

Quantitative and Qualitative Analysis of Antibiotics in the Intensive Care Unit (ICU)

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Abstract

The high incidence of infection in the ICU requires frequent use of antibiotics, thereby increasing the risk of developing antibiotic resistance when used irrationally. To assess the quantity and quality of antibiotic use, the World Health Organization (WHO) recommends using the Anatomical Therapeutic Chemical (ATC) classification system or the Defined Daily Dose (DDD) method. In that study, 25 articles were analyzed, including 21 quantitative research articles and four qualitative research articles. These articles were obtained from three databases: PubMed Central (PMC), Research Gate, and Google Scholar. The most commonly used antibiotics in the ICU are ceftriaxone (1×2g, IV) with a DDD value of 358,139/100 bed-days, meropenem (3×2g, IV) with a DDD value of 289,747/100 bed-days, and piperacillin-tazobactam (4×4.5g, IV) with a DDD value of 164,816/100 bed-days. These values indicate the number of antibiotics used in relation to 100 days of sleep. In addition, evaluation of the quality of antibiotic use in the ICU revealed that it is generally characterized by irrational use. By conducting such research, healthcare professionals can optimize the use of antibiotics in the ICU, leading to more effective treatment outcomes while minimizing the development of antibiotic resistance.

Keywords: Antibiotics, ATC/DDD, Gyssens, intensive care unit

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1 Introduction

The intensive care unit (ICU) is among hospital's departments with high antibiotics prescribed around ten times more than other wards/units [1]. High antibiotics use in the ICU indicates a high rate of infection. Sepsis and pneumonia are two infections that happen to patients who are then treated in the ICU. Rapid antibiotic therapy is required to treat these infections, notably sepsis, one hour after diagnosis and at optimal doses [1].

Antibiotics resistance occurs when the minimum inhibitory concentration (MIC) of antibiotics in a specific individual cannot be attained at standard doses [2]. Antibiotics resistance can be influenced by a lot of factors, one of which is the improper use of antibiotics. Antibiotics resistance has been widely reported in Indonesia. According to data from several hospitals in Indonesia, 13–26% of *Methicillin-resistant Staphylococcus aureus* (MRSA) attained methicillin resistance, while *Escherichia coli* and *Klebsiella pneumonia* attained 25–57% and 32–56%, respectively [3]. According to the results of the antimicrobial resistant studies in Indonesia (AMRIN-Study), 43% of *Escherichia coli* were resistant to antibiotics. Ampicillin (34%), cotrimoxazole (29%), and chloramphenicol (25%) are among the antibiotics that have developed resistance. Additionally, tests on 781 hospitalized patients revealed that 81% of *Escherichia coli* were resistant to ampicillin (73%), cotrimoxazole (56%), chloramphenicol (43%), ciprofloxacin (22%), and gentamicin (18%) [4].

Antibiotics use is reduced gradually to minimize the risk of resistance. This method entails modifying an antibiotics therapy to decrease the incidence of resistance prompted by the use of a broad-spectrum empiric therapy

regimen[5]. The therapy in question is substituted if some strategies are implemented such as shifting from broad-spectrum to narrow-spectrum antibiotics, cutting the number of antibiotics used, lowering antibiotic doses, decreasing antibiotics administration frequency, and discontinuing an antibiotics therapy [6].

In Indonesia, the government has launched the Antimicrobial Resistance Control Program (PPRA) to counteract antibiotics resistance at hospitals. It aims to prevent 1) the development of resistant bacteria as a result of antibiotic selection pressure through prudent antibiotic use. 2) the spread of resistant bacteria by enforcing infection prevention and control principles more strictly [4].

Antibiotics use evaluation is one indicator of the effectiveness of resistance control at hospitals. The aim of this evaluation is to collect quantitative and qualitative data on antibiotics use patterns in hospitals. Quantitatively, the WHO recommends classifying antibiotics use according to anatomical therapeutic chemical (ATC) and quantifying antibiotics use as a defined daily dose (DDD)/100 bed-days. DDD is the average daily maintenance dose for adults [7]. Meanwhile, on a qualitative level, the Gyssens' assessment flow is used to categorize the quality of antibiotics use [4].

