Epidemiology of Infections Caused by Multidrug-Resistant Gram-Negative Bacteria in Adult Hospitalized Patients at Siriraj Hospital

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Objective: *To investigate the clinical characteristics, risk factors, outcomes, antibiotic treatment and complications of hospitalized patients infected with multi-drug resistant (MDR) gram-negative bacteria in Siriraj Hospital.*
Material and Method: *A cross sectional study was performed in all hospitalized patients at Siriraj Hospital who had positive culture for Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter baumannii during February to May 2012. Clinical characteristics, risk factors and outcomes of MDR gram-negative bacteria were analyzed.*
Results: *The prevalence of overall MDR gram-negative bacteria was 48.8%. The percentage of MDR organism was 37.8% for Extended Spectrum Beta Lactamase (ESBL)-producing Enterobactericeae, 39.3% for carbapenem-resistant P. aeruginosa and 88.7% for MDR A. baumannii. Infections caused by MDR organisms were associated with admission to medical wards, respiratory tract origin and hospital onset of infection. The significant risk factor of overall MDR organism infection was previous antibiotic use within 1 year (adjusted odd ratio 6.818, 95% CI = 1.337- 34.770). Rate of inappropriate antibiotic use was 56.7% for initial empirical regimen and under treatment was significantly higher in MDR group. The 30-day and 90-day survival rates of MDR group were significant lower than non-MDR group (58.8% vs. 75.0%, p = 0.013 at 30th day and 43% vs. 63%, p = 0.012 at 90th day). Antibiotic associated adverse effect found 42.9% in MDR group and 20.0% in non-MDR group (p<0.001).*
Conclusion: *The strongest risk factor for acquiring MDR gram-negative infection was previous antibiotic use. Inadequate empirical antimicrobial treatment was common in patients infected with MDR pathogens, resulting in unfavorable outcome and mortality.*

Keywords: *Multi-drug resistant, Drug resistance, Gram-negative bacteria, Epidemiology*

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The prevalence of multidrug resistant (MDR) bacterial infection is increasing worldwide and associated with high morbidity and mortality, prolonged hospitalization and increased healthcare cost[1-4]. Among gram-negative resistant bacteria, Extended Spectrum Beta Lactamase (ESBL)-producing Enterobacteriaceae, carbapenem-resistant *Pseudomonas aeruginosa* and MDR *Acinetobacter baumannii* are great burden pathogens, frequently related to a high selective pressure of broad spectrum antimicrobial agents, such as extended-spectrum cephalosporins, β-lactam/β-lactamase inhibitor (BLBI), carbapenems and fluoroquinolones[2,5,6]. In 2006, the prevalence of nosocomial infection (NI) in Thailand was 6.5%, with highest prevalence in university hospitals (7.6%) and gram-negative bacteria were responsible for 70.2% of all pathogens. *P. aeruginosa*, *Klebsiella spp.*, and *A. baumannii* were the leading culprit isolates[7].

Antimicrobial stewardship programs (ASPs) are an effective strategy to reduce antimicrobial resistance, which would result in reduction of cost and duration of hospital stay[8-10]. A crucial problem for

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ASPs is overuse of antibiotics, especially in empirical treatment period. In general, primary physicians prescribe broad-spectrum antibiotics for empirical treatment of nosocomial pneumonia based on the healthcare associated pneumonia (HCAP) guideline[11]. However, some studies showed that the current HCAP guideline provides a poor predictor for resistant pathogens, and overtreatment was more common in HCAP patients. Therefore, individual risk stratification approaches should be considered[12-14]. Epidemiological data of healthcare associated infection in each hospital setting is useful for antibiotics selection.

The present study selected the patients based on modified CDC/NHSN surveillance definition of health care-associated infection (HAI)[15] to investigate the epidemiology of infections caused by three gram-negative bacteria, which were Enterobacteriaceae, *P. aeruginosa* and *A. baumannii*, and compared the characteristics, risk factors and outcomes between drug resistant and non-drug resistant organisms.

