Research Article [Primadiamanti *et al.*, 5(3): March, 2014:3367-3373]
CODEN (USA): IJPLCP ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES
(Int. J. of Pharm. Life Sci.)

Antibiotics Management and outcome of Therapy for Patients with Community-Acquired Pneumonia in Hospital Pulau Pinang, Malaysia

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Abstract

To evaluate outcome of antibiotics therapy for community-acquired pneumonia (CAP) in medical ward of Hospital Pulau Pinang, Malaysia. A retrospective study was conducted. Subjects in this study were hospitalized patients with CAP diagnosis. Data were obtained from medical record of patients. National Antibiotic Guideline 2008 from Ministry of Health, Malaysia (MOH) was used. All data were analyzed using Statistical Package for the Social Sciences (SPSS). Among 323 patients included in this study, there were 188 (58.20%) patients whom treated with antibiotics that accordant to guideline and 135 (41.80%) patients were treated with antibiotics that discordant to guideline. This study showed that there were significant differences in improvement for heart rate and white blood cell (WBC) reduction between two groups. Length of stay (LOS) in guideline-adherent group was not significantly different with guideline-discordant group. Deaths were found only in guideline-discordant group with three patients. Application of available antibiotic guideline of CAP in prescribing showed better outcomes of therapy than guideline-discordant prescribing; effective in WBC count, improving heart rate of patients, shorter LOS, and no mortality.

Key-Words: Community-acquired pneumonia, Hospitalized, Antibiotic, Guideline, Malaysia

Introduction

Community-acquired pneumonia (CAP) is one of infectious diseases that cause morbidity and mortality, especially in Asia-Pacific regions [1]. Although some guidelines had been made by several organizations, treatment for CAP in Asian countries, including Malaysia, should be based on epidemiological data of microorganisms and antibiotics resistance data [2]. As the most common causative microorganism for CAP, *Streptococcus pneumoniae* resistance to β-lactams is increasing [2-4]. But, *Streptococcus pneumoniae* isolates are still susceptible to β-lactams in some CAP studies in Asia, including Malaysia [2, 5-7]. Therefore, β-lactams still become the choice of antibiotic for CAP guideline therapy due to their activities against *Streptococcus pneumoniae.*

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The occurrence of atypical microorganisms that cause CAP is increasing. Even though a review defines that antibiotics for atypical microorganisms in hospitalized CAP patients do not give benefit for survival or clinical efficacy [8], current guidelines recommend the use of antibiotics that may cover atypical microorganisms, including Malaysia [9-12]. Those antibiotics are consisted of combination of β-lactam and macrolide or fluoroquinolone monotherapy [9-14]. Addition of macrolide to a β-lactam regimen or fluoroquinolone monotherapy for CAP treatment may improve survival and LOS [15].

In some studies, patients that received antibiotics according to guideline showed better outcomes than those who received antibiotics discordant to guideline. Outcomes included time to reach clinical stability, LOS and mortality. Treatment failure was also lower in guideline-adherent group [13, 16]. Otherwise, some studies showed that LOS and mortality in guideline-adherent group were not significantly different between guideline-adherent group and guideline-discordant group [14, 17]. It is important to evaluate the outcome therapy of CAP even though some studies do not show better outcomes from the impact of applied guideline in

treating hospitalized patients with CAP. However, antibiotics guideline must be taken into consideration when selecting the appropriate antibiotics for therapy of CAP, including Malaysia. Outcome of therapy still needed to be monitored to evaluate the antibiotics use for hospitalized patients with CAP.

Material and Methods

Study Design

This was cross-sectional study. Data were collected from medical record of patients that had been registered and diagnosed with CAP. Patients' list was obtained from Chest Ward and Medical Record Office.

