invasive Staphylococcus aureus infections in three regions of Korea, 2009–2011: a multi-center cohort study. BMC Infect Dis. 2013;13:581.

4. Kim C-J, Kim H-B, Oh M-d, Kim Y, Kim A, Oh S-H, Song K-H, Kim ES, Cho YK, Choi YH: The burden of nosocomial staphylococcus aureus bloodstream infection in South Korea: a prospective hospital-based nationwide study. BMC Infect Dis. 2014;14(1):590.

5. Healthcare associated infection surveillance data, Infectious Disease Portal, Korea Diseases Control and Prevention Agency [http://www.kdca.go.kr/npt/biz/npp/iss/haistatisticsMain.do]

6. Stewardson AJ, Allignol A, Beyersmann J, Graves N, Schumacher M, Meyer R, Tacconelli E, De Angelis G, Farina C, Pezzoli F: The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible Enterobacteriaceae and Staphylococcus aureus in European hospitals, 2010 and 2011: a multicentre retrospective cohort study. Euro Surveill. 2016;21(33).

7. Puchter L, Chaberny IF, Schwab F, Vonberg R-P, Bange F-C, Ebadi E: Economic burden of nosocomial infections caused by vancomycin-resistant enterococci. Antimicrob Infect Control. 2018;7(1):1.

8. Cheah A, Spelman T, Liew D, Peel T, Howden B, Spelman D, Grayson M, Nation R, Kong D: Enterococcal bacteraemia: factors influencing mortality, length of stay and costs of hospitalization. Clin Microbiol Infect. 2013;19(4):E181-9.

9. Kramer TS, Remschmidt C, Werner S, Behnke M, Schwab F, Werner G, Gastmeier P, Leistner R: The importance of adjusting for enterococcus species when assessing the burden of vancomycin resistance: a cohort study including over 1000 cases of enterococcal bloodstream infections. Antimicrob Resist Infect Control. 2018;7(1):133.

10. Vargas-Alzate CA, Higueta-Gutiérrez LF, López-López L, Cienfuegos-Gallet AV: Quínceno JUN: High excess costs of infections caused by carbapenem-resistant Gram-negative bacilli in an endemic region. Int J Antimicrob Agents. 2018;51(4):601–7.

11. Bartsch S, McKinnell J, Mueller L, Miller L, Gohil S, Huang S, Lee B: Potential economic burden of carbapenem-resistant Enterobacteriaceae (CRE) in the United States. Clin Microbiol Infect. 2017;23(1):48. E48-e9.

12. Lee NY, Lee HC, Ko NY, Chang CM, Shih H-I, Wu CJ, Ko WC: Clinical and economic impact of multidrug resistance in nosocomial Acinetobacter baumannii bacteremia. Infect Control Hosp Epidemiol. 2007;28(6):713–9.

13. You JH, Choi K-w, Wong Ty, Ip M, Ming W-k, Wong Ry-k, Chan S-n, Tse H-t, Chau CT, Lee NL: Disease burden, characteristics, and outcomes of methicillin-resistant Staphylococcus aureus bloodstream infection in Hong Kong. Asia Pac J Public Health. 2017;29(5):451–61.

14. Pauwels RA, RabeKF: Burden and clinical features of chronic obstructive pulmonary disease (COPD). Lancet. 2004;364(9434):613–20.

15. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J: The global burden of diabetic foot disease. Lancet. 2005;366(9498):1719–24.

16. Engelgau MM, Geiss LS, Saadine JB, Boyle JP, Benjamin SM, Gregg EW, Tierney EF, Rios-Burrows N, Mokdad AH, Ford ES: The evolving diabetes burden in the United States. Ann Intern Med. 2004;140(11):945–50.

17. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM: Forecasting the global burden of Alzheimer's disease. Alzheimers Dement. 2007; 3(3):186–91.

18. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM: Forecasting the global burden of Alzheimer’s disease. Alzheimers Dement. 2007; 3(3):186-91.

Figures

MDRO: multidrug-resistant organisms; MRSA: methicillin-resistant S. aureus; MSSA: methicillin-susceptible S. aureus; LOS: lengths of stay; MRAB: multidrug-resistant A. baumannii; ABA: A. baumannii; MRPA: multidrug-resistant P. aeruginosa; PAE: P. aeruginosa; CRE: carbapenem-resistant

Figure 1

Flow of case and control (one with susceptible organism infection and one with no infection) selection for each type of bacteraemia.

MDRO: multidrug-resistant organisms; MRSA: methicillin-resistant S. aureus; MSSA: methicillin-susceptible S. aureus; LOS: lengths of stay; MRAB: multidrug-resistant A. baumannii; ABA: A. baumannii; MRPA: multidrug-resistant P. aeruginosa; PAE: P. aeruginosa; CRE: carbapenem-resistant
**Enterobacteriaceae; VRE: vancomycin-resistant Enterococcus**

**Figure 2**

Survival curve of each multidrug-resistant organism bacteremia.

MDR: multidrug-resistant; MRSA: methicillin-resistant *S. aureus*; MRAB: multidrug-resistant *A. baumannii*; MRPA: multidrug-resistant *P. aeruginosa*; CRE: carbapenem-resistant Enterobacteriaceae; VRE: vancomycin-resistant Enterococcus

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- 04BacteremiaMDROsuppletetable210821.docx
- renameddb704.tif