Shiraz E-Med J. 2021 January; 22(1):e99779. doi: 10.5812/semj.99779.

Published online 2020 September 16. **Research Article**

Factors Associated with Multidrug-Resistant Pathogens in Community-Acquired Pneumonia Patients Hospitalized in a Provincial Teaching Hospital in Indonesia

Arto Yuwono Soeroto [1,*], Ining Kartika Tarmidi [2], Guntur Darmawan [2], Geraldo Laurus [2] and Prayudi Santoso [1]

[1]Division of Respiratory and Critical Illness, Department of Internal Medicine, Faculty of Medicine, Hasan Sadikin General Hospital, Universitas Padjadjaran, Bandung, Indonesia
[2]Department of Internal Medicine, Faculty of Medicine, Hasan Sadikin General Hospital, Universitas Padjadjaran, Bandung, Indonesia

[*]*Corresponding author*: Division of Respiratory and Critical Illness, Department of Internal Medicine, Faculty of Medicine, Hasan Sadikin General Hospital, Universitas Padjadjaran, Bandung, Indonesia. Email: a.y.soeroto@unpad.ac.id

Received 2019 December 10; **Revised** 2020 May 23; **Accepted** 2020 May 23.

Abstract

Background: Pneumonia has high rates of morbidity and mortality in Indonesia. Infections caused by multidrug-resistant (MDR) pathogens are not only found in patients with nosocomial pneumonia but are also reported in patients with community-acquired pneumonia (CAP). Only a few studies have analyzed the factors associated with MDR pathogenic infections, especially in developing countries such as Indonesia. Therefore, the identification of such factors can help to predict the infections caused by MDR pathogens in CAP patients.

Objectives: This study aimed to determine factors associated with MDR pathogenic infections in CAP patients admitted to Hasan Sadikin General Hospital, Bandung, West Java Province, Indonesia.

Methods: This is an observational analytic study which compared 85 patients with MDR pneumonia and 70 patients with pneumonia caused by non-MDR pathogens from March to May 2018. Sputum of all adults patient > 18 years old with CAP who had the Murray and Washington's criteria was collected. In vitro test was performed based on the Kirby-Bauer method with Clinical and Laboratory Standards Institute (CLSI) 2018 protocols. This study was ethically approved by the Ethics Committee of the Hasan Sadikin Hospital.

Results: One hundred and fifty five patients with positive sputum culture were investigated. Overall, 85 (54%) patients had MDR pathogens in their cultures. *Klebsiella pneumoniae* was the most common pathogen found in the CAP patients (37/155; 23.9%), while *Acinetobacter baumannii* accounted for the highest proportion of MDR pathogens (18/85; 21.2%). Multivariate logistic regression analysis showed that the immobilization status was the only associated factor for MDR pathogenic infections in CAP patients (adjusted prevalence ratio = 1.862 [1.432 - 2.420]; P < 0.001).

Conclusions: This study highlighted the need for early risk assessment of infections caused by MDR pathogens, especially immobilization status in CAP patients. Also, the local pathogen pattern should be considered to prescribed antibiotics for CAP patients. The findings showed that antibiotics against MDR pathogens should be prescribed for CAP patients with immobilization.

Keywords: Community-Acquired Pneumonia, Multidrug-Resistant Pathogen

1. Background

Despite advances in antibiotic treatments, pneumonia still has high rates of morbidity and mortality (1). So, in lower-middle-income countries, it's the third leading cause of mortality, following ischemic heart diseases and stroke (2). Advances in antibiotic use have influenced the shift in pneumonia pathogenic patterns and led to the development of antibiotic resistance (1, 3).

Today, pneumonia, caused by multidrug-resistant (MDR) pathogens is not only limited to hospital-acquired or nosocomial infections but also can be found in patients with community-acquired pneumonia (CAP) (4). Multiple studies are performed on the infections caused by MDR pathogens in CAP patients in several hospitals of the United States and Japan (5-8). Despite the controversial findings of these studies, the most important risk factors for MDR infections include a history of antibiotic use, radiological findings of bilateral infiltrates and parapneumonic effusions, the severity of oxygenation based on the ratio of the partial pressure of oxygen in arterial

blood to the fraction of inspired oxygen (PaO_2/FiO_2), non-ambulatory status or immobilization, and presence of one healthcare-associated pneumonia (HCAP) criterion (3, 6-8).

