

## Original Research Article

# Rational Antimicrobial Use in an Intensive Care Unit in Jakarta, Indonesia: A Hospital-Based, Cross-Sectional Study

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### Abstract

**Purpose:** To analyze the rationality of antimicrobial usage and factors influencing it over the period of January to December 2010 in Fatmawati General Hospital, Jakarta, Indonesia.

**Methods:** Present study was conducted in the intensive care unit of Fatmawati General Hospital, Jakarta, Indonesia. Gyssens method was used to assess the rationality of antimicrobial use. Data for this retrospective, cross-sectional study were drawn from patients' medical record files. Multivariate analysis with ordinal logistic regression was used to determine the dominant factors affecting the appropriateness of antimicrobial use.

**Results:** Data for 410 patients from the intensive care unit (ICU) was collected. There were 912 antimicrobial regimens prescribed for these patients. Based on Gyssens method, 805 antimicrobial regimens were empirical and 107 definitive. Of the empirical regimens, 596 (74.03 %) were inappropriate, while of the definitive regimens, 84 (78.51 %) were inappropriate. Site of infection, comorbid conditions and economic status of patients were the main factors that influenced the appropriateness of antimicrobial treatment choice.

**Conclusion:** A higher degree of irrational use of antimicrobial agents occurs in the ICU of the hospital studied, this can lead to increase in the burden of disease.

**Keywords:** Rational use, Antimicrobial, Empirical treatment, Gyssens method, Intensive care

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## INTRODUCTION

Antibiotics use is common in hospitalized patients especially in surgical procedures and Intensive Care Unit (ICU) as a therapy for infection or prophylactic measures [1-3]. Increasing antimicrobial resistance due to irrational use of antimicrobial agents is a serious issue worldwide [4]. Different studies have reported the inappropriate use of antimicrobial agent in developing countries [5]. Hadi *et al* reported that 44 to 97 % of patients in an

Indonesian hospital were prescribed with unnecessarily antibiotics regimen [6].

Gyssens *et al* developed a new protocol for appropriate use of antimicrobial while working in University Hospital Nijmegen, Netherland in 1996. They studied the impact of interventions and compared the results with study carried before improved guidelines. A decrease in antibiotic use before and after regimen was noticed. Gyssens *et al* determined categories of rational antimicrobial prescription regarding

appropriateness, pharmacodynamic and socioeconomic status of patient [7]. Several studies were carried out to evaluate appropriateness of antibacterial usage on the basis of Gyssens protocol.

In 2010, Parisot *et al* evaluated the quality of antibiotic usage in intensive care units of two Hospitals in France and results revealed that among 113 patients, 7 % were prescribed with too broad spectrum antimicrobial agents, 8 % unjustified associated, 20 % wrong posology, 1 % incorrect route of administration, 6 % wrong interval and 7 % were lacking plasmatic dosage [8]. Apisarntharak *et al* found a decrease trend of irrational use of antimicrobial agents from 91-25 % before and after antibiotic control program in a teaching hospital of Thailand [9]. Usman Hadi and colleagues conducted a study to investigate the appropriate use of antibiotics in two teaching hospital of Java, Indonesia using the Gyssens method. They found that 84 % patients were prescribed with antibiotics and 60% of them were inappropriate and 34 % antibiotic prescriptions in Hospital A and 48 % in Hospital B were without indications [6].

Previous studies conducted in Fatmawati General Hospital (FGH), Indonesia focused on the intensity, quantity and sensitivity of antibiotics usage [10]. FGH has never developed any guidelines for clinicians regarding the use of antibiotics and that can result in irrational choices of antibiotics. No studies have also been carried out to investigate the appropriateness of antimicrobial usage in FGH using Gyssens method. The aim of this study, therefore, was to assess the appropriateness of antimicrobial agents prescribed in ICU of FGH.