Inclusion and Exclusion Criteria

Universal sampling technique was performed. All hospitalized patients with CAP diagnosis that eligible for this study were taken. Eligibility criteria for patients with CAP that included in this study were registered patients at the hospital during the period between January 1, 2008 through December 31, 2011; adult patients with age ≥ 18 years old; hospitalized patients with CAP diagnosis. Patients were excluded from this study if patients had received antibiotics in the last seven days or had been hospitalized within the last seven days before admission to hospital, patients needed more than 14 days for therapy and patients that needed Intensive Care management. Three hundred and twenty three patients were selected based on inclusion and exclusion criteria.

Data Collection

Data were collected from medical record that provided the information such as signs and symptoms of CAP, physical examination and laboratory values. Besides that, medical record also recorded name of antibiotics given, route of administration, dosage, frequency and duration of administration.

Ethical Approval

Approval had been obtained from Clinical Research Center (CRC) Hospital Pulau Pinang and Ministry of Health, Malaysia. Information from Medical Record Office had been collected with the permission of Hospital Pulau Pinang approval and Ministry of Health, Malaysia. This study also had been registered with the National Medical Research Register (NMRR) with NMRR-12-59-10937.

Statistical Analysis

Independent sample t-test or non-parametric Mann-Whitney test were used to explain improvement for signs, symptoms and laboratory values between guideline-adherent and guideline-discordant group. Length of stay (LOS) based on guideline-adherent and guideline-discordant group was analyzed with independent sample t-test. Mortality among hospitalized patients was analyzed with Fisher-exact test.

Results and Discussion

Among 323 patients included in this study, 188 (58.2%) patients were given antibiotics therapy that accordant to guideline. The most prescribed antibiotics were combination of amoxicillin/clavulanate and azithromycin with 145 (77.1%) patients and followed by combination of ampicillin/sulbactam and azithromycin with 31 (16.5%) patients (Table 1). There were seven (3.7%) patients received combination of macrolides and cephalosporins in guideline-adherent group (Table 1). In this study, there was one patient that received combination of piperacillin/tazobactam and azithromycin (Table 1). This patient might be suspected as CAP patient with *Pseudomonas* infection. Furthermore, 135 (41.8%) patients received guideline-discordant therapy (Table 1). The most prescribed antibiotics were amoxicillin/clavulanate monotherapy with 51 (37.8%) patients and followed by ampicillin/sulbactam monotherapy with 25 (18.5%) patients (Table 1). There were 13 (9.6%) patients treated with combination of tetracycline and β-lactam/β-lactamase inhibitor in guideline-discordant group, followed by macrolide alone with 12 (8.9%) patients (Table 1).

Table 1: Antibiotics therapy for hospitalized patients with CAP

	Guideline-adherent	n (%)	Duration (days)	Guideline-discordant	n (%)	Duration (days)
			Mean ± SD			Mean ± SD
1	Amoxicillin/clavulanate + azithromycin	145 (77.1)	4.05 ± 1.85	Amoxicillin/clavulanate monotherapy	51 (37.8)	3.86 ± 2.12
2	Ampicillin/sulbactam + azithromycin	31 (16.5)	4.00 ± 2.00	Ampicillin/sulbactam monotherapy	25 (18.5)	3.96 ± 1.62
3	Erythromycin ethylsuccinate + ampicillin/sulbactam	1 (0.5)	7.00	Macrolide alone	11 (8.1)	2.67 ± 1.07
4	Erythromycin ethylsuccinate +	3 (1.6)	4.33 ± 2.52	Tetracycline + β-lactam/β-lactamase	13 (9.6)	3.38 ± 1.04

	amoxicillin/clavulanate			inhibitor		
5	Piperacillin/tazobactam + azithromycin	1 (0.5)	8.00	Third-generation of cephalosporin (ceftazidime) alone	4 (3.0)	6.25 ± 2.22
6	Macrolide + cephalosporin	7 (3.7)	4.58 ± 1.51	Other antibiotics	31 (23.0)	4.81 ± 1.97
Total		**188 (58.20)**			**135 (41.80)**	

Table 2 showed improvement of signs and symptoms as effectiveness of CAP management for hospitalized patients between guideline-adherent and guideline-discordant group. The data showed that there was a significant difference in improvement for heart rate between these two groups. However, other data did not show significant difference in improvement for other signs and symptoms between these two groups (Table 2).