2. Objectives

So far, no study has evaluated the factors associated with MDR pathogenic infections in CAP patients in Indonesia. Therefore, the identification of contributing factors can help to predict MDR pathogenic infections in CAP patients.

3. Methods

This cross-sectional study was conducted from March to May 2018. In total, 155 patients were participated, 85 patients with MDR pneumonia, and 70 patients with pneumonia caused by non-MDR pathogens. Sputum of all adult patients > 18 years old with CAP was collected. To be included in the current study, the sputum samples should have the Murray and Washington's criteria (leukocytes > 25 per low-power field and epithelial cells < 10 per low-power field). Patients were excluded if CAP was diagnosed outside before the patient being referred to Hasan Sadikin General Hospital or if commensal bacteria (*Streptococcus milleri* or viridans streptococci including *Streptococcus mitis*, *Streptococcus mutans*, *Streptococcus oralis*, *Streptococcus sanguinis*, and *Streptococcus sobrinus*) were found in the sputum culture.

MDR pathogens were defined as bacteria showing resistance to at least one antibiotic from three or more antimicrobial classes (9). The HCAP criteria were as follows being hospitalized in the past three months, dialysis, intravenous therapy in the last 30 days, and residence in a nursing home. Having a history of antibiotic use was defined as using oral or intravenous intake of antibiotics for a minimum of two days in the past 30 days (4, 7). Besides, immobilization was defined as being bedbound for three days or more (10). Microorganism identification and antibiotic resistance tests were performed using a colorimetric detection system, and turbidimetry was performed using the Vitek 2 Compact Instrument. In vitro resistance test was performed based on the Kirby-Bauer method with CLSI 2018 protocols.

Bivariate analysis was performed using the chi-square test or Fisher's test. Variables with P values < 0.25 or theoretically important were included in the multivariate logistic regression analysis. A P value of < 0.05 was considered as statistically significant. All statistical analyses were performed in SPSS version 25 for Windows. This study was ethically approved by the Ethics Committee of Dr. Hasan Sadikin Hospital. Informed consent was taken from all participants.

4. Results

Between March and May 2018, sputum samples of 256 CAP patients were examined using the Gram staining, culturing, and sensitivity tests. The sputum samples of 69 (26.1%) patients did not meet the inclusion criteria. Also, for 11 (4.15%) patients, the sputum cultures showed no microorganism growth, and for 21 (9.05%) patients, the sputum cultures revealed commensal bacterial and fungal growth. Finally, 155 patients were included in the analysis and divided into two groups: 85 (54.8%) patients with sputum cultures showed the presence of MDR pathogens, and 70 (45.2%) patients with sputum cultures showed non-MDR pathogens.

The basic demographic characteristics of the participants are presented in Table 1. The study sample included 82 (52.9%) male and 73 (47.1%), female CAP patients. The MDR group consisted of more females (n = 45; 61.6%), while the non-MDR group consisted of more males (n = 42; 51.2%). The mean age of the participants was 54 years.

With 37 (23.9%) positive culture results, the *Klebsiella pneumoniae* was the most frequently found pathogen (Table 2). Out of 37 (45.9%) cultures, 17 were from the MDR group, while the remaining 20 (54.1%) cultures belonged to the non-MDR group. *Acinetobacter baumannii* was the most frequently found MDR pathogen (21.2%).

Bivariate analysis, as presented in Table 1, showed that factors associated with MDR pathogenic infections in CAP patients were immobilization status (P < 0.001) and the presence of one HCAP criterion (P = 0.047). However, a history of antibiotic use, radiological findings of bilateral infiltrates, parapneumonic effusion, and PaO_2/FiO_2 ratio were not significantly associated with the MDR pathogens.