Material and Method

A cross sectional study was performed by analysis of all clinical specimens which were culture positive for Enterobacteriaceae, *P. aeruginosa* and *A. baumannii* at Siriraj Hospital, Bangkok, Thailand, during a 4 months period, from February to May 2012. Data of positive clinical specimens were retrieved from the Department of Microbiology. Eligible cases included 1) age $\geq$15 years, 2) fulfilled with CDC/NHSN surveillance definition that suggestive of true infection and 3) having adequate clinical data for analysis (available data in medical record and further necessary data). Exclusion criteria included patients who had contaminated clinical specimens or colonization.

Criteria of infection and MDR organisms

The diagnostic criteria for infections were modified from the CDC/NHSN surveillance definition of healthcare-associated infection. The definition of MDR organism is the bacteria resistant to carbapenems, fluoroquinolones and aminoglycosides at least one agent in each class.

Inappropriateness of antibiotic treatment

Inappropriateness of antibiotics treatment divided to 3 categories, overtreatment, undertreatment and inappropriate dose. Overtreatment means using antibiotic broader than necessary (*e.g.* use carbapenem for ESBL-negative Enterobacteriaceae). Under treatment means giving antibiotics which not covered the organism (e.g. ceftriaxone for ESBL-producing Enterobacteriaceae). Inappropriate dose was decided depend on creatinine clearance based standard dose.

Outcomes and complication

Cure of infection was referred to heal completely of symptoms and signs of infection without ongoing antibiotic course. Infection improved means subsidence of symptoms and signs of infection, but not completely heals or currently received the antibiotics. Antibiotic-associated diarrhea was referred to as diarrhea following antibiotic treatment with or without *Clostridium difficile* assay confirmation, but already excluded other possible causes. Antibiotic-associated adverse effect means allergy or side effects from receiving antibiotics (e.g. gastrointestinal disturbance, nephrotoxicity, hematological problem, drug fever).

The sample size was calculated by prevalence estimation as follows: ESBL-producing Enterobacteriaceae 50%, MDR *P. aeruginosa* 20%, and MDR *A. baumannii* 70%. The acceptable type II error was 10% and type I error was 5%. Therefore, the estimated sample sizes were 97 episodes of Enterobacteriaceae infection, 62 episodes of *P. aeruginosa* infection and 81 episodes of *A. baumannii* infection. The medical records of enrolled patients were systematically reviewed by an investigator. The following features were analyzed: demographic data, infection characteristics, suspected risk factor for MDR organism, microbiological testing, antimicrobial administration, outcomes and complications. The study was approved by Siriraj Institutional Review Board (SIRB).

Statistical analysis

All statistical analyses were performed using PASW statistics 18.0. For univariate analyses, qualitative variables or relative frequencies were reported with amount of patient and percentage, whereas quantitative variables were reported with means, standard deviation, minimum and maximum. The p-values were calculated by Chi-square for normal distributive discrete data, Fisher's exact test for non-normal distributive discrete data, student t-test for normal distributive continuous data, and Man-Whitney U test for non-normal distributive continuous data. A p-value below 0.05 was considered statistically significant. For any significant risk factor variables from univariate analysis with p-value below 0.2, multivariate analysis was performed using logistic regression analysis for crude odds ratio and linear regression

analysis for adjusted odds ratio; and 95% confidence interval were calculated for all odds ratio.

Results

During the study period, a total of 215 episodes of infection were documented in 192 patients. Demographic and clinical characteristic of 192 included patients were compared in Table 1. Patients admitted to medicine wards were more likely to be infected with MDR organisms than non-MDR organisms (67.7% vs. 53.1%, p = 0.039). Approximately 88% of 186 patients had one or more underlying diseases. Heart diseases, lung diseases, malignancy and diabetes comprised about one-third of the underlying disease, whereas kidney disease and immunosuppressive drug use comprised about one-fifth. However, there was no statistically significant difference between non-MDR and MDR populations.