Numerous quantitative and qualitative studies on antibiotics use have been conducted. The most recent quantitative study conducted in 2019 at a hospital in New Delhi's ICU revealed an extremely high antibiotics DDD value of 560.11/100 bed-days. According to the prescription analysis, it found beta-lactams as the most frequently prescribed antibiotics (78%) followed by aminoglycosides (56%) and carbapenems (42%) [8]. In Indonesia,

quantification of antibiotics use has been widely conducted, such as ICU and the tropic infection ward at Dr. Soetomo General Hospital in Surabaya. Antibiotics use was at 68.56/100 bed-days based on DDD values, with ceftriaxone being the most frequently used antibiotics (39.37/100 bed-days) [9]. Qualitative research done in the Erasmus Medical Center in the Netherlands found 90 antibiotics (29.3%) were deemed unsuitable for prescription out of 307 antibiotics prescriptions in total [10].

The existence of an antimicrobial resistance control program, one of which is a periodic quantitative and qualitative analysis of antibiotics, in conjunction with the application of antibiotic use guidelines, socialization of antibiotic types, and antibiograms, is expected to lower and increase the antibiotic use frequency in parallel with the increased quality of antibiotics use. Due to the variety of conditions mentioned previously, the authors conducted a literature review focusing on the quantity and quality of antibiotics use in intensive care patients. The results of this review would provide an overview of the quantity and quality of antibiotics use in the ICU.

2 Methods

This study was a literature review through data collection such as reading, article analysis, journals, and other types of literature on similar subjects. The literature search was conducted on several databases, including PubMed Central (PMC) [<https://www.ncbi.nlm.nih.gov/pmc/>], ResearchGate [<https://www.researchgate.net/>], and Google Scholar [<https://scholar.google.co.id/>].

The literature search was carried out using some keywords, namely "Antibiotic AND DDD/100 AND Intensive Care Unit", "Antibiotic AND Resistance AND DDD/100 AND Intensive Care Unit", "Antibiotic Quality Gyssens in ICU".

2.1 Inclusion Criteria

The publication used should meet some criteria: (a). original article/research, case report, and meta-analysis published, (b). addressing quantitative analysis with DDD/100 patient-days or DDD/100 bed-days or qualitative analysis with Gyssens' flow or quantitative and qualitative analyses in ICU . The samples used were from adult patients (≥ 18 years)

2.2 Exclusion Criteria

Publications in languages other than Indonesian and English are excluded.

3 Results and Discussions

With keyword search on PMC database, 91 articles were identified, five of which met the inclusion and exclusion criteria. The same procedure was conducted on Google Scholar database, which yielded 1,490 articles. Additionally, each article was scanned to find out their inclusion and exclusion criteria, and eventually the screening resulted in 15 articles. The number of records in the ResearchGate database exceeded 4,089 records. Overall, 43 articles met the inclusion and exclusion criteria. After comparing the results (same articles from different keywords or databases), a total of 25 articles were selected. They consist of 21 quantitative studies and four qualitative studies.

The data extraction process utilized all selected articles, 21 of which were quantitative research and four of which were qualitative research. Out of 21 articles, 20 articles discussed the value of DDD antibiotics in the ICU. Five of these articles included DDD values for antibiotics groups, 15 included DDD values for antibiotic types, and one included only DDD values for total antibiotics consumption. The total antibiotics use in DDD/100 bed days is shown in Figure 1 for each article.