Table 2: Improvement of signs and symptoms of hospitalized patients with CAP between guideline-adherent and guideline-discordant group

Signs and symptoms	Guideline-adherent		Guideline-discordant		*p*-value*
	n	Resolved in days (Mean ± SD)	n	Resolved in days (Mean ± SD)	
Fever	142	2.32 ± 1.85	87	2.06 ± 1.49	0.245
Chills	29	2.28 ± 1.31	20	2.00 ± 1.30	0.470
Shortness of breath	139	2.78 ± 2.03	82	2.63 ± 1.91	0.607
Dry cough	17	3.65 ± 2.50	7	3.14 ± 1.95	0.639
Productive cough	94	3.40 ± 1.92	62	3.64 ± 1.97	0.449
Hemoptysis	4	2.50 ± 1.00	3	3.33 ± 0.58	0.186
Chest pain	24	2.29 ± 1.20	24	2.21 ± 1.06	0.800
Auscultation	88	3.11 ± 1.96	74	2.94 ± 1.77	0.571
Heart rate	**52**	**1.77 ± 1.23**	**38**	**2.45 ± 1.87**	**0.041****
Blood pressure	93	2.78 ± 2.05	51	3.08 ± 2.30	0.417

*Independent sample t-test was used for chills, shortness of breath, dry cough, productive cough, chest pain, auscultation, heart rate and blood pressure; Mann-Whitney test was used for fever and hemoptysis.
** *p*-value < 0.05 was significant value.

Table 3 showed laboratory values that included the value of WBC count, neutrophils count and urea level between guideline-adherent and guideline-discordant group. There was significant difference in WBC reduction between two groups. Otherwise, there were no other significant differences in neutrophils count and urea level (Table 3).

Table 3: Improvement of laboratory values of hospitalized patients with CAP between guideline-adherent and guideline-discordant group

Laboratory values	Guideline-adherent		Guideline-discordant		*p*-value*
	n	Reduction (Mean ± SD)	n	Reduction (Mean ± SD)	
White blood cell	17	5.51 ± 6.33	12	1.16 ± 3.41	**0.040****
Neutrophils	92	1.69 ± 7.48	63	1.47 ± 9.31	0.911
Urea	94	0.08 ± 1.52	73	0.05 ± 1.96	0.960

* Independent sample t-test was used for white blood cell; Mann-Whitney test was used for neutrophils and urea.
** *p*-value < 0.05 was significant value.

Length of stay (LOS) and mortality were also measured as outcome of CAP management in this study. Table 4 showed length of stay (LOS) and mortality in guideline-adherent group and guideline-discordant group (Table 4).

Table 4: Length of stay (LOS) and mortality in guideline-adherent group and guideline-discordant group

	Guideline-adherent (n=188)	Guideline-discordant (n=135)	*p*-value*
Length of stay (Mean ± SD, days)	4.72 ± 2.06	4.90 ± 2.26	0.457
Mortality			
Death (no. of patients)	0 (0.0)	3 (100.0)	0.072
Survived (no. of patients)	188 (58.8)	132 (41.3)	

* Independent sample t-test was used for length of stay (LOS); Fisher-exact test was used for mortality.

Antibiotics Therapy

Earlier administration of initial empirical antibiotics was required in order to get better clinical outcome and improve survival rate [18]. A study stated that empirical antibiotics therapy for hospitalized patients with CAP had equal clinical efficacy to microorganisms-directed treatment approach [19]. In some clinical series, causative microorganisms in CAP patients could not be identified. However, failure to identify the microorganisms did not influence the outcome [20]. But, once microorganisms could be identified, adjusted antibiotics should be administered [18].