## EXPERIMENTAL

This is a retrospective, cross-sectional study conducted in Intensive Care Unit (ICU) of Fatmawati General Hospital (FGH). The data were drawn from registration forms, daily instruction forms and medical records of those patients who were treated with antimicrobial regimens and hospitalized for at least 48 h in ICU of FGH, during January-December 2010. Gyssens protocol was applied to determine appropriateness of antimicrobial agents prescribed in FGH. Gyssens *et al* divided antimicrobial usage in six main categories, appropriate (category 0), inappropriate timing (category I), inappropriate dose and route of administration (category IIa, IIb, IIc), inappropriate duration (category IIIa, IIIb), inappropriate type (IVa, IVb, IVc, IVd),

inappropriate indication (category V), and incomplete data (category VI) [5].

## Statistical analysis

Descriptive analysis of data was carried out on the basis of characteristics of the research subjects by using bivariate and multivariate analyses. SPSS version 17 software was used to analyze the data while keeping the degree of confidence as 95 % with a *p*-value of 0.05. Findings of this study were compared with available literature to determine appropriateness of antimicrobial usage in the ICU of FGH. The Sanford Guide to Antimicrobial Therapy (2010), Drug Information Handbook (2010); Applied Therapeutics: The Clinical Use of Drugs (2009), Pharmacotherapy: A Pathophysiologic Approach (2008) and Principles and Practice of Infectious Disease (2005), were used to assess the rationality of antimicrobial use [11-15].

## RESULTS

There were 819 patients treated in the ICU of FGH from January to December 2010 and 410 of them met the inclusion criteria of this study. Among these 410 patients, 200 (48.78 %) patients belonged to poor families while 118 (28.78 %) patients have health insurance. There were 31 types of antimicrobial agents used in 912 regimens prescribed to these patients. Antimicrobial agents in 805 (88.27 %) prescriptions were used as empirical therapy and in 107 (11.73 %) prescription was definitive therapy. There were 156 (38 %) Patients who underwent surgical procedures such as laparotomy, appendectomy and craniotomy were treated with antimicrobials as an empirical therapy. Information regarding antimicrobial agents used in ICU of FGH is mentioned in Table 1.

The most commonly used empirical antimicrobial was ceftriaxone, used in 281 regimen (34.91 %). The second most frequently prescribed empirical antibacterial was metronidazole with 84 (10.43 %) regimens whereas levofloxacin and meropenem were used in 66 and 48 empirical regimens. Cefoperazone, ciprofloxacin and ceftazidime were also common empirical antimicrobials in our cohort. The top 3 antimicrobials used as definitive therapy were phosphomycin, meropenem and ciprofloxacin, used in 25 (23.36 %), 18 (16.82 %) and 10 (9.35 %) regimens respectively.

**Table 1:** Antimicrobial profile of patients in the ICU of Fatmawati General Hospital, Jakarta, Indonesia

Antimicrobial	Empirical	(%)	Definitive	(%)
Amikacin	13	1.61	8	7.48
Ampicillin-sulbactam	28	3.48	9	8.41
Azithromycin	1	0.12	0	0.00
Ethambutol	15	1.86	0	0.00
Fluconazole	12	1.49	0	0.00
Phosphomycin	19	2.36	25	23.36
Gentamicin	7	0.87	2	1.87
Imipenem-cilastatin	12	1.49	4	3.74
Isoniazide	14	1.74	0	0.00
Kanamycin	1	0.12	0	0.00
Clarithromycin	1	0.12	0	0.00
Levofloxacin	66	8.20	8	7.48
Meropenem	48	5.96	18	16.82
Metronidazole	84	10.43	0	0.00
Micafungin	1	0.12	0	0.00
Ofloxacin	2	0.25	1	0.93
Pyrazinamide	10	1.24	0	0.00
Rifampicin	16	1.99	0	0.00
Cefepime	9	1.12	3	2.80
Cefixime	0	0.00	2	1.87
Cefoperazone	44	5.47	3	2.80
Cefoperazone-sulbactam	23	2.86	0	0.00
Cefotaxime	5	0.62	0	0.00
Cefotiam	1	0.12	0	0.00
Cefpirome	4	0.50	1	0.93
Ceftazidime	31	3.85	9	8.41
Ceftizoxime	9	1.12	0	0.00
Ceftriaxone	281	34.91	1	0.93
Ciprofloxacin	41	5.09	10	9.35
Streptomycin	6	0.75	0	0.00
Vancomycin	1	0.12	3	2.80
<b>Total</b>	<b>805</b>	<b>100.00</b>	<b>107</b>	<b>100.00</b>