Multiple logistic regression analysis, as presented in Table 3, was performed with six factors that were theoretically related to MDR pathogenic infections in CAP patients. The results showed that only immobilization status was associated with MDR pathogenic infections in CAP patients (adjusted prevalence ratio = 1.862 [1.432 - 2.420]; P < 0.001).

5. Discussion

As mentioned before, out of 256 CAP patients, 155 (58.5%) had positive sputum cultures. Labelle et al. (11)

Table 1. Basic Characteristics of the Participants[a]

Basic Characteristics	Total	MDR	Non-MDR	P Value
Demographics				
Age	54 ± 19	56 ± 19	51 ± 19	0.169
Sex				0.108
Male	82 (52.9)	40 (48.8)	42 (51.2)	
Female	73 (47.1)	45 (61.6)	28 (38.4)	
Presence of one HCAP criterion				0.047[b]
Yes	48 (31.0)	32 (66.7)	16 (33.3)	
No	107 (69.0)	53 (49.5)	54 (50.5)	
History of antibiotic use				0.226
Yes	31 (20.0)	20 (64.5)	11 (35.5)	
No	124 (80.0)	65 (52.4)	59 (47.6)	
Immobilization				< 0.001[b]
Yes	24 (15.5)	22 (91.7)	2 (8.3)	
No	131 (84.5)	63 (48.1)	68 (51.9)	
Blood gas analysis				0.499
PaO_2/FiO_2 ratio < 300	104 (67.1)	59(56.7)	45(43.3)	
PaO_2/FiO_2 ratio ≥ 300	51 (32.9)	26 (51.0)	25 (49.0)	
Thorax radiological findings				
Infiltrates				0.857
Bilateral	63 (40.6)	34 (54.0)	29 (46.0)	
Unilateral	92 (59.4)	51 (55.4)	41 (44.6)	
Parapneumonic effusions				0.681
Yes	16 (10.3)	8 (50.0)	8 (50.0)	
No	139 (89.7)	77 (55.4)	62 (44.6)	

[a] Values are expressed as No. (%) or mean ± SD.
[b] Significant.

found that 49.5% of pneumonia patients had positive sputum cultures. This study excluded 101 patients, including 69 (26.1%) patients who could not provide a representative sputum sample, 21 (9.1%) patients whose sputum culture showed fungi and commensal bacteria, and 11 (4.15%) patients whose sputum culture showed no microorganism growth.

Non-growth in the culture may be attributed to the previous antibiotic use or inadequate sputum quality (12, 13). In the present study, the bivariate analysis showed that factors related to MDR pathogenic infections in CAP patients were immobilization status and presence of one HCAP criterion ($P < 0.001$ and 0.047, respectively). In patients who had a history of antibiotic use, the occurrence of MDR pathogenic infection tended to be higher (64.5%), meanwhile, the difference was not significant ($P = 0.226$). This finding may be due to recall bias since the data were collected from the patients' history, not their medical records.

On the other hand, radiological findings of bilateral infiltrate, parapneumonic effusions, and PaO_2/FiO_2 ratio < 300 were not associated with MDR pathogenic infections. This finding is inconsistent with the results reported by Falcone et al. (8), which showed that these factors were significantly associated with MDR pathogenic infections. Plain chest radiography (CXR) is used to identify pulmonary in-

Table 2. Frequency and Percentage of Bacterial Cultures[a]