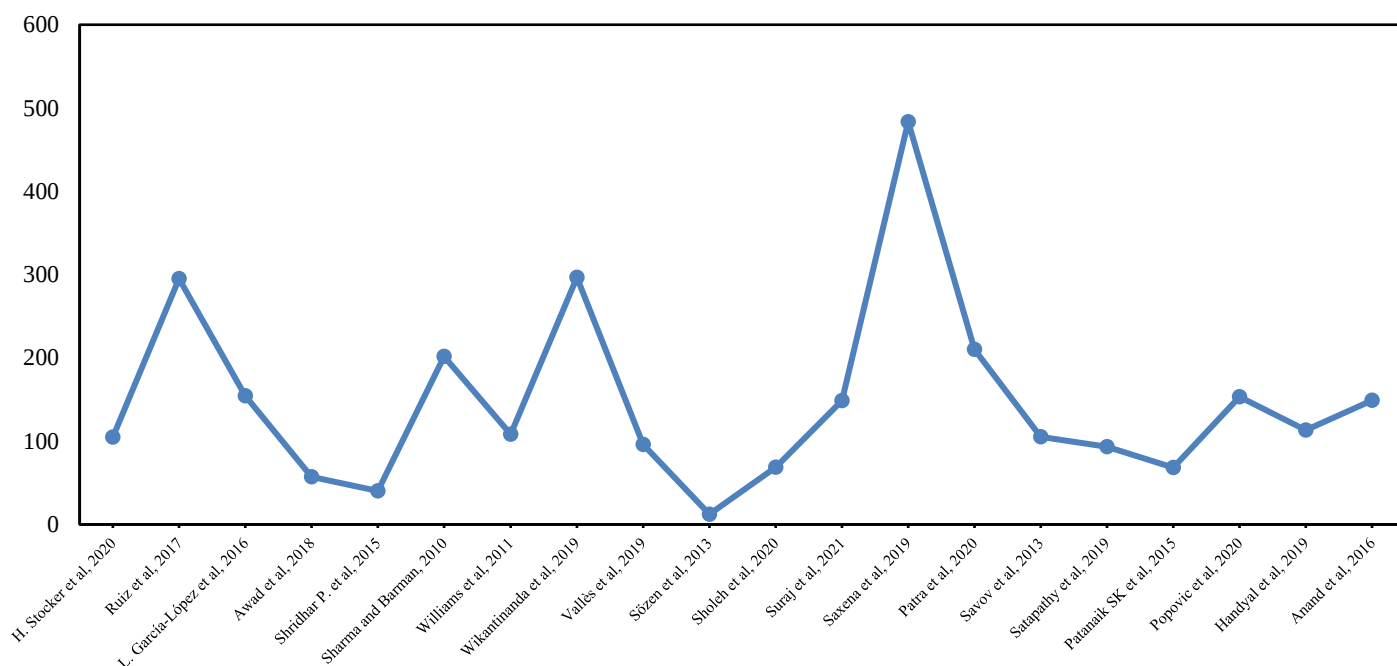


Figure 1 Total Antibiotic Consumption in ICU in DDD/100 Bed-days [23], [18], [28], [29], [30], [31], [13], [9], [8], [11], [34], [35], [36], [16], [37], [38], [40].

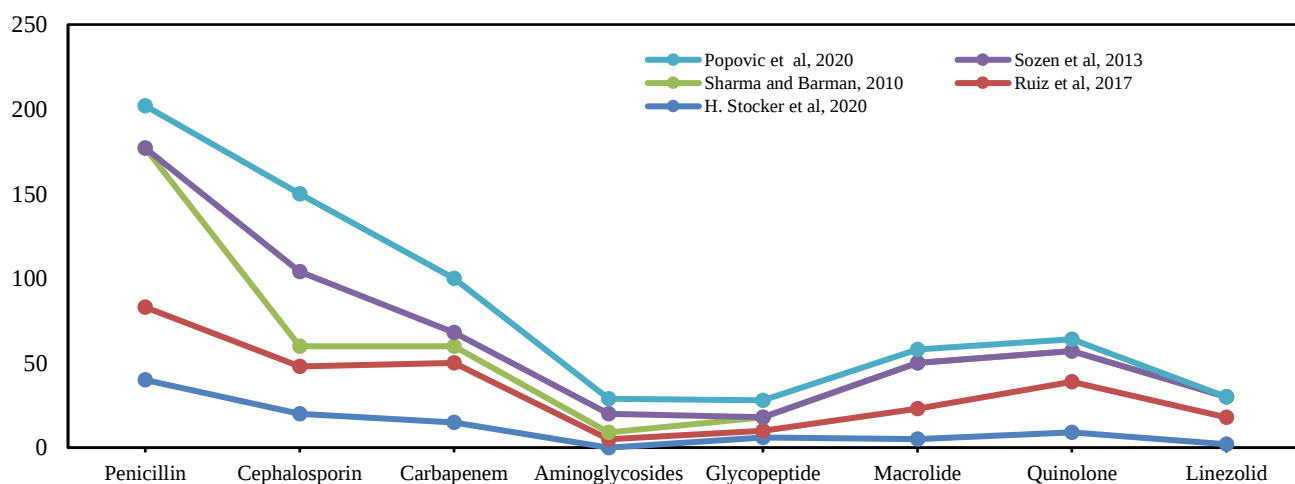


Figure 2 DDD Graph by Class of Antibiotics Used in ICU from Five Articles

The total overall use of antibiotics in each ICU was high. The graph above illustrates the extent to which antibiotics are used in a study conducted [16]. The study was conducted at a tertiary care government hospital in Delhi, India with a DDD of 483.51/100 bed-days. This means that 483-484 patients received antibiotics within 100 days of hospitalization. Metronidazole (3×400mg, PO or 3×500mg, IV) was the antibiotics most highly consumption in this study, with a DDD value of 100.9/100 bed-