A total of 215 (29.7%) episodes of infection from 724 culture-positive specimens were enrolled, which involved 192 patients who had qualified by complete eligible criteria. Table 2 demonstrates the proportion of MDR organisms shown as total episodes and specified species. Overall, MDR organism shared 49% of total infection episodes. ESBL-producing strains were found 37.3% of all Enterobacteriaceae. For *P. aeruginosa* infection, there were 18% MDR and 39.3% carbapenem-resistant strains. MDR *A. baumannii* was taking part in 89% of all strains. Frequency of isolated organisms, site of infection, concomitant infection, empirical treatment and onset of infection are demonstrated in Table 3. There were differences between the non-MDR and MDR group in patients with respiratory tract infection (41.8% vs. 61%, p = 0.005), wound infection (14.5% vs. 3.8%, p = 0.007) and hospital onset of infection (60.0% vs. 82.9%, p<0.001).

Risk factors associated with MDR organism infection

The univariate analysis of potential risk factors is shown in Table 4. Admission to a private hospital was a protective factor (80% vs. 31.6%, p = 0.005) and previous antibiotics use within 1 year was a risk factor for MDR bacterial infection (73.7% vs. 92.1%, p<0.001). Other factors such as ongoing hemodialysis, previous OPD visit, previous admission and duration from the last discharge were not statistically significant.

Factors with a p-value less than 0.2 were subject to multivariate analyses as shown in Table 5. Last previous admission to a private hospital had too

Table 1. Demographic and clinical characteristics of 192 hospitalized patients who were infected with gram-negative bacteria (Enterobacteriaceae, *P. aeruginosa*, *A. baumannii*)

Patient characteristics	Total (n = 192)	Non-MDR bacterial infection (n = 96)	MDR bacterial infection (n = 96)	p-value
Age (mean ± SD, years)	63.20±19.6	63.61±19.8	62.78±19.6	0.769
Gender, n (%)				0.559
Male	110 (57.3)	57 (59.4)	53 (55.2)	
Female	82 (42.7)	39 (40.6)	43 (44.8)	
Department, n (%)				
Medicine	116 (60.4)	51 (53.1)	65 (67.7)	0.039
Surgery	43 (22.4)	22 (22.9)	21 (21.9)	0.863
Orthopedics	15 (7.8)	11 (11.5)	4 (4.2)	0.060
OB/GYN	5 (2.6)	3 (3.1)	2 (2.1)	0.650
Eye/ENT	8 (4.2)	7 (7.3)	1 (1.0)	0.065
Radiology	4 (2.1)	1 (1.0)	3 (3.1)	0.311
Others	1 (0.5)	1 (1.0)	0 (0)	-
Underlying disease, n= 186 (%)	166 (88.2)	80 (87.0)	86 (90.5)	0.440
Heart	60 (32.3)	33 (36.3)	27 (28.4)	0.253
Lung	42 (22.6)	22 (24.2)	20 (21.1)	0.611
Malignancy	62 (33.3)	30 (33.0)	32 (33.7)	0.917
Diabetes mellitus	55 (29.6)	30 (33.0)	25 (26.3)	0.320
Liver	19 (10.2)	7 (7.7)	12 (12.6)	0.266
HIV infection	2 (1.1)	2 (2.2)	0 (0)	0.238
Kidney	44 (23.8)	20 (22.2)	24 (25.3)	0.627
Immunosuppressive drug use	36 (20.3)	16 (18.4)	20 (22.2)	0.527

Table 2. Organism of interest by episode of infection

Organism of interest	Total (n = 215)	Non-MDR bacterial infection (n = 110)	MDR bacterial infection (n = 105)
All organism, n(%)	215	105 (49)	110 (51)
Enterobacteriaceae, n(%)	83	52 (63)	31 (37)
Escherichia coli	31	11	20
Klebsiella pneumoniae	31	21	10
Klebsiella oxytoca	1	1	0
Enterobacter cloacae	7	6	1
Enterobacter koseri	2	2	0
Proteus mirabilis	6	6	0
Citrobacter freundii	2	2	0
Others	3	3	0
Carbapenem resistant *P. aeruginosa,* n (%)	61	37 (61)	24 (39)
MDR *P. aeruginosa,* n (%)		51 (82)	11 (18)
A. baumannii, n (%)	71	8 (11)	63 (89)

Table 3. Characteristic of 215 episodes of infection and antimicrobial administration