### Correlation of rationality or appropriateness

In the treatment of infection related main illnesses, 468 (51.32 %) empirical antimicrobial regimen were used. Ceftriaxone was used in 217 (46.37 %) of these regimens. According to Gyssens categories, Inappropriate use of ceftriaxone (category I-V) for treating infection-related main illnesses was seen in a total of 189 (49.35 %) regimens, and only 28 (32.94 %) regimens were found to be appropriate (category 0). In 143 (62.72 %) regimens, ceftriaxone was found inappropriate regarding the spectrum of antimicrobial activity (category IV). The inappropriate duration of ceftriaxone use was found in 18 (29.51 %) regimens employed to treat infection related main illness.

Metronidazole was the second most frequently used antibiotic as it was employed in 77 (16.45 %) regimens. There were 151 (36.83 %) antibiotic regimens that contain metronidazole. It was found that 26 (42.62 %) regimens containing metronidazole were inappropriate either

regarding the duration of therapy (category III) or inappropriate concomitant agents. The use of metronidazole in combination with meropenem, cefoperazone or sulbactam for the therapy of post operative intraabdominal infections without indication (category V) was seen in 17 (30.36 %) regimens.

Meropenem was found in 26 (5.56 %) prescriptions indicated for infection related main illnesses like sepsis and intraabdominal surgery. The choice of meropenem was found inappropriate in 12 (5.26 %) regimens (category IV) whereas inappropriate use of meropenem (category I-V) in patients was seen in 26 (6.79 %) regimens. The correlation between rationality of empiric antimicrobial use and the presence of infection-related main illnesses was tested by Chi-square and it is given in Table 2. It was found that appropriateness of empirical antimicrobial treatment was significantly influenced by the presence of infection related main disease ( $p < 0.001$ ).

**Table 2:** Correlation between rationality/appropriateness of empiric antimicrobial use with the presence of infection-related main illnesses, based on Gyssens method

Variable	Gyssens category						Total	P-value
	0	1	2	3	4	5		
Infection-related main illness present	124	8	40	47	95	23	337	< 0.001
Infection-related illness absent	85	9	29	61	228	56	468	
<b>Total</b>	<b>209</b>	<b>17</b>	<b>69</b>	<b>108</b>	<b>323</b>	<b>79</b>	<b>805</b>	

**Table 3:** Correlation between rationality/appropriateness of empiric antimicrobial use and the presence of infection-related accompanying illness based on Gyssens method

Variable	Gyssens category						Total	P-value
	0	1	2	3	4	5		
Presence of infection-related accompanying illness	124	8	40	47	94	23	336	<0.001
Absence of infection-related accompanying illness	85	9	29	61	229	56	469	
Total	209	17	69	108	323	79	805	