days. Metronidazole was the most frequently used antibiotics because the bacteria isolated in this study (*Klebsiella sp.*) were resistant to beta-lactam antibiotics (cephalosporins and piperacillin-tazobactam) and *S. aureus*, MRSA, needs combination with metronidazole[8].

When compared to other studies from the same country, total antibiotic use in this current study was extremely high; the DDD value was 210.1/100 bed-days and 201.6/100 bed-days[11], [12]. Antibiotics use, which also

demonstrates a high rate of antibiotic consumption in the ICU, was investigated in the ICU of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. The total amount of antibiotics use reached a high DDD value of 296.71 /100 bed-days, with levofloxacin (1 x 500mg, PO/IV) as the most frequently used antibiotics (143.18/100 bed-days)[13].

DDD analysis of five articles in Figure 2 reveals that eight most frequently used antibiotics classes were penicillins, cephalosporins, carbapenems, aminoglycosides, glycopeptides, macrolides, quinolones, and linezolid. The antibiotics classes like penicillin, cephalosporin, and carbapenem are the most frequently used. Penicillin had the highest antibiotics use with a DDD value of 84.9/100 bed-days, owing primarily to the use of a combination of penicillin-beta-lactamase inhibitors [13]. Penicillin is still chosen and is

widely used in various infection treatment[14]. Except for allergic reactions, penicillin is generally well tolerated[15].

Cephalosporins are also the most frequently used class of antibiotics in the ICU. Cephalosporins had the highest DDD value of 47.3/100 bed days, shown in a study conducted at a tertiary health care center in Vojvodina, Serbia[16]. Turkey's Isparta State Hospital also demonstrated a high DDD value at 47.3/100 bed days[17]. The widespread use of cephalosporin antibiotics should be a cause for concern, given the increasing prevalence of MRSA and ESBL, particularly in Indonesia, which has increased from 18% (2010) to 24% (2012) for MRSA and from 22% (2010) to 53% (2012) for ESBL. The carbapenem group has a relatively high DDD value with a maximum of 39.17/100 bed days [18].