Characteristics	Total (n = 215)	Non-MDR bacterial infection (n = 110)	MDR bacterial infection (n = 105)	p-value
Site of infection, n (%)				
Respiratory tract	110 (51.2)	46 (41.8)	64 (61.0)	0.005
Genitourinary tract	37 (17.2)	16 (14.5)	21 (20.0)	0.290
Wound & soft tissue	20 (9.3)	16 (14.5)	4 (3.8)	0.007
CRBSI	1 (0.5)	1 (0.9)	0 (0)	1.000
Intra-abdominal	10 (4.7)	6 (5.5)	4 (3.8)	0.749
Endocarditis	1 (0.5)	1 (0.9)	0 (0)	1.000
Central nervous system	1 (0.5)	1 (0.9)	0 (0)	1.000
Bone & joint	9 (4.2)	7 (6.4)	2 (1.9)	0.172
Primary bacteremia	11 (5.1)	7 (6.4)	4 (3.8)	0.936
Multiple site	12 (5.6)	6 (5.5)	6 (5.7)	0.934
Others	3 (1.4)	3 (2.7)	0 (0)	0.247
Concomitant infection, n (%)	74 (34.4)	42 (38.2)	32 (30.5)	0.235
Empirical treatment, n (%)	197 (91.6)	102 (92.7)	95 (90.5)	0.551
Onset of infection				
Hospital onset	153 (71.2)	66 (60.0)	87 (82.9)	<0.001
First day of infection episode after admission (mean $\pm$ SD, days)	22.22$\pm$30.26	26.08$\pm$38.87	19.30$\pm$21.37	0.855

CRBSI = catheter-related blood stream infection

low a number to analyze. Wound dressing at hospital over the past year remained insignificant. Previous antibiotics use within 1 year was an independent risk factor for MDR bacterial infection (adjusted odds ratio = 6.818, 95% CI = 1.337-34.770, p = 0.021).

Appropriateness of antimicrobial administration

Table 6 presents the inappropriateness of antibiotic administration rate, 56.7% for the first time, and declines to 33.3% and 16.7% for the second and third times, respectively. However, there was no significant difference between non-MDR and MDR bacterial infection groups. The types of inappropriate antimicrobial use are mainly under treatment (78%) and they were significantly different between non-MDR and MDR groups (65% vs. 91%, p = 0.001).

Outcomes and complication of infection

As shown in Table 7, clinical outcomes at the first week after antibiotic treatment of MDR group were

Table 4. Risk factors for MDR organism infection

Patient characteristics	Total (n = 215)	Non-MDR bacterial infection (n = 110)	MDR bacterial infection (n = 105)	p-value
Hemodialysis, n (%)	9 (4.2)	4 (3.6)	5 (4.8)	0.744
Nursing home staying, n (%)	1 (0.5)	1 (0.4)	0 (0)	1.000
OPD visit: Siriraj, n (%)	154 (71.6)	77 (70.0)	77 (73.3)	0.588
OPD visit: Other hospitals, n (%)	70 (32.6)	38 (34.5)	32 (30.5)	0.524
Outpatient IV medication, n (%)	6 (2.8)	3 (2.7)	3 (2.9)	1.000
Wound dressing at hospital over past year, n (%)	24 (11.2)	16 (14.5)	8 (7.6)	0.107
Healthcare personnel, n (%)	1 (0.5)	0 (0)	1 (1.0)	0.488
Previous admission in 5 yr, n (%)	140 (65.1)	69 (62.7)	71 (67.6)	0.452
Last previous admission: Siriraj Hospital, n = 141 (%)	107 (75.9)	54 (78.3)	53 (73.6)	0.519
Last previous admission: private hospital, n = 34 (%)	18 (52.9)	12 (80.0)	6 (31.6)	0.005
Duration of last admission, mean ± SD; days (min, max)	23.7±68.1 (1, 585)	32.9±95.6 (1, 585)	15.3±21.5 (1, 131)	0.988
Duration from last discharge to this admission, mean ± SD; days (min, max)	149.78±280.62 (1, 1,095)	165.32±297.90 (1, 1095)	135.6±265.32 (1, 1080)	0.270
Previous antibiotic use within 1 year, n = 196 (%)	163 (83.2)	70 (73.7)	93 (92.1)	<0.001
Duration of antibiotic use during the past 90 days prior to admission, mean ± SD; days (min, max)	16.93±12.23 (3, 80)	16.54±12.78 (3, 63)	17.23±11.85 (3, 80)	0.367