Initial antibiotics therapy within the first 24 hours of hospitalization was evaluated based on National Antibiotic Guideline of Ministry of Health (MOH) Malaysia 2008. This guideline recommended the use of macrolides in combination with other antibiotics [9]. Macrolides in combination therapy also had better anti-inflammatory activity than their antimicrobial activity [21]. Macrolides could modulate the immune response through reducing the pro-inflammatory response to infectious stimuli that caused sepsis or organ dysfunction. Macrolides also had an activity that could reduce the interference of respiratory epithelial cells by *Streptococcus pneumoniae* [21-22]. Macrolides worked as antimicrobial activity by inhibiting protein synthesis, while β-lactams had cell wall of microorganisms as their target. Therefore, β-lactams and macrolides could work synergistically even though they had different mechanisms and site of action [23-24]. Besides that, antibiotics treatments for non-severe CAP that caused by atypical pathogens were also active for CAP caused by *Legionella*. Macrolides were recommended antibiotics for treating CAP caused by *Legionella* [25].

Antibiotics therapy must cover *Streptococcus pneumoniae* and atypical microorganisms [18]. Antibiotics that had atypical coverage for hospitalized patients with CAP were also advantageous for patients with *Legionella* infection [8]. A meta-analysis showed that in moderate CAP the relative risk for treatment failure was significantly lower in patients with *Legionella* infection that received antibiotics against atypical microorganisms [26]. In this study, there were 188 (58.20%) patients whom treated with antibiotics that accordant to guideline and 135 (41.80%) patients were treated with antibiotics that discordant to guideline.

All prescribed antibiotics in guideline-adherent group were either combination of β-lactam/β-lactamase inhibitor or cephalosporins with macrolide. Combination of extended-spectrum cephalosporin or β-lactam/β-lactamase inhibitor with a macrolide had activity against drug-resistant *Streptococcus pneumoniae* [21]. β-lactam/β-lactamase inhibitor was used to provide coverage against typical respiratory microorganisms. Macrolide was used to provide coverage against atypical microorganisms such as *Legionella pneumophila*, *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*. In this study, most common macrolides that being used were azithromycin and erythromycin ethylsuccinate. In guideline-adherent group, the most prescribed antibiotics were amoxicillin/clavulanate + azithromycin (77.1%). Amoxicillin/clavulanate was one of the most common prescribed agents that given for CAP patients, especially for patients whom resistant pathogens were suspected [27]. Azithromycin could prevent the reversible inhibition of *Legionella* growth. Azithromycin had better pharmacokinetic profile than other macrolides, such as once in a day administration and shorter course of therapy. Therefore, it was the best choice among macrolides in treating hospitalized CAP caused by *Legionella* [25].

In guideline-discordant group, the most prescribed antibiotics were β-lactam/β-lactamase inhibitor monotherapy (amoxicillin/clavulanate monotherapy and ampicillin/sulbactam monotherapy); followed by macrolide monotherapy and tetracycline + β-lactam/β-lactamase inhibitor. In some studies, β-lactam/β-lactamase inhibitor or macrolide monotherapy were not more effective than combination of β-lactam/β-

lactamase inhibitor and macrolide [21, 28-29]. Tetracycline such as doxycycline was alternative therapy for macrolide that could cover atypical microorganisms. It could also be used as combination of β-lactam/β-lactamase inhibitor and tetracycline, such as amoxicillin/clavulanate and doxycycline [30-31].

Improvement of signs, symptoms and laboratory values

Signs and symptoms that being monitored were fever, chills, shortness of breath, dry cough, productive cough, hemoptysis, chest pain, auscultation, heart rate and blood pressure. In this study, significant difference only occurred in improvement for heart rate between guideline-adherent and guideline-discordant group. In guideline-adherent group, heart rate of patients was improving faster than guideline-discordant group. Otherwise, other signs and symptoms such as fever, chills, shortness of breath, dry cough, productive cough, hemoptysis, chest pain, auscultation and blood pressure were not significantly different between guideline-adherent and guideline-discordant group. Number of patients that had improvement of fever, shortness of breath and heart rate between guideline-adherent group and guideline-discordant group were significantly different. These findings revealed that accordance to guideline therapy could affect the improvement of fever, shortness of breath and heart rate. But, other signs and symptoms were not likely affected.