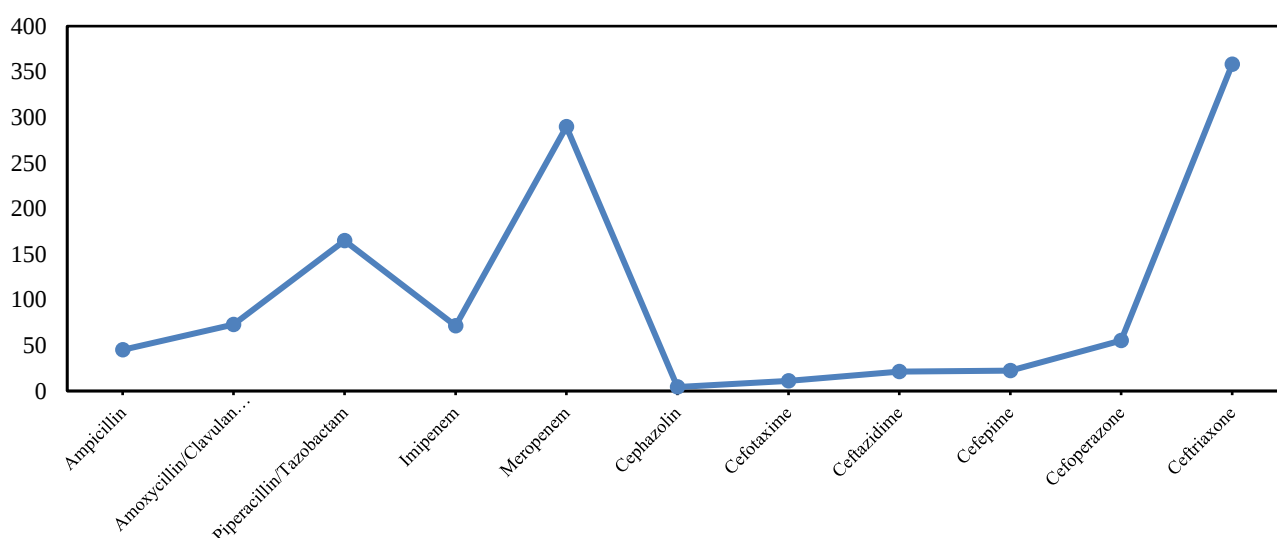


Figure 3 DDD Graph of Total Antibiotics by Type of Antibiotics Most Frequently Used in the Intensive Care Unit (ICU) [19],[20]

Figure 3 demonstrates the most frequently used antibiotics which were also classified into three major groups: cephalosporins (primarily ceftriaxone), carbapenems (primarily meropenem), and penicillins (primarily piperacillin-tazobactam). Based on the figure, ceftriaxone (1 x 2g, IV) was the most frequently used antibiotics, and it had the highest total use in DDD/100 bed-days. Ceftriaxone was used 358.139 times per 100 bed-days in total with the highest consumption occurring at

Government Hospitals in Delhi, India, at 44.8 times per 100 bed days. The total use of ceftriaxone revealed that 357-358 patients received the antibiotic ceftriaxone (J01DD04) during their 100 days of hospitalization, according to the WHO's DDD standard of 2 grams[8]. Because ceftriaxone is well tolerated and has a broad-spectrum activity against both gram-positive and gram-negative bacteria, it is frequently used in the ICU as an empiric therapy for a variety of infections[19]. Additionally,

unlike other types of cephalosporins and beta-lactams, ceftriaxone does not require dose adjustment in patients with kidney disorders and thus is preferred because it is easier to administer. In the studies cited above, the most common infections were respiratory tract infections, pneumonia (CAP/VAP/HAP), and sepsis. Ceftriaxone is the first-line intravenous antibiotics in the treatment of infections with severe symptoms according to the NICE Guidelines [20]. Additionally, guidelines for antibiotics therapy in the ICU recommend ceftriaxone for the treatment of pneumonia and sepsis.

Meropenem is classified as a "watch group antibiotics," which means that its use carries a significant risk of developing resistance[7]. Meropenem is preferred over imipenem in the treatment of sepsis because it has a higher affinity for PBP2 and PBP3 in *P. aeruginosa*[21]. Along with carbapenems and cephalosporins, the penicillin group was highly utilized. The most frequently used type of penicillin was determined to be a combination of piperacillin (4 x 4.5g, IV) and a beta-lactamase inhibitor (tazobactam) according to 12 research articles. The total use of piperacillin-tazobactam was 164,816 DDD/100 bed-days, with the highest consumption recorded in the critical care unit of a tertiary hospital in Bhubaneswar, Odisha, India, at 31.57 DDD/100 bed-days [11]. Piperacillin was frequently used in combination with tazobactam, a beta-lactamase inhibitor. It aims to broaden piperacillin's

spectrum of activity against bacteria that have developed resistance to beta-lactamase production. This combination was administered via injection because piperacillin cannot be absorbed orally. Respiratory tract infections, pneumonia (CAP/VAP/HAP), and sepsis were the most frequently encountered infections in the previous study. According to the British National Formulary, one of the initial therapies for sepsis and HAP involves the use of piperacillin-tazobactam. This is also consistent with the guidelines for an antibiotics therapy in the ICU, saying the same combination of antibiotics is used to treat CAP. This is one of the reasons why piperacillin-tazobactam are frequently used in the ICU[22].

3.1 Antibiotics DDD in ICU with interventions

The Antimicrobial Stewardship Program (ASP) is one of the tools for optimizing antibiotics use to accomplish one of GAP's goals in combating antimicrobial resistance through reduction of overused or improper antibiotics use. A well-designed ASP achieves the best clinical outcomes while minimizing the adverse effects of unnecessary antibiotics use. These adverse events, which occurred to 20% of patients, include the emergence of antibiotics resistance and drug toxicity[22]. Five quantitative research articles with interventions were identified during the search process; each article uses the Antimicrobial Stewardship Program (ASP) as an intervention in a different manner.

