The Risk Factors of Multidrug-Resistant Organisms in Hospitalized Patients with Community-Acquired Pneumonia in Dr. Soetomo Hospital Surabaya, Indonesia

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ABSTRAK

Latar belakang: *multidrug-resistant organisms (MDRO) penyebab pneumonia merupakan kasus yang krusial. Infeksi MDRO menjadi masalah utama pada community-acquired pneumonia (CAP). Beberapa faktor berperan terhadap terjadinya infeksi MDRO pada CAP. Tujuan penelitian ini adalah menganalisis MDRO sebagai etiologi pasien CAP rawat inap beserta faktor risikonya di RSUD Dr. Soetomo sebagai salah satu rumah sakit rujukan di Indonesia Timur.* ***Metode:*** *penelitian ini merupakan observasional analitik dengan kohort retrospektif, dilakukan pada Januari 2016 sampai Desember 2018. Data dikumpulkan dari rekam medis pasien. Diagnosis Cepat Otomatis (Phoenix TM) digunakan sebagai metode standar untuk uji kultur dan kepekaan. Beberapa faktor risiko dianalisis terhadap terjadinya infeksi MDRO.* ***Hasil****: lima patogen yang umum ditemukan pada pasien CAP rawat inap adalah Acinetobacter baumannii 244/1364 (17,9%), Klebsiella pneumoniae 134/1364 (9,8%), Pseudomonas aeruginosa 91/1364 (6,7%), Escherichia coli 58/1364 (4,3%), dan Enterobacter cloacae 45/1364 (3,3%). Terdapat 294/1364 (21,5%) MDRO yang diisolasi dari pasien CAP. Infeksi MDRO berhubungan dengan riwayat rawat inap sebelumnya, malignansi, penyakit kardiovaskular, dan penyakit paru struktural dengan nilai p masing-masing 0,002, <0,001, 0,024, dan <0,001.* ***Kesimpulan****: insiden MDRO pada CAP tinggi (21,5%). Faktor risiko yang berhubungan adalah riwayat rawat inap sebelumnya, malignansi, penyakit kardiovaskular, dan penyakit paru struktural.*

Kata kunci**:** *faktor risiko, multidrug-resistant organisms, community-acquired pneumonia.*

ABSTRACT

Background: *multidrug-resistant organisms (MDRO) caused pneumonia has become a crucial case. MDRO infection has been a problem concern to community-acquired pneumonia (CAP). A lot of factors play roles in CAP with MDRO infection. This study aimed to analyze MDRO as the etiology of hospitalized patients with CAP along with its risk factors in Dr. Soetomo Hospital as one of the top referral hospitals in east Indonesia.* ***Methods:*** *this retrospective cohort study was conducted from January 2016 to December 2018. Data were collected from patients' medical records. Automatic Rapid Diagnosis (Phoenix TM) was used as a standard method for culture and susceptibility test. Various risk factors were analyzed for MDRO infection.* ***Results:*** *five most common pathogens in hospitalized patients with CAP were Acinetobacter baumannii 244/1364 (17.9%), Klebsiella pneumoniae 134/1364 (9.8%), Pseudomonas aeruginosa 91/1364 (6.7%), Escherichia coli 58/1364 (4.3%), and Enterobacter cloacae 45/1364 (3.3%). There were 294/1364 (21.5%) MDROs isolated from patients with CAP. MDRO infection was linked to previous hospitalization, malignancy, cardiovascular disease,*

and structural lung disease with p values of 0.002, <0.001, 0.024, and <0.001, respectively. ***Conclusion:*** *the incidence of MDRO in CAP is high (21.5%). The risk factors related were previous hospitalization, malignancy, cardiovascular disease, and structural lung disease.*

Keywords: *risk factors, multidrug-resistant organisms, community-acquired pneumonia.*

INTRODUCTION

Multidrug-resistant organism (MDRO) is defined as pathogens which are resistant to one or more class of antimicrobial agents and often to all but one or two commercial antimicrobial agents. Concerning examples are such as carbapenem-resistant *Enterobacteriaceae* (CRE), multidrug-resistant *Acinetobacter baumannii,* extended spectrum beta-Lactamase-producing Gram-negative bacilli (ESBLs), Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Staphylococcus aureus* (VISA/VRSA), Vancomycin-resistant *Enterococci* (VRE), and multidrug-resistant *Streptococcus pneumonia* (MDRSP).[1]

MDROs infections have become a serious issue to community-acquired pneumonia (CAP). Based on hospital data from low and middle-income countries (LMIC), the total incidence of community-acquired extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli* and *Klebsiella pneumoniae* infections is increasing progressively.[2,3]