Culture Results	Total (N = 155)	MDR (N = 85)	Non-MDR (N = 70)
Klebsiella pneumoniae* subsp. *pneumoniae	37 (23.9)	17 (20.0)	20 (28.6)
Acinetobacter baumannii	30 (19.4)	18 (21.2)	12 (17.1)
Pseudomonas aeruginosa	28 (18.1)	13 (15.3)	15 (21.4)
Enterobacter cloacae	11 (7.1)	11 (12.9)	0 (0.0)
Escherichia coli	9 (5.8)	8 (9.4)	1 (1.4)
Staphylococcus aureus	7 (4.5)	2 (2.4)	5 (7.1)
Staphylococcus epidermidis	4 (2.6)	4 (4.7)	0 (0.0)
Streptococcus pneumoniae	3 (1.9)	0 (0.0)	3 (4.3)
Achromobacterxylosoxidans	2 (1.3)	2 (2.4)	0 (0.0)
Acinetobacter lwoffii	2 (1.3)	1 (1.2)	1 (1.4)
Burkholderiacepacia	2 (1.3)	1 (1.2)	1 (1.4)
Proteus mirabilis	2 (1.3)	1 (1.2)	1 (1.4)
Pseudomonas putida	2 (1.3)	1 (1.2)	1 (1.4)
Pseudomonas stutzeri	2 (1.3)	0 (0.0)	2 (2.9)
Staphylococcus haemolyticus	2 (1.3)	2 (2.4)	0 (0.0)
Achromobacterdenitrificans	1 (0.6)	1 (1.2)	0 (0.0)
***Acinetobacter* spp.**	1 (0.6)	0 (0.0)	1 (1.4)
Aeromonas hydrophila	1 (0.6)	0 (0.0)	1 (1.4)
Enterobacter aerogenes	1 (0.6)	1 (1.2)	0 (0.0)
Enterococcus faecalis	1 (0.6)	1 (1.2)	0 (0.0)
Enterococcus faecium	1 (0.6)	1 (1.2)	0 (0.0)
Klebsiella oxytoca	1 (0.6)	0 (0.0)	1 (1.4)
Klebsiella pneumoniaesubsp.ozaenae	1 (0.6)	0 (0.0)	1 (1.4)
Raoultellaplanticola	1 (0.6)	0 (0.0)	1 (1.4)
Staphylococcus xylosus	1 (0.6)	0 (0.0)	1 (1.4)
Stenotrophomonas maltophilia	1 (0.6)	0 (0.0)	1 (1.4)
Streptococcus salivarius	1 (0.6)	0 (0.0)	1 (1.4)

[a]Values are expressed as No. (%).

filtrates indicative of pneumonia and to evaluate treatment outcomes. However, it only plays a limited role in the identification of specific pathogens responsible for pneumonia, as confirmed in the current study where radiological findings were not associated with MDR pathogenic infections. Indeed, bacterial pneumonia may induce a wide range of CXR patterns (14). Moreover, several studies have described unspecific radiological findings attributed to atypical pathogens (15).

According to the multivariate analysis, the immobilization status was the strongest factor associated with the MDR pathogenic infection, with an adjusted prevalence ratio of 1.862 (1.432 - 2.420; $P < 0.001$). This finding is in agreement with some of the previous studies, which included immobilization status in their scoring system to predict MDR pathogenic infections in CAP patients (3, 6). Immobilization reduced the mechanical function of the lungs, which led to an increased risk of colonization and infection with respiratory tract bacteria, including Gram-negative bacteria (16, 17). This may explain why im-

Table 3. Multivariate Analysis of Factors Related to MDR Pathogenic Infections in CAP Patients

Variables	Prevalence Ratio	Adjusted Prevalence Ratio	P Value
History of antibiotic use	1.231 (0.902 - 1.679)	1.094 (0.744 - 1.610)	0.647
Bilateral infiltrates	0.974 (0.727 - 1.304)	0.833 (0.620 - 1.119)	0.225
Parapneumonic effusions	0.903 (0.541 - 1.507)	1.027 (0.586 - 1.802)	0.925
PaO_2/FiO_2 ratio < 300	1.113 (0.810 - 1.528)	1.123 (0.803 - 1.571)	0.497
Immobilization	1.906 (1.537 - 2.363)	1.862 (1.432 - 2.420)	< 0.001[a]
Presence of one HCAP criterion	1.346 (1.021 - 1.775)	1.180 (0.832 - 1.674)	0.354

[a] Significant.

mobilization was associated with the occurrence of MDR pathogenic infections in the present study.