### Correlation between rationality of empiric antimicrobial therapy and infection-related illnesses

The common infection related accompanying illnesses in the ICU of FGH were pneumonia, pleural effusion, and fungal infections. Data of 191 (46.59 %) patients with infection related concomitant illnesses was assessed on Gyssens protocol. The most common antimicrobial agent used as the empiric therapy to treat infection-related accompanying illness was ceftriaxone, used in 63 (18.75 %) regimens. The choice of ceftriaxone to treat these morbidities was found to be the inappropriate choice (category IV) in 33 (35.11 %) regimens and inappropriate duration of administration (category III) in 10 (21.28 %) regimens. Inappropriate use of ceftriaxone in treating infection-related accompanying illnesses was found in 50 (23.58 %) regimens. In contrast, the appropriate use of ceftriaxone (category 0) was seen in 13 (10.48 %) regimens. Levofloxacin was second most common antimicrobial agent used as an empiric therapy to treat infection related accompanying illness as it was found in 58 (17.26 %) regimens. Use of levofloxacin without indication (category V) was seen in 4 (17.39 %) regimens. Inappropriate use of levofloxacin (category I-V) for managing aforementioned accompanying illnesses was seen in 34 (16.04 %) regimens. In contrast, the appropriate use was found in 24 (19.35 %) regimens.

The third most widely used antimicrobial empiric therapy in infection-related accompanying

illnesses was ciprofloxacin, given in 29 (8.63 %) regimens. Inappropriate use of ciprofloxacin, related to duration of therapy (Category III) was found in 8 (17.02 %) regimens whereas irrational use of ciprofloxacin in all categories (category I-V) was found in a total of 21 (6.25 %) regimens. The correlation between the rational empiric antimicrobial therapy and infection related to accompanying illnesses was found significant ( $p < 0.001$ ), as shown in Table 3.

### Correlation between the rationality of empiric antimicrobial agents and doctor's approach

Patients treated in the ICU of FGH remain under the observation of more than one doctor. Patient remained under treatment of some specialists before admitted to the ICU. Clinicians who were involved in the prescription of antimicrobial agents for patients treated in the ICU include anesthesiologists (intensive care consultants), surgeons (neurosurgeons, thoracic surgeons, digestive surgeons, general surgeons, and oncologic surgeons) 310 (38.51 %) were from empiric therapy, while 14 pulmonologists were from definitive group of therapy. Further details are shown in Table 4.

Frequency of prescribed empiric antimicrobial agents in the ICU of our hospital by surgeons was recorded in 310 (38.51 %) regimens. Ceftriaxone was observed in 161 (51.94 %) regimens, approximately half of the total antimicrobial prescriptions made by surgeons. Inappropriate prescription of ceftriaxone (category I-V) made by surgeons was seen in

**Table 4:** Antimicrobial prescriptions by specialists based on the type of therapy

Clinicians' category	Type of antimicrobial therapy				Total
	Empiric	(%)	Definitive	(%)	
Intensive Care Consultants	142	17,64	64	59.81	206
Surgeons	310	38,51	15	14.02	325
Pulmonologists	161	20,00	14	13.08	175
Internists	96	11,93	13	12.15	109
Obstetricians and gynecologists	34	4,22	1	0.93	35
Neurologists	42	5,22	0	0.00	42
Orthopedic surgeons	20	2,48	0	0.00	20
Total	805	100	107	100.00	912

146 (55.09 %) regimens. There were 15 (33.33 %) ceftriaxone prescriptions by surgeons that were appropriate according to Gyssens method (category 0). Metronidazole was the second most commonly implied empiric antibiotic by the clinicians. Inappropriateness in metronidazole containing regimens prescribed by surgeons was related to the duration of therapy (category III) in 17 (44.74 %) regimens and without indication (category V) in 14 (40 %) regimens. There were 25 (55.56 %) appropriate (category 0) and 35 (13.21 %) (category I-V) inappropriate metronidazole regimen implied by surgeons.

The second most common doctors who prescribed empiric antimicrobial agents in the ICU were the intensivists, in 142 (17.64 %) regimens. The most frequent empiric antimicrobial agent prescribed by intensivists was ciprofloxacin, in 24 (16.9 %) regimens. Irrational approach related to the duration of therapy (category III) was seen in 6 (20.69 %) regimens. There were 6 (14.29 %) appropriate regimens (category 0) and 18 (18 %) inappropriate regimens (category I-V) of ciprofloxacin by intensivists. Ampicillin-sulbactam combination was observed as the second most frequent antimicrobial agent implied in 20 (14.08 %) regimens by intensivists. Empirical therapy of ampicillin-sulbactam in 9 (26.47 %) regimens by intensivists was inappropriate choice (category IV). Ampicillin-sulbactam was used as an empiric therapy in patients with CAP and sepsis.