Patients with MDRO infection have a higher risk of hospitalization, higher costs, require a longer duration of being hospitalized, and negatively affect the clinical outcomes.[4-6] The risk factors of the MDR infections are antimicrobial therapy in the previous 90 days, being hospitalized for the last 5 days or more, high rates of antibiotic resistance in the community or the particular hospital unit, and immunosuppressive disease and/or therapy.[7] Other variables may play roles in the incidence of MDRO. There are only a few data explaining the risk factors for MDRO isolation in CAP. However, concern for the presence of these pathogens drives the physicians to prescribe an empiric broad-spectrum antibiotic for CAP. Lately, the idea of MDRO has gained lots of attention during the past decade in both literature and clinical practice. Pneumonia cases in the community, which caused by MDRO, show a real and emerging problem.

According to American Thoracic Society (ATS) guideline (2005), healthcare-associated pneumonia (HCAP) includes any patient who was hospitalized in an acute care hospital for two or more days within 90 days of the infection; residence in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic.[7] In the 2016 ATS guideline, HCAP could be included in the upcoming CAP guidelines because patients with HCAP, like those with CAP, frequently present from the community and are initially cared for in the emergency department. The consideration of HCAP to be included as CAP was due to the reported studies that many patients with HCAP are not at high risk for MDR pathogens and although interaction with the healthcare system is potentially a risk for MDR pathogens, underlying patient characteristics are also important independent determinants of risk for MDR pathogens.[8] In community-acquired pneumonia, it was important to identify the proportion of MDRO as the etiology, especially in Indonesia. This study aimed to analyze MDRO as the etiology of hospitalized patients with CAP patients along with its risk factors in Dr. Soetomo Hospital as one of the top referral hospitals in east Indonesia.

METHODS

This was a retrospective observational analytic study with a cohort design, conducted at the Dr. Soetomo Hospital in Surabaya, Indonesia. Data were collected from patients' medical records. The number of sample was adjusted to the number of CAP cases with complete medical records. The study population was 1,441 patients diagnosed with CAP. Considering the invalid

data or incomplete medical records, the final sample was 1,364 patients.

All patients aged 18 years and older, and diagnosed with CAP from January 2016 to December 2018 were included in the study. Patients with incomplete medical records' were excluded. Automatic rapid diagnosis (Phoenix TM), conducted at microbiology laboratory in Dr. Soetomo General Hospital, was used as a standard method of culture and susceptibility testing in CAP patients.

Pneumonia was defined as the existence of pulmonary opacity in chest x-ray during inpatient treatment which relates to more than one of the following signs and symptoms: (1) new or worsened cough with or without sputum production; (2) fever (37.8 ^{0}C) or hypothermia (35.6 ^{0}C); or abnormal number of white blood cell (leucopenia or leukocytosis), or the value of C-reactive protein beyond the local upper limit.

Community-acquired pneumonia (CAP) refers to pneumonia that is acquired in the community as compared to the healthcare system. CAP is commonly defined as an acute infection of the pulmonary parenchyma that is associated with at least some symptoms of acute infection, accompanied by the presence of an acute opacity on a chest radiograph or auscultatory findings consistent with pneumonia (such as altered breath sounds and/ or localized rales), in a patient not hospitalized or residing in a long-term care facility for ≥14 days before onset of symptoms. Symptoms of acute lower respiratory infection may include several (in most studies, at least 2) of the following: fever or hypothermia, rigors, sweats, new cough with or without sputum production or change in color of respiratory secretions in a patient with chronic cough, chest discomfort, or the onset of dyspnea. Most patients also have nonspecific symptoms, such as fatigue, myalgias, abdominal pain, anorexia, and headache.[9]

In this study, previous hospitalization was defined as previous inpatient treatment in the previous 90 days before the onset of symptoms and not being hospitalized for ≥14 days before the onset of symptoms. MDRO was defined as pathogens which resistant to one or more classes of antimicrobial agents, and usually to all commercially available antimicrobial agents, saving one or two agents. MDRO Criteria used in this study was from a standardized international terminology describing acquired resistance profile by the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC).[10] Methicillin-resistant Staphylococcus aureus (MRSA) and all pathogens which are resistant to ≥1 agent in ≥3 antimicrobial categories were considered to be MDR pathogens in this study. Antimicrobial categories used in this study were aminoglycosides, carbapenems, cephalosporins, antipseudomonal penicillin + β-lactamase inhibitors, penicillin + β-lactamase inhibitors, tetracyclines, glycylcyclines, fluoroquinolones, monobactams, and phosphonic acids.