In the current study, the commonly found pathogens were *Klebsiella pneumoniae* and *Acinetobacter baumannii*. This finding is inconsistent with a study conducted in the United States (18), which found that *Streptococcus pneumoniae* was the most common pathogen. Another study conducted in some Asian countries also found that the most common pathogen was *Streptococcus pneumoniae* in patients with CAP (19). However, the present results are in accordance with those reported by Archana et al. from India (20) and Farida et al. (21) from Indonesia. Generally, these differences might be attributed to several factors. Unsuitable transfer of samples may reduce the isolation of more fastidious bacteria, such as *Streptococcus pneumoniae* (22). Also, the high temperature and humidity of West Java and Indonesia promote the growth and virulence of Gram-negative bacilli (GNB); therefore, the incidence of infections caused by GNB may be higher in tropical regions (23). It is worth mentioning that infections caused by GNB are usually more severe and require hospitalization; therefore, the prevalence of *Klebsiella pneumoniae* may be higher in hospitalized patients (24).

Even though *Klebsiella pneumoniae* was the most common pathogen in the present study, *Acinetobacter baumannii* accounted for the highest proportion of MDR pathogens (18/85; 21.2%). Two possible mechanisms can be used to explain these findings; upregulation of innate resistance processes by *A. baumannii* and capacity of *A. baumannii* to acquire external factors to modify its susceptibility to antibiotics. Through these mechanisms, *A. baumannii* is easily modified by resistance determinants and becomes resistant to several classes of antibiotics (25).

In the present study, the prevalence of MDR pathogens was 54.8%, which is lower than that reported in Ethiopia (76%) (26), but higher than the rates reported from two cities in Europe, where the prevalence rates were 3.3 and 7.6%, respectively (27). There are several possible explanations for the higher antibiotic resistance in developing countries, including inappropriate prescriptions, inadequate patient education, limited diagnostic facilities, lack of surveillance of resistance development, poor quality of available antibiotics, clinical misuse, and availability of antibiotics (28, 29).

Lack of surveillance of bacterial resistance has led to the inadequate information of health professionals in developing countries about the causative bacterial and antimicrobial patterns. Therefore, health professionals mostly rely on broad-spectrum antibiotics rather than local bacterial profiles; this practice may have led to the development of resistance. On the other hand, poor quality of available antibiotics results from the absence of appropriate regulations in antimicrobial marketing, especially in developing countries, which in turn leads to the poor quality of pharmacological agents because of factors such as storage and distribution. In fact, due to these poor conditions, drugs may be degraded and contain less than the stated dose, implying that patients consume drugs lower than the optimal dose.

Antimicrobials can also be purchased without a prescription, and the frequency of antimicrobial self-medication is high (30). Clinical misuse of antibiotics may also explain why *Klebsiella pneumoniae*, not *Streptococcus pneumoniae* (accepted globally as the most common bacteria in CAP patients), is the most common species found in the present study. In this regard, Sakeena et al. (31) reported a high rate of non-prescription sales of antibiotics in the community pharmacies of developing countries.

Amoxicillin is one of the most commonly purchased antibiotics. Similarly, Auta et al. (32) found that penicillin was the most commonly recommended and supplied medicine for the treatment of upper respiratory tract infection. These antibiotics majorly eradicate Gram-positive bacteria, such as *Streptococcus pneumoniae*; this

may partly explain the low prevalence of *Streptococcus pneumoniae* in our study.

However, the current study has some limitations that should be noted. Data related to the underlying disease (including cardiovascular disease, malignancy, and neurological disorder) that could affect the etiologic of CAP were not investigated. Blood culture and serologic tests to identify other important etiologies, such as *Chlamydia pneumonia*, *Mycoplasma pneumonia*, and *Legionella pneumophila*, were not performed due to the limitation of resources. Another limitation of this study is the recall bias of antimicrobial use based on anamnesis. Further studies are recommended to determine other possible risk factors for MDR pathogenic infections in CAP patients.

5.1. Conclusions

Immobilization is associated with the occurrence of MDR pathogenic infections in Indonesian CAP patients. Sputum cultures with positive MDR pathogens were found in 85 (54.8%) CAP patients. In this study, *Klebsiella pneumoniae* was the most common pathogen, as it was found in 37 (23.9%) patients, although *Acinetobacter* accounted for a higher percentage of MDR pathogens (21.32%).