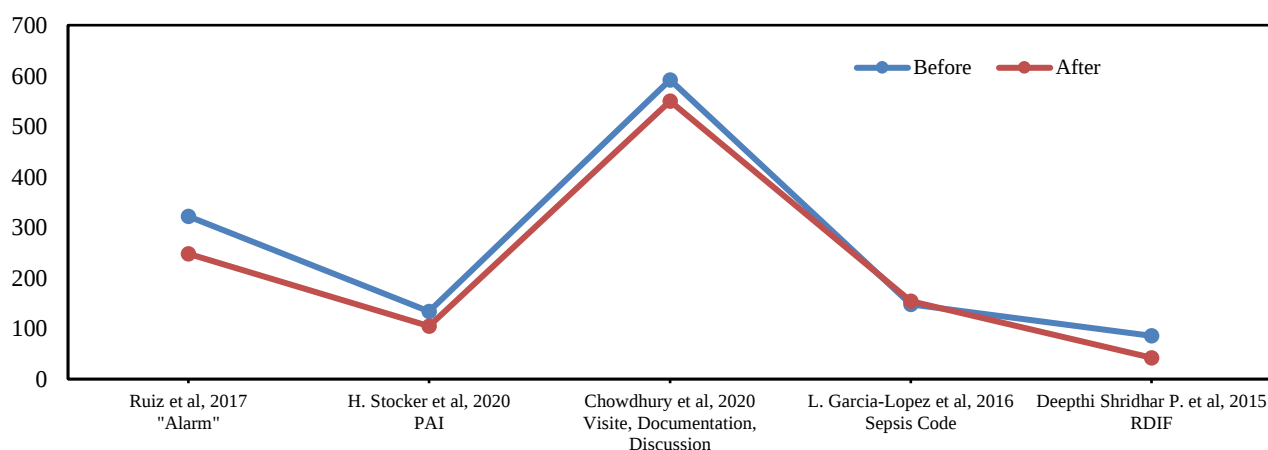


Figure 4 DDD Graph of Total Antibiotics Consumption in ICU based on ASP Method from Five Articles [18][23][39][28][30]

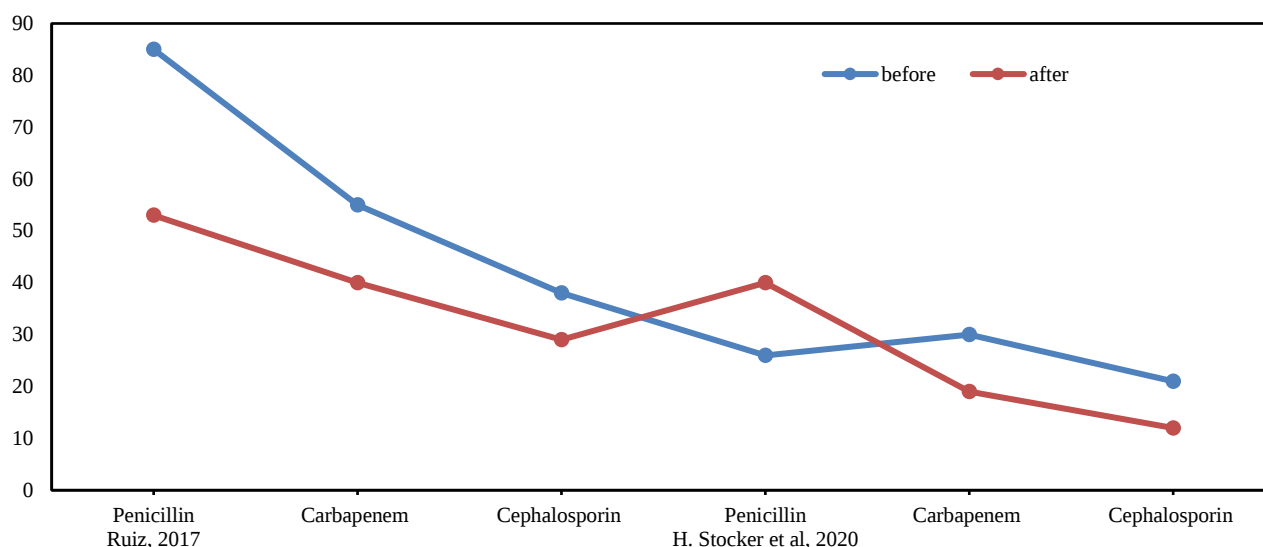


Figure 5 Graph of Changes in DDD Class of Antibiotics in the ICU Before and After ASP Administration from Two Articles [18][23]