Variables evaluated as the possible risk factors were age, previous hospitalization, malignancy, diabetes mellitus, chronic obstructive pulmonary disease (COPD), cardiovascular disease, renal failure, structural lung disease. A variety of risk factors variables were analyzed for MDRO infection. Underlying diseases were regarded as active co-morbid if the signs or symptoms appeared or if the patients received treatment for the diseases. Renal failure was determined when the creatinine was >2 mg/dl or twice the baseline creatinine in a patient with chronic renal failure. Cardiovascular failure was determined when inotropic drugs were required, and hepatic failure was determined when bilirubin level was >2 mg/dl.

All variables in this study were categorical variables. Chi-square test or Fisher's exact test was used for statistical analysis. Variables with $p<0.25$ were included in multivariate logistic regression. Statistical result was considered significant if the p-value was <0.05. SPSS 21.0 was used for the statistical analysis.

This study was approved by the Institutional Review Board/ Ethics Committee review, with the approval number of 295/Panke.KKE/IV/2017 on 19 April 2017.

RESULTS

Of 1,441 patients with CAP, 77 (5.3%) of them did not have complete medical records and were excluded from the study. We collected complete data of 1,364 patients diagnosed with CAP, see **Table 1**.

Of the 1,364 patients with CAP, 84 (6.2%) had negative sputum cultures, 490 (35.9%) had normal flora and the isolated pathogens were 790 (57.9%). The five most common pathogens isolated were *Acinetobacter baumannii* with 244 (30.9%), followed by *Klebsiella pneumoniae* with 134 (17%), *Pseudomonas aeruginosa* with 91 (11.5%), *Escherichia coli* with 58 (7.3%), and *Enterobacter cloacae* with 45 (5.7%). This result is presented in **Table 2**.

Of the 1,364 patients with sputum culture data, there were 294 (21.6%) MDRO in this study as presented in **Table 3**. The five most common MDR pathogens were MDR *Acinetobacter baumannii,* MDR *Klebsiella pneumonia,* MDR *Escherichia coli,* MDR *Pseudomonas*

Table 1. Demography of CAP patients (N=1,364) in Dr. Soetomo Hospital on January 2016 to December 2018.

	N (%)		Total
	MDRO	Non MDRO	
Sex			
- Male	176 (21.1)	660 (78.9)	836
- Female	118 (22.3)	410 (77.7)	528
Age, Mean (SD)	51.08 (17.435)	51.55 (16.255)	51.45 (16.511)
Age range			
- >65 years old	64 (24.2)	201 (75.8)	265
- ≤65 years old	230 (20.9)	869 (79.1)	1099

CAP: Community-acquired pneumonia; MDRO: multidrug-resistant organism.

Table 2. The pathogens profile of sputum culture method (N=790) of CAP patients in Dr. Soetomo Hospital, from January 2016 to December 2018.

Isolated organisms	Count (N)	Percentage (%)
Acinetobacter baumannii	244	30.9
Klebisiella pneumoniae	134	17.0
Pseudomonas aeruginosa	91	11.5
Escherichia coli	58	7.3
Enterobacter cloacae	45	5.7
Stenotrophomonas maltophilia	23	2.9
Streptococcus pneumoniae	18	2.3
Enterobacter aerogens	8	1.0
Staphylococcus aureus	8	1.0
Pseudomonas putida	8	1.0
Other respiratory tract bacteria	153	19.4

CAP: Community-acquired pneumonia.

Table 3. Bacterial profile in MDRO.

MDR Pathogens	N (294)	Percentage
MDR *Acinetobacter baumannii*	106	36.1
MDR *Klebsiella pneumoniae*	80	27.2
MDR *Escherichia coli*	43	14.6
MDR *Pseudomonas aeruginosa*	25	8.5
MDR *Enterobacter cloacae*	19	6.5
MDR *Enterobacter aerogens*	4	1.4
MDR *Stenotrophomonas maltophilia*	3	1.0
MDR *Staphylococcus aureus*	2	0.7
Other MDR Pathogens	12	4.1

MDRO: Multidrug-resistant organism; MDR: Multidrug-resistant.

aeruginosa, and MDR *Enterobacter cloacae*. Other MDR pathogens were MDR *Serratia marcescens,* MDR *Acinetobacter spp,* MDR *Citrobacter freundii,* MDR *Kluyvera intermedia,* MDR *Burkholderia cepacia,* MDR *Pantoea agglomerans,* MDR *Enterococcus raffinosus.*

Of the 1,364 patients, there were 294 (21.6%) MDRO and 1,070 (78.4%) non-MDRO. According to **Table 4**, variables associated with developing MDRO were previous hospitalization, malignant disease, cardiovascular disease, and structural lung disease with p values of 0.002, <0.001, 0.024, and <0.001.