Table 5. Multivariate analysis of risk factors for MDR organisms

Factor	Crude OR	95% CI of crude OR	Adjusted OR	p-value	95% CI of adjusted OR
Wound dressing at hospital over past year	0.485	0.198-1.186	0.416	0.119	0.138-1.254
Previous antibiotic use within 1 year	4.152	1.767-9.757	6.818	0.021	1.337-34.770

significantly poorer than non-MDR group in terms of curative rate (0% vs. 3.6%), worsening of infection (16.2% vs. 10%) and death from infection (14.3% vs. 7.3%), however, these were not significantly different at the end of the antibiotic course. MDR group had lower survival rates than the other group at both 30 days (58.8% vs. 75.0%, p = 0.013) and 90 days (43.0% vs. 63.0%, p = 0.012). The length of fever was 5.02±4.23 days in non-MDR group versus 6.11±5.44 days in MDR group (p = 0.008).

Complications of antibiotic use were defined for drug allergy, antibiotic-associated diarrhea (AAC) and other associated effects. There was significantly higher incidence of AAC (48.6% vs. 27.3%, p = 0.001) and other side effects (42.9% vs. 20.0%, p<0.001) in MDR group.

Subgroup analysis was performed based on type of previous antibiotic use (Table 8). Previous use of ceftriaxone was a significant risk for acquiring ESBL-producing Enterobacteriaceae infection (13.6% vs. 41.4%, p = 0.007). Previous use of imipenem, meropenem, piperacillin/tazobactam and fluoroquinolones were not shown to be associated with these infections.

Discussion

In the present study, we revealed that the prevalence of MDR gram-negative bacterial infection was 49% (105 of 215 episodes), and ESBL-producing Enterobacteriaceae, MDR *P. aeruginosa*, carbapenem-resistant *P. aeruginosa* and MDR *A. baumannii* isolates were responsible for 37%, 18%, 39% and 89%, in each subgroup, respectively. The incidences of MDR organisms in this study were high and similar to studies from other countries[16-18]. Previous study in a teaching

Table 6. Appropriateness of antimicrobial administration

Patient characteristics	Total (n = 215)	Non-MDR bacterial infection (n = 110)	MDR bacterial infection (n = 105)	p-value
First antimicrobial regimen, n				
Inappropriate use, n (%)	122 (56.7)	60 (54.5)	62 (59.0)	0.505
Reason of inappropriate, n = 122 (%)				0.001
Overtreatment	24 (19.7)	20 (33.3)	4 (6.5)	
Undertreatment	96 (78.7)	39 (65.0)	57 (91.9)	
Inappropriate dose	2 (1.6)	1 (1.7)	1 (1.6)	
Second antimicrobial regimen, n = 120				
Inappropriate use, n (%)	40 (33.3)	21 (31.8)	19 (35.2)	0.697
Reason of inappropriate, n = 40 (%)				0.284
Overtreatment	17 (42.5)	12 (57.1)	5 (26.3)	
Undertreatment	22 (55.0)	8 (38.1)	14 (73.7)	
Not suitable for source	1 (2.5)	1 (4.8)	0 (0)	
Third antimicrobial regimen, n = 24				
Inappropriate use, n (%)	4 (16.7)	1 (7.7)	3 (27.3)	0.300
Reason of inappropriate, n = 4 (%)				
Overtreatment	2 (66.7)	0 (0)	2 (100)	
Undertreatment	1 (33.3)	1 (100)	0 (0)	

hospital in southern Thailand in 2004 showed that the prevalence of ESBL isolates was about 20% of gram-negative bacteria[19]. The National Antimicrobial Resistance Surveillance of Thailand (NARST) study revealed that the prevalence of MDR *A. baumannii* was 20% in 2005[20]. Approximately 20-30% of *P. aeruginosa* was also MDR in some hospitals in central and eastern Thailand and about 15% was meropenem-resistant overall[21]. The prevalence of MDR organisms in our study was higher than previous studies, implying that there is an increasing MDR bacterial infection in clinical practice.