The third most common doctors who prescribed empiric antibiotics were pulmonologists, in 155 (19.25 %) regimens. They most commonly prescribed levofloxacin as empiric therapy in 35 (22.58 %) regimens. Inappropriate duration of treatment with levofloxacin was found in 9 (47.37 %) regimens.

The second most frequently prescribed empiric antimicrobial agent by pulmonologists was ceftriaxone, in 27 (17.42 %) regimens. Inappropriate prescription of ceftriaxone by pulmonologists as an inappropriate choice (category IV) was found in 11 (50 %) regimens. There were 6 (8.11 %) appropriate prescription (category 0) and 21 (25.93 %) inappropriate prescriptions (category I-V) of ceftriaxone by pulmonologists.

The internists prescribed antimicrobial agents in 98 (12.17 %) regimens. The most frequently prescribed antimicrobial was again ceftriaxone, in 36 (36.73 %) regimens. Ceftriaxone was chosen by internists as an empiric therapy for chronic pulmonary disease in 21 (45.65 %) regimens. There were 6 (33.33 %) appropriate regimens (category 0) and 30 (37.5 %) inappropriate regimens of ceftriaxone by internists.

Neurologists prescribed 42 (5.22 %) antimicrobial regimens. They most frequently prescribed ceftriaxone, in 24 (57.14 %) regimens. It was inappropriate type of empiric therapy for infectious diseases (category IV) in 14 (58.33 %) regimens. The prescriptions of ceftriaxone by neurologists was found to be appropriate (category 0) in 6 (60 %) regimens and inappropriate (Categories I - V) in 18 (56.25 %) regimens.

## DISCUSSION

The most commonly used empirical antimicrobial agent in our cohort was ceftriaxone (34.91 %). The choice of ceftriaxone was based upon the knowledge of the prescriber and the economic status of the patient. Phosphomycin was most frequently prescribed antibacterial drug with 25 (23.36 %) definitive therapy regimens. Choice of Phosphomycin was based upon bacterial culture sensitivity test of sputum and pus of patients. Bacteria such as *P. aeruginosa*, *A. Baumannii* and

*Klebsiella* sp were isolated from these cultures. These micro organisms often develop multi-drug resistant and found in patients with severe infections and contribute to high mortality rate [16]. Phosphomycin related bacterial resistance frequently observed by the researchers [16].

Ceftriaxone was used in 217 (46.37 %) regimens employed to treat infection related main illness. Ceftriaxone was main drug prescribed in abdominal and cranial surgeries. In 143 (62.72 %) regimens, ceftriaxone was found inappropriate (category IV). Ceftriaxone was used as single agent in post laparotomy patients. Intraabdominal infections can be caused by either gram negative or gram positive bacteria, more likely by anaerobic bacteria. Cephalosporins do not possess antimicrobial activity against anaerobic bacteria that can result in failure of therapy. Conversely, they should be used together with an anti-anaerobic agent. Inappropriate antibiotic choice in treating intraabdominal infection can cause poor patient outcome [17].

Ceftriaxone was the most common antimicrobial agent used as empiric therapy to treat infection-related accompanying diseases (63 regimens). Ceftriaxone was often used in treating infection-related comorbidities such as community-acquired pneumonia (CAP) and sepsis. Ceftriaxone used in treating CAP and sepsis was often as a monotherapy. In many cases, the patients were in septic shock because of the inappropriate use of ceftriaxone. Antimicrobial agents used to treat sepsis was based on the location of the infection. The ideal antibiotic used for treating sepsis should have low resistance, minimal side effects, and a good strength in combating pathogenic bacteria based on the location of the infection [18]. Patients with severe sepsis or septic shock warrant broad spectrum therapy until the causative pathogen and its antibiotic susceptibilities are defined. Restriction of antibiotics as a strategy to reduce the development of antimicrobial resistance or to reduce cost is not an appropriate initial strategy in these patients [12].