Figure 4 describes that the application of ASP resulted in positive results regardless of the method used, with a decrease in the total antibiotics consumption in the ICU. The "alarm" criteria are one of the methods for implementing ASP at hospitals. This method was used in a study conducted at Valencia's University Hospital and Polytechnic La Fe from October 2014 to September 2015. If antimicrobial therapy meets these criteria, it is necessary to review and closely monitor the patients.

The use of several antibiotics classes which resulted in a significant increase is depicted in Figure 5. Penicillin consumption appears to increase after the application of ASP. This demonstrates that, despite a general decline in empirical therapies, antibiotics prescription has increased in groups deemed adequate[23]. If the assessment demonstrates adequate potency, penicillin will be the primary choice for various infectious therapies[14]. Apart from allergic reactions, penicillin is a widely tolerated antibiotics[15].

3.2 The quality of antibiotics in the ICU by the Gyssens method

The Gyssens method is used to assess the appropriateness of antibiotics therapy by categorizing it into six categories: the accuracy of indications, the accuracy of selection based on effectiveness, toxicity, price, and spectrum, the duration of administration, the dose, the interval, the route, and the time of administration. It is a widely used tool for evaluating the quality of antibiotics therapy in many countries, including Indonesia[24].

The database search yielded four qualitative research articles that met the inclusion criteria. Figure 6 depicts the antibiotics quality profile in the ICU based on the comparison results of the articles. It further depicts rational antibiotics use, denoted by category 0, and irrational antibiotic use, denoted by categories I–IV. Category 0 antibiotics are indicated effective, non-toxic, appropriate in price and spectrum, dose, interval, route, and time of administration.

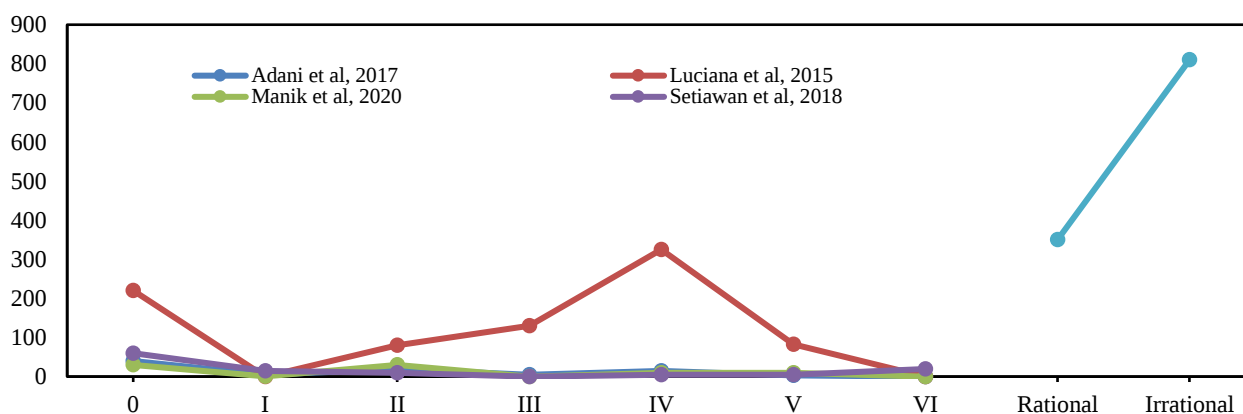


Figure 6 The Quality of Antibiotics Consumption based on Gyssens Method. Rational Use (Category 0). Irrational Use (Category I-VI) [26][25][27][6].