Demographic characteristics of patients in the present study did not show significant differences in age, gender and underlying diseases between non-MDR and MDR groups. The prevalence of MDR bacterial infection of internal medicine ward was significantly higher than the other wards. The prevalence study in Canada (CANWARD 2008) also showed higher prevalence of ESBL-producing Enterobacteriaceae infection in medicine ward[22]. Respiratory tract infection had a higher MDR infection in our study (61% vs. 41.8%) because the larger amount of critically-ill patients than at other infection sites. Non-MDR organism most likely caused wound and soft tissue infections because most of the patients had a low rate of previous broad-spectrum antibiotics and more community onset of infection. In the present study, the majority of patients had hospital onset of infection (153 of 215 episodes, 71.2%) and MDR organisms were more prevalent than non-MDR pathogens (82.9% vs. 60%). However, there were 66 of 153 (43.1%) of hospital onset infections that were caused by non-MDR bacterial infection. Therefore, patients who had hospital onset infection did not always require broad-spectrum antibiotics for MDR organism. Individualized risk factors, severity of infection judgment, tests and local epidemiologic data should be applied for selection or adjustment of antibiotic administration.

Antibiotic use within 1 year before hospitalization was a significant factors for overall MDR organism infections, which is similar to other studies[12,23-25]. Last previous admission in private hospital was the protective factor because there was not the tertiary care center as Siriraj Hospital and had lower rate of using the broad-spectrum antibiotics. Inappropriate use of antibiotics is a leading cause of MDR organism infection, and brought about the worst clinical outcomes[10,26-28]. The present study evaluated the antibiotic use in all enrolled patients. For first antibiotic regimen of 215 infected episodes, the authors found that 91.6% received empirical treatment and 56.7% were inappropriately treated, but no difference was found between non-MDR and MDR subgroups. The most common reason for inappropriate antibiotic use was under treatment, especially in MDR group. Among 122 episodes of the inappropriate antimicrobial

Table 7. Outcomes and complication of infection

Patient characteristics	Total (n = 215)	Non-MDR bacterial infection (n = 110)	MDR bacterial infection (n = 105)	p-value
Clinical outcome at 1st week after antibiotic treatment, n (%)				0.01
Cure of infection	4 (1.9)	4 (3.6)	0 (0)	
Infection improved	152 (70.7)	84 (76.4)	68 (64.8)	
Infection worsened	28 (13.0)	11 (10.0)	17 (16.2)	
Die of infection	23 (10.7)	8 (7.3)	15 (14.3)	
Die of other causes	3 (1.4)	2 (1.8)	1 (1.0)	
Others	5 (2.3)	1 (0.9)	4 (3.8)	
Clinical outcome at the end of antibiotic treatment, n (%)				0.221
Cure of infection	61 (28.4)	36 (32.7)	25 (23.8)	
Infection improved	96 (44.7)	53 (48.2)	43 (41.0)	
Die of infection	41 (19.1)	14 (12.7)	27 (25.7)	
Die of other cause	11 (5.1)	5 (4.5)	6 (5.7)	
Others	6 (2.8)	2 (1.8)	4 (3.8)	
Evidence of superinfection, n (%)	25 (11.6)	14 (12.7)	11 (10.5)	0.607
Evidence of reinfection, n (%)	37 (17.3)	18 (16.4)	19 (18.3)	0.713
Survive after end of antibiotic				
30 days, n = 210 (%)	141 (67.1)	81 (75.0)	60 (58.8)	0.013
90 days, n = 160 (%)	85 (53.1)	51 (63.0)	34 (43.0)	0.012
Microbiological outcome, n = 95 (%)				0.086
Eradicate	54 (56.8)	30 (66.7)	24 (48.0)	
Persist	27 (28.4)	8 (17.8)	19 (38.0)	
New infection	14 (14.7)	7 (15.6)	7 (14.0)	
Length of fever, mean ± SD; days	5.80±4.92	5.02±4.23	6.11±5.44	0.008
Length of stay, mean ± SD; days	42.46±46.98	40.14±48.93	44.37±45.01	0.134
Duration of infectious episode, mean ± SD; days (min, max)	15.82±15.10 (1, 101)	18.88±19.06 (2, 101)	12.62±8.25 (1, 60)	0.016
Antibiotic allergy	2 (0.9)	0 (0)	2 (1.9)	0.237
Antibiotic associated diarrhea	81 (37.7)	30 (27.3)	51 48.6)	0.001
Antibiotic associated adverse effect	67 (31.23)	22 (20.0)	45 (42.9)	<0.001

