Antibiotic Consumption for Pneumonia