In our cohort, levofloxacin was used for inappropriate duration (category III) in 15 (31.91 %) regimens. The administration of 750 mg of levofloxacin to treat patients with bronchopneumonia was for 6 - 17 days. Prolonged use of levofloxacin in the treatment of pneumonia might be due to the absence of evaluation of therapy on transfer of the patients to general ward where antibiotic was continued. Dunbar *et al* found that 750 mg of levofloxacin per day for 5 days was at least as effective as

500 mg per day for 10 days to treat mild-to-severe CAP. Moreover, high-dose and short-course of levofloxacin regimen maximizes concentration dependent antibacterial activity, decreases the potential of drug resistance and show better patient compliance [19,20].

Ciprofloxacin was the third most widely used antimicrobial empiric therapy in infection-related accompanying illnesses (29 regimens). Use of ciprofloxacin in the ICU of FGH was mainly intended to treat CAP and nosocomial pneumonia. Inappropriate duration of ciprofloxacin was found in 8 regimens. The administration of ciprofloxacin as a therapy for CAP and sepsis was continued for 14 - 25 days. Clinical evaluation revealed that ciprofloxacin was failed to improve patient condition. Successful antibiotic therapy is assessed by a febrile phase for 48-72 h following minimum of 5 days antimicrobial treatment [21]. Mild to moderate gastrointestinal tract adverse events were observed with ciprofloxacin. Reported adverse effects of ciprofloxacin are photosensitivity, diarrhea, vomiting and nausea, liver function abnormalities, insomnia, headache and rash [22].

Ceftriaxone was found to be an inappropriate antimicrobial therapy (category IV) in 110 (64.71 %) regimens made by surgeons. Inappropriate choice of antimicrobial agent was mostly found in patients who underwent abdominal surgeries. *Bacteroides fragilis* was the most prominent pathogen causing intraabdominal infections. Cephalosporins were often used to treat intraabdominal infections, but they do not exhibit anti-anaerobic properties and must be used in conjunction with an anti-anaerobic agent. *Bacteroides fragilis* showed sensitivity towards metronidazole, carbapenem, and inhibitors of beta lactam-beta lactamase activity. This was the reason why the use of cephalosporins to treat intraabdominal infections were often combined with metronidazole [17,23].

Pulmonologists prescribed levofloxacin as empiric antimicrobial therapy 35 regimens. It was prescribed to treat CAP and HAP in the ICU of FGH. Inappropriate duration of therapy with levofloxacin was seen in 9 regimens. Levofloxacin (750 mg) was used for 6-13 days, while 500 mg of levofloxacin was used for 22 days. Patients with CAP were given a combination of ceftriaxone and 750 mg dose of levofloxacin. After patients showed clinical improvements, they were moved to the general ward and the antibiotics were continued even though their supporting data (white cell count, temperature and chest x-ray) showed

improvements. Patients suffering from CAP were also given a combination of ceftriaxone and 500 mg dose of levofloxacin. This combination was used for 22 days as the patients were transferred to the general ward and it was continued because the chest X-ray of the patients showed pleural effusion. Levofloxacin is a concentration-dependent antimicrobial agent, a high-dose (750 mg), short-course (5-day) was based on the rationale that higher concentration peaks lead to increased killing of the pathogen, decreased resistance development and higher patient compliance with the shorter course. It was reported that patients with mild to severe CAP, 750 mg of levofloxacin per day for 5 days was as safe and well tolerated as 500 mg per day for 10 days [24,25].

## CONCLUSION

Based on Gyssens method, infection-related main illnesses, infection-related accompanying illnesses and doctors contribute significantly to the rationality or appropriateness of empiric antimicrobial use with a p-value of <0.01. Infection-related main illnesses, infection-related accompanying illnesses, doctors, age, and insurance did not contribute to the rationality of definitive antimicrobial use.

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