regimen at first time, the almost episodes (120 episodes, 98.3%) were modified to second regimen, but the inappropriate use remain occurred 40 episodes (33.3%). For the second regimens, inappropriate use in non-MDR group became overtreatment (57.1%) due to non-recognition of drug de-escalation in antimicrobial stewardship programs; the inappropriate use in MDR group remains undertreatment (73.7%) because the physician underestimated of MDR organisms or did not follow the microbiological reports.

Clinical outcomes of MDR bacterial infection in the present study were poorer than non-MDR infection. The authors observed the clinical outcome at the first week after antibiotic treatments. There were a higher rate of unfavorable outcomes (16.2% vs. 10.0%) and infection-related mortality (14.3% vs. 7.3%) in MDR group compared with another group. Furthermore, the mortality rate at 30 days and 90 days, length of fever and duration of infectious episode were significantly higher in MDR group. These findings were similar to other previous studies[23,29,30]. Antibiotic associated diarrhea (AAC) is one of the most common complications of antibiotic use, especially for broad spectrum agents with prolonged use[31,32]. In the present study, the rate of clinical diagnosis of AAC was 37.7% and it was significantly higher in MDR group; however, this may be confounded by other causes of diarrhea, such as osmotic or drug-induced diarrhea. Other antibiotic-associated adverse effects, such as nephrotoxicity, gastrointestinal disturbance, hematologic problem and drug fever were also significantly higher in MDR group. The incidence of

Table 8. Type of previous use antibiotics and MDR infections

Type of previous antibiotic use	Non-MDR group, n (%)	MDR group, n (%)	p-value
Enterobacteriaceae group			
Ceftriaxone	6 (13.6)	12 (41.4)	0.007
Piperacillin/Tazobactam	7 (15.9)	4 (13.8)	1.000
Imipenem	1 (2.3)	0 (0)	1.000
Meropenem	4 (9.1)	3 (10.3)	1.000
Fluoroquinolones	5 (11.4)	7 (24.1)	0.150
P. aeruginosa			
Ceftriaxone	12 (27.9)	1 (9.1)	0.261
Imipenem	7 (16.3)	2 (18.2)	1.000
Meropenem	12 (27.9)	6 (54.5)	0.150
Piperacillin/Tazobactam	9 (20.9)	3 (27.3)	0.693
Fluoroquinolones	8 (18.6)	3 (27.3)	0.693
A. baumannii			
Ceftriaxone	3 (37.5)	20 (32.8)	1.000
Imipenem	1 (12.5)	8 (13.1)	1.000
Meropenem	2 (25.0)	35 (57.4)	0.132
Colistin	1 (12.5)	6 (9.8)	1.000
Piperacillin/Tazobactam	3 (37.5)	14 (23.0)	0.397
Fluoroquinolones	2 (25.0)	13 (21.3)	1.000

antibiotic allergy was too low to show the difference between the two groups.

According to the previous use of antibiotics was the significant risk factor for MDR bacterial infection in the present study, therefore subgroup study to the type of previous use antibiotic was performed. Ceftriaxone has significantly related to ESBL-producing Enterobacteriaceae infection, but other drugs did not show the risk correlation. Meropenem seems to be related with multidrug-resistant *P. aeruginosa* and *A. baumannii* infection, but it was too small number of population to bring about the significant. The limitations of our study are inadequate population to determine the significance in some factors, especially in subgroup analysis.

In conclusion, MDR gram-negative bacterial infection is a growing burden both globally and in Thailand; immediate action is required to prevent further spread. Previous use of antibiotics is a strong predictor of MDR organism infection. Therefore, the appropriate antibiotic use and antibiotic stewardship programs are the important strategies for controlling MDR organism infection. Epidemiological data are one important key of antibiotic stewardship programs for dealing with increasing drug-resistant situation. The expectation of the present study is to encourage the implementation of antibiotic administrative strategy in our hospital and/or other hospitals with similar settings.