Variables with a P<0.02 based on Chi-square or Fisher's exact test were entered into a multivariate logistic regression model using binary regression binary logistic. Logistic regression showed that malignancy and structural lung disease were both associated with a 2-fold increased risk of MDRO infection (**Table 5**).

DISCUSSION

Our study found 1,364 patients with community-acquired pneumonia (CAP), consisting of 836 (60.3%) men and 528 (38.7%) women. The mean age was 51.45 years. Patients age >65 years old were 265 (19.4%) and age ≤65 years old were 1099 (80.6%). Previous study found that the risk of pneumonia increases as the increases of age. Vinogradova et al.[11] reported that among 17,172 cases of pneumonia, there were 47.3% patients age ≥65 years old.

Of the 1,364 patients with CAP, 84 (6.2%) were negative in sputum culture and 490 (35.9%) were normal flora. Another study found a

Table 4. The risk factors of patients who developed community-acquired pneumonia in Dr. Soetomo Hospital, from January 2016 to December 2018.

Variables		MDRO (n=294/21.6%)	Non MDRO (n=1,070/78.4%)	P Value
		N (%)	N (%)	
Age	Age >65 y.o (n=265)	64 (24.2)	201 (75.8)	0.252
	Age ≤65 y.o (n=1099)	230 (20.9)	869 (79.1)	
Renal Failure	With Renal Failure (n=32)	8 (25.0)	24 (75.0)	0.631
	No Renal Failure (n=1332)	286 (21.5)	1046 (78.5)	
Diabetes Mellitus	With Diabetes Mellitus (n=160)	37 (23.1)	123 (76.9)	0.607
	No Diabetes Mellitus (n=1204)	257 (21.3)	947 (78.7)	
COPD	With COPD (n=56)	10 (17.9)	46 (82.1)	0.492
	No COPD (n=1308)	284 (21.7)	1024 (78.3)	
Hepatic Failure	With Hepatic Failure (n=46)	13 (28.3)	33 (71.7)	0.260
	No Hepatic Failure (n=1318)	281 (21.3)	1037 (78.7)	
Cardiovascular Disease	With cardiovascular Disease (n=158)	45 (28.5)	113 (71.5)	0.024
	No Cardiovascular Disease (n=1206)	249 (20.6)	957 (79.4)	
Previous Hospitalization	With Previous Hospitalization (n=648)	163 (25.2)	485 (74.8)	0.002
	No Previous Hospitalization (n=716)	131 (18.3)	585 (81.7)	
Malignancy	With Malignancy (n=140)	49 (35)	91 (65)	<0.001
	No Malignancy (n=1224)	245 (20)	979 (80)	
Structural Lung Disease	With Structural Lung Disease (n=102)	40 (39.2)	62 (60.8)	<0.001
	No Structural Lung Disease (n=1262)	254 (20.1)	1008 (79.9)	

Based on chi-square test or Fisher's exact test. MDRO: Multidrug-resistant organism; COPD: chronic obstructive pulmonary disease.

Table 5. Multivariate analysis of risk factors for MDRO infection in CAP patients.

Variables	P	OR	95% CI
Previous Hospitalization	<0.001	1.737	1.320-2.286
Malignancy	<0.001	2.134	1.455-3.131
Cardiovascular Disease	0.006	1.744	1.174-2.591
Structural Lung Disease	<0.001	2.816	1.833-4.327

MDRO: Multidrug-resistant organism; CAP: Community-acquired pneumonia; OR: odds ratio.

higher number of negative bacterial cultures of sputum in pneumonia with 131 (78.44%) and 61 (61%).[12,13] Of the 790 pathogens, five most common were *Acinetobacter baumannii* with number of 244 (30.9%), *Klebsiella pneumoniae* 134 (17%), *Pseudomonas aeruginosa* 91 (11.5%), *Escherichia coli* 58 (7.3%), and *Enterobacter cloacae* 45 (5.7%).