Footnotes

Authors' Contribution: Study concept and design: AYS, IKT, and PS. Acquisition of data: IKT, GD, and GL. Analysis and interpretation of data: AYS, IKT, GL, GD, and PS. Drafting of the manuscript: AYS, GL, and GD. Critical revision of the manuscript for important intellectual content: AYS, GL, GD, IKT, and PS. Statistical analysis: AYS, IKT, and PS. Administrative, technical, and material support: AYS, IKT, GL, GD, and PS. Study supervision: AYS and PS.

Conflict of Interests: All authors declare no conflict of interest.

Ethical Approval: Ethic approval number LB.04.01/A05/EC/051/III/2018 by Ethics Committee of Hasan Sadikin General Hospital (http://st299755.sitekno.com/).

Funding/Support: This study has no funding support or grant.

Informed Consent: All patients diagnosed with community-acquired pneumonia who was admitted to Hasan Sadikin General Hospital, were explained all about the study, benefit, and the risk. After patients/the person in charge of the patient agree, informed concerned are obtained by signing in the inform concern form. After patients/the person in charge of the patient signing the inform concern, anamnesis and sputum collection were done.

References

1. Mizgerd JP. Lung infection—a public health priority. *PLoS medicine*. 2006;**3**(2). e76.
2. World Health Organzation. *The top 10 causes of death*. 2018, [cited 11th November]. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
3. Shindo Y, Ito R, Kobayashi D, Ando M, Ichikawa M, Shiraki A, et al. Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. *American journal of respiratory and critical care medicine*. 2013;**188**(8):985–95.
4. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *American Journal of Respiratory and Critical Care Medicine*. 2005;**171**(4):388.
5. Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS. Epidemiology and outcomes of health-care–associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest*. 2005;**128**(6):3854–62.
6. Shindo Y, Sato S, Maruyama E, Ohashi T, Ogawa M, Hashimoto N, et al. Health-care-associated pneumonia among hospitalized patients in a Japanese community hospital. *Chest*. 2009;**135**(3):633–40.
7. Aliberti S, Di Pasquale M, Zanaboni AM, Cosentini R, Brambilla AM, Seghezzi S, et al. Stratifying risk factors for multidrug-resistant pathogens in hospitalized patients coming from the community with pneumonia. *Clinical infectious diseases*. 2011;**54**(4):470–8.
8. Falcone M, Russo A, Giannella M, Cangemi R, Scarpellini MG, Bertazzoni G, et al. Individualizing risk of multidrug-resistant pathogens in community-onset pneumonia. *PLoS One*. 2015;**10**(4). e0119528.
9. Magiorakos A-P, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clinical microbiology and infection*. 2012;**18**(3):268–81.
10. Jennifer Brach, Caterina Rosano, Stephanie Studenski. Mobility. In: Halter JB, Ouslander JG, Tinetti M, Studenski S, High KP, Asthana S, editors. *Hazzard's Geriatric Medicine and Gerontology*. **6th**. 6 ed. New York: McGraw-Hill Education; 2008. p. 1397–409.
11. Labelle AJ, Arnold H, Reichley RM, Micek ST, Kollef MH. A comparison of culture-positive and culture-negative health-care-associated pneumonia. *Chest*. 2010;**137**(5):1130–7.
12. Fukuyama H, Yamashiro S, Kinjo K, Tamaki H, Kishaba T. Validation of sputum Gram stain for treatment of community-acquired pneumonia and healthcare-associated pneumonia: a prospective observational study. *BMC infectious diseases*. 2014;**14**(1):534.
13. Miyashita N, Shimizu H, Ouchi K, Kawasaki K, Kawai Y, Obase Y, et al. Assessment of the usefulness of sputum Gram stain and culture for diagnosis of community-acquired pneumonia requiring hospitalization. *Medical Science Monitor*. 2008;**14**(4):CR171–6.
14. Morgan AJ, Glossop AJ. Severe community-acquired pneumonia. *BJA Education*. 2015;**16**(5):167–72. doi: 10.1093/bjaed/mkv052.
15. Müller NL, Franquet T, Lee KS, Silva CIS. *Imaging of Pulmonary Infections*. Lippincott Williams & Wilkins; 2007.
16. Marrie TJ. Acute Bronchitis and Community-Acquired Pneumonia. In: Grippi MA, Elias JA, Fishman J, Kotloff RM, Pack AI, Senior RM, et al., editors. *Fishman's Pulmonary Diseases and Disorders*. **5th**. New York: McGraw-Hill Education; 2015. p. 1966–81.
17. Niederman MS. Gram-negative colonization of the respiratory tract: pathogenesis and clinical consequences. *Seminars in respiratory infections*. 1990. p. 173–84.

18. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. Community-acquired pneumonia requiring hospitalization among US adults. *New England Journal of Medicine*. 2015;**373**(5):415–27.
19. Song J, Oh WS, Kang C, Chung DR, Peck KR, Ko KS, et al. Epidemiology and clinical outcomes of community-acquired pneumonia in adult patients in Asian countries: a prospective study by the Asian network for surveillance of resistant pathogens. *International journal of antimicrobial agents*. 2008;**31**(2):107–14.
20. Chintaman AC, Ghadage DP, Bhore AV. Bacteriological Profile of Community Acquired Pneumonia in a Tertiary Care Hospital. *Int. J. Curr. Microbiol. App. Sci*. 2017;**6**(4):190–4.
21. Farida H, Gasem MH, Suryanto A, Keuter M, Zulkarnain N, Satoto B, et al. Viruses and Gram-negative bacilli dominate the etiology of community-acquired pneumonia in Indonesia, a cohort study. *International Journal of Infectious Diseases*. 2015;**38**:101–7.
22. Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. *Clinical Infectious Diseases*. 2011;**52**(suppl_4):S296–304.
23. Eber MR, Shardell M, Schweizer ML, Laxminarayan R, Perencevich EN. Seasonal and temperature-associated increases in gram-negative bacterial bloodstream infections among hospitalized patients. *PloS one*. 2011;**6**(9). e25298.
24. Grosso A, Famiglietti A, Luna CM. Community-acquired pneumonia due to gram-negative bacteria. *Community Acquired Infection*. 2015;**2**(4):117.
25. Peleg AY, Seifert H, Paterson DL. Acinetobacter baumannii: emergence of a successful pathogen. *Clinical microbiology reviews*. 2008;**21**(3):538–82.
26. Temesgen D, Bereded F, Derbie A, Biadglegne F. Bacteriology of community acquired pneumonia in adult patients at Felege Hiwot Referral Hospital, Northwest Ethiopia: a cross-sectional study. *Antimicrobial Resistance & Infection Control*. 2019;**8**(1):101.
27. Aliberti S, Cilloniz C, Chalmers JD, Zanaboni AM, Cosentini R, Tarsia P, et al. Multidrug-resistant pathogens in hospitalised patients coming from the community with pneumonia: a European perspective. *Thorax*. 2013;**68**(11):997–9.
28. Chokshi A, Sifri Z, Cennimo D, Horng H. Global contributors to antibiotic resistance. *Journal of global infectious diseases*. 2019;**11**(1):36.
29. Ayukekbong JA, Ntemgwa M, Atabe AN. The threat of antimicrobial resistance in developing countries: causes and control strategies. *Antimicrobial Resistance & Infection Control*. 2017;**6**(1):47.
30. Ocan M, Obuku EA, Bwanga F, Akena D, Richard S, Ogwal-Okeng J, et al. Household antimicrobial self-medication: a systematic review and meta-analysis of the burden, risk factors and outcomes in developing countries. *BMC public health*. 2015;**15**(1):742.
31. Sakeena MHF, Bennett AA, McLachlan AJ. Non-prescription sales of antimicrobial agents at community pharmacies in developing countries: a systematic review. *International journal of antimicrobial agents*. 2018;**52**(6):771–82.
32. Auta A, Hadi MA, Oga E, Adewuyi EO, Abdu-Aguye SN, Adeloye D, et al. Global access to antibiotics without prescription in community pharmacies: A systematic review and meta-analysis. *Journal of Infection*. 2019;**78**(1):8–18.