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Potential conflicts of interest

None.

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ระบาดวิทยาของการติดเชื้อแบคทีเรียแกรมลบที่ดื้อยาต้านจุลชีพหลายขนานในผู้ป่วยผู้ใหญ่ที่รับไว้รักษาที่โรงพยาบาลศิริราช

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วัตถุประสงค์: เพื่อทราบลักษณะทางคลินิก ปัจจัยเสี่ยง ผลของโรค การใช้ยาปฏิชีวนะและภาวะแทรกซ้อนในการรักษา ผู้ป่วยผู้ใหญ่ที่ติดเชื้อแบคทีเรียแกรมลบที่ดื้อยาต้านจุลชีพหลายขนานที่รับไว้รักษาที่โรงพยาบาลศิริราช

วัสดุและวิธีการ: การศึกษานี้ทำโดยเก็บข้อมูลผู้ป่วยในผู้ใหญ่ของโรงพยาบาลศิริราชที่มีผลการเพาะเชื้อจากสิ่งส่งตรวจ ขึ้นเชื้อแบคทีเรียแกรมลบได้แก่ Enterobacteriaceae, P. aeruginosa และ A. baumannii ระหว่าง เดือนกุมภาพันธ์ ถึง เดือนพฤษภาคม พ.ศ. 2555 แล้วนำมาวิเคราะห์ถึงลักษณะทางคลินิก ปัจจัยเสี่ยง และผลการรักษาของโรคติดเชื้อดังกล่าว

ผลการศึกษา: พบอุบัติการณ์ของการติดเชื้อแบคทีเรียแกรมลบดื้อยาต้านจุลชีพหลายขนานรวมร้อยละ 48.8 จำแนกตามกลุ่มเชื้อ ได้แก่ Extended Spectrum Beta Lactamase (ESBL)-producing Enterobacteriaceae พบร้อยละ 37.8 เชื้อ carbapenem-resistant P. aeruginosa พบร้อยละ 39.3 และเชื้อ MDR A. baumannii พบร้อยละ 88.7 ปัจจัยที่สัมพันธ์กับการติดเชื้อดื้อยา ได้แก่ การรักษาที่หอผู้ป่วยอายุรศาสตร์การติดเชื้อทางเดินหายใจและการติดเชื้อในโรงพยาบาล ปัจจัยเสี่ยงที่มีนัยสำคัญ ได้แก่ การได้รับยาปฏิชีวนะมาก่อนในระยะเวลา 1 ปี (Adjusted OR = 6.818, 95% CI = 1.337-34.770) อัตราความไม่เหมาะสมของการใช้ยาปฏิชีวนะขนานแรกพบร้อยละ 56.7 และพบว่ามีการให้ยาไม่ครอบคลุมเชื้อในกลุ่มติดเชื้อดื้อยาสูงกว่าอย่างมีนัยสำคัญ อัตรารอดชีวิตที่ 30 วัน ของกลุ่มติดเชื้อดื้อยาเท่ากับร้อยละ 58.8 เทียบกับร้อยละ 75 ของกลุ่มติดเชื้อไม่ดื้อยา (p = 0.013) อัตรารอดชีวิตที่ 90 วันของกลุ่มติดเชื้อดื้อยาเท่ากับร้อยละ 43 เทียบกับร้อยละ 63 ของกลุ่มติดเชื้อไม่ดื้อยา (p = 0.012) ผลไม่พึงประสงค์ทางยาพบร้อยละ 42.9 ในกลุ่มติดเชื้อดื้อยาและร้อยละ 20 ในกลุ่มติดเชื้อไม่ดื้อยา (p<0.001)

สรุป: ปัจจัยเสี่ยงที่สำคัญที่สุดของการติดเชื้อดื้อยาหลายขนานในโรงพยาบาลศิริราชคือ การได้รับยาปฏิชีวนะมาก่อน ผู้ป่วยกลุ่มนี้มักได้ยาต้านจุลชีพไม่ครอบคลุมเชื้อตั้งแต่แรกเป็นสาเหตุของผลการรักษาที่ไม่พึงประสงค์และอัตราตายที่สูงขึ้น