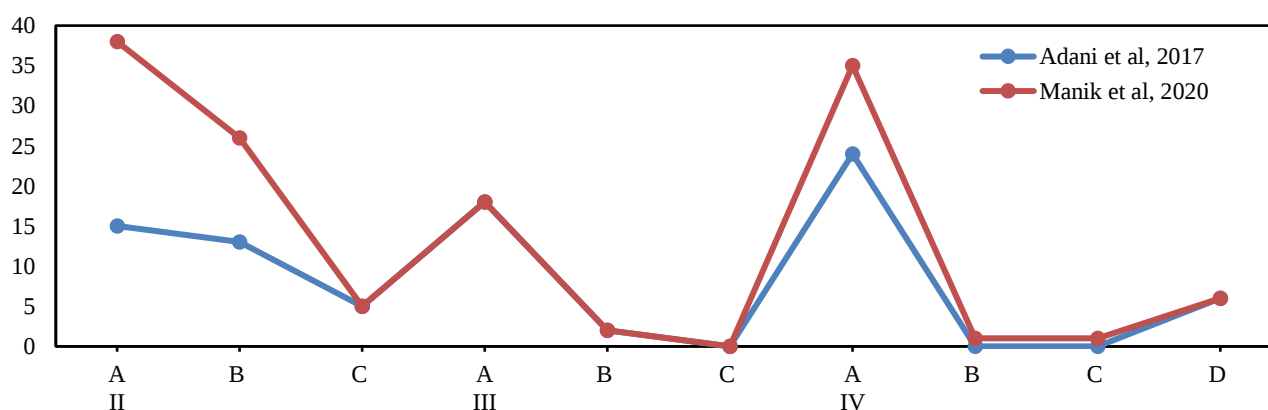


Figure 7 Distribution of the Quality of Irrational Use of Antibiotics by Gyssens Category [26][27]

Appropriate antibiotics use can be seen in previous research done by Adani et al. (2017), who found that 35% of 118 antibiotics regimens (86 empiric therapies and 32 definitive therapies) were appropriate and rational (Category 0). This is also evident in research conducted in the ICU of Jakarta's Fatmawati General Hospital. Out of the 912 treatment regimens (805 empiric therapies and 107 definitive therapies), 209 used appropriate antibiotics[25]. Another study by Setiawan et al. (2018) found that 52.73% of 110 antibiotics regimens were used appropriately, while Manik et al. (2020) found that 29 of the 96 total regimens were used appropriately.

Figure 6 also demonstrates that the most irrational use of antibiotics occurs in category IV because of misuse predominating. Category IV indicates that the antibiotics use is irrational as there are more effective, safe, affordable, and narrower-spectrum antibiotics available

(Category IV). This could be because antibiotics use guidelines have not been implemented properly.

Two of the four articles [26], [27] provide a more comprehensive assessment of the Gyssens category of irrational antibiotics use (categories II and IV) (Figure 7). This figure shows the most irrational use of antibiotics happens due to improper dosing (category IIA). Improper dosing includes overdosing, underdosing, and extra dosing. Additionally, the high rate of irrational antibiotics use was caused by less effective antibiotics (category IVA). This is demonstrated in a study by Adani et al. (2017) in which 86 of 118 antibiotics regimens were empiric. According to this study, the empiric antibiotics therapy is less effective in Dr. Hasan Sadikin General Hospital due to inappropriate sensitivity of existing bacteria to antibiotics. Giving antibiotics at the incorrect interval (Category IIB) also appears quite high and

results in irrational use. Antibiotics use errors occur when the patient does not receive the prescribed dose (too fast or too long). It is feared that it may significantly alter drug absorption, for example, when drugs are taken with or without food. It is critical to adhere to the scheduled time intervals because erroneous use intervals can result in underdose or overdose. The use of antibiotics in Category IIIA and IIIB is only seen in previous research conducted by Adani et al. (2017). In such a category, the antibiotics was given in a longer (IIIA) or shorter (IIIB) duration, which may affect the therapy outcome and promote potential antibiotics resistance.

4 Conclusions

- a. The most widely used antibiotics in the ICU were ceftriaxone (1 x 2g, IV) with a DDD value of 358,139 /100 bed-days, meropenem (3 x 2g, IV) with a DDD value of 289,747 DDD/100 bed-days, and piperacillin-tazobactam (4 x 4.5g, IV) with a DDD value of 164,816 DDD/100 bed-days. Interventions in antibiotics use can reduce the quantity of antibiotics use and increase appropriate antibiotics use.
- b. The quality of antibiotics in the ICU based on the Gyssens assessment generally indicates irrational antibiotics use.

5 Declarations

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5.2 Authors Contributions

The names of the authors listed in this journal contributed to this research.

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5.4 Conflict of Interest

The authors have no conflicts of interest in this investigation.

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