Of the 1,364 CAP patients, there were 294 (21.5%) MDRO. This was more than the study in the United States that reported there were 5/263 (1.9%) MDRO in CAP.[14] A study in Italy reported the prevalence of MDRO in CAP was 8.1% in Italy (especially MRSA, MDR *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[15] Whereas, a study in Spain reported 22/68 (32%) MDR *Pseudomonas aeruginosa* in CAP.[16]

The five most common MDRO (**Table 3**) were MDR *Acinetobacter baumannii,* MDR *Klebsiella pneumonia,* MDR *Escherichia coli,* MDR *Pseudomonas aeruginosa,* and MDR *Enterobacter cloacae.* Rice,[17] stated that *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and Enterobacter species are highly important because they comprise the largest part of the nosocomial infections and they represent the paradigms of pathogenesis, transmission, and resistance as well. Previous study by Sievert et al,[18] also showed the occurrence of multidrug-resistant gram-negative bacteria (*Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Enterobacter* spp.

Various factors have been shown to predispose patients to MDROs infection including patients' severity of illness, functional disability, advanced dementia, dialysis, diabetes mellitus, renal failure, structural lung disease, and chronic obstructive pulmonary disease (COPD), liver failure or other organ failure and surgical procedures, indwelling devices (urinary catheters and/or feeding tubes), fecal incontinence, previous antibiotic exposure, recent hospitalization, traveling to high prevalence countries and antimicrobial use during travels.[19-21]

Patients with a history of previous hospitalization were considered as CAP in this study. In the previous 2005 ATS guideline, patients who were hospitalized in an acute care hospital for two or more days within 90 days of the infection are considered as HCAP,[7] but in the 2016 ATS guideline, HCAP was included in CAP because patients with HCAP are similar to those with CAP, frequently present from the community and are initially cared for in emergency department.[8] Our study found that infection of MDRO were associated with previous hospitalization (OR=1.737; 95% CI=1.320-2.286), malignancy (OR=2.134; 95% CI=1.455-3.131), cardiovascular disease (OR=1.744; 95% CI=1.174-2.591), and structural lung disease (OR=2.816; 95% CI=1.833-4.327) as presented in **Table 5**. Previous hospitalization in CAP patients should be a concern due to the higher risk for MDRO infection.

The infection of certain MDR pathogens may be associated with certain variables. Huang et al,[22] reported that MDR *Acinetobacter baumannii* infection was associated with sex, age, hospitalization times, history of cancer, HAI, ICU days, mechanical ventilation, indwelling catheters, the combined use of antimicrobial agents before infection, and the use of third-generation cephaloglycin. Mody et al.[23] showed that MDR *Acinetobacter baumannii* caused infection in older adults treated as inpatients in a long term, particularly older adults using invasive devices and/or those with underlying accompanying diseases. Nursing home (NH) residents also bear a number of the risk factors that likely to allow MDR *Acinetobacter baumannii* colonization or infection, including chronic obstructive pulmonary disorder, cardiac and renal failure, diabetes mellitus, dementia, presence of wounds, and use of antibiotics and invasive devices, for example, urinary catheters.

Research by Silva[24] found that malignant underlying disease is the major risk for infection by ESBL-producing *Klebsiella pneumoniae*. However, other identified risks such as urinary and central venous catheter, and other invasive devices, anemia, as well as older age were not related to such infections. Cheng et al,[25] reported that ESBL-producing bacteremic pneumonia (*Escherichia coli* and *Klebsiella pneumoniae* that produces ESBL), often occurred in adults

with comorbidities.

Dantas et al.[26] reported that common independent risk factors for antimicrobial *Pseudomonas aeruginosa* resistance are previous antibiotic use, length of hospitalization being 30 days or longer prior to *Pseudomonas aeruginosa* infection, hemodialysis, tracheostomy, pulmonary source of bacteremia and Intensive Care Unit admission. Functional status, pulmonary comorbidity, nursing home residence, previous hospitalization, and previous antibiotic therapy are factors that have a remarkable relationship with the acquiescence of potentially drug-resistant pathogens in immunocompetent patients inflicted with pneumonia outside the hospital.[27] Two possible factors for the impact of previous hospitalization and nursing home residency on resistant pathogen infection including; first, the impact could be related to exposure to a broad antibiotic coverage in these settings that leads to selection pressure for resistance. Second, the tenacity of MDR pathogens in various wards and transmission among healthcare providers and patients is increasing, and powerful healthcare policies are needed to reduce these pathogens.[28,29]

The limitation of this study was the variables of recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection, and history of attending a hospital and hemodialysis clinic in patients with comorbid of renal failure were not analyzed for risk factors of MDRO infection.

CONCLUSION

The occurrence of MDRO in CAP is high (21.5%). The most common pathogen is *Acinetobacter baumannii.* The crucial factors associated with MDRO in CAP are previous hospitalization, malignancy, cardiovascular disease, and structural lung disease.

CONFLICT OF INTEREST

There is no conflict of interest.

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