Laboratory values that being observed were WBC count, neutrophils count and urea level between guideline-adherent and guideline-discordant group. There was significant difference in WBC reduction between guideline-adherent and guideline-discordant group. Reduction of white blood cell and neutrophils count during therapy showed decline of infections, due to antibiotics. Accordance to guideline was more effective than discordant to guideline in reducing WBC count. Urea level measurement enabled patients to be stratified according to severity, treatment site and increasing risk of mortality [32]. Urea level was one of the criteria of severity measurement in CAP diagnosis [12]. Therefore, reduction on urea level into normal range could indicate effectiveness of CAP management. Otherwise, there was no other significant difference in neutrophils count and urea level.

Outcome of therapy

Length of stay (LOS) in guideline-adherent group was 4.72 ± 2.06 days, while guideline-discordant group showed LOS of 4.90 ± 2.26 days. Length of stay (LOS) in guideline-adherent group was not significantly different with guideline-discordant group. However, LOS in guideline-adherent group was shorter than guideline-discordant group. The mortality between two groups was not significantly different. Deaths were found only in guideline-discordant group with three patients.

In this study, application of available antibiotic guideline of CAP showed better outcomes of therapy. Outcomes included mortality and LOS. These were consistent to other studies that stated guideline-adherent treatment was associated with decreased mortality and treatment failure [13, 16].

All prescribed antibiotics in guideline-adherent group were combination of β-lactam/β-lactamase inhibitor and macrolide. In guideline-discordant group, the most prescribed antibiotics were β-lactam/β-lactamase inhibitor monotherapy (amoxicillin/clavulanate monotherapy and ampicillin/sulbactam monotherapy); followed by macrolide monotherapy and tetracycline + β-lactam/β-lactamase inhibitor. Therefore, combination of β-lactam/β-lactamase inhibitor and macrolide in guideline-adherent group could decrease mortality and shorten LOS compared to β-lactam/β-lactamase inhibitor monotherapy or macrolide monotherapy. These results were consistent to other similar studies that focused on mortality and LOS as outcome therapy. Combination of β-lactams and macrolides showed better outcomes than β-lactams monotherapy [21, 28-29]. Martinez *et al* stated that not adding macrolide to β-lactam-based initial antibiotics regimens might cause in-hospital mortality [28]. Antibiotics therapy that used β-lactam monotherapy did not give better outcome than β-lactam plus macrolide [29].

In guideline-adherent group, there were few patients who received combination of macrolides and cephalosporin. This combination could decrease mortality and shorten LOS. This was consistent to other studies [21, 33]. A review stated that initial empirical combination therapy of cephalosporin and macrolide for hospitalized patients with CAP was related to decreased mortality and shorter length of stay (LOS) than treatment with cephalosporin monotherapy [21]. The other retrospective study of 12.945 inpatients showed that initial treatment of CAP with second-generation or third-generation of cephalosporin plus macrolide was associated with reduction of 30-day mortality in patients with PSI classes IV and V [33].

Limitation of study

This study was designed as retrospective study. Therefore, insufficient data could be found in completing information, such as patients' socio-economic status, patients' weight and height, signs and

symptoms at the end of therapy, laboratory values or other related data.

Conclusion

Application of available antibiotic guideline of CAP in prescribing showed better outcomes of therapy than guideline-discordant prescribing; effective in reducing WBC count, improving heart rate of patients, shorter LOS, and no mortality.

Acknowledgement

This research was supported in part by a grant from RU-PGRS Universiti Sains Malaysia 1001/PFARMASI/835003. We thanked Hospital Pulau Pinang, Malaysia for collaboration with this study.

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How to cite this article

Primadiamanti A., Sulaiman S.A. and Gillani S. W. (2014). Antibiotics management and outcome of therapy for patients with community-acquired pneumonia in hospital Pulau Pinang, Malaysia. *Int. J. Pharm. Life Sci.*, 5(3):3367-3373.

Source of Support: Nil; Conflict of Interest: None declared

Received: 07.02.14; Revised: 13.02.14; Accepted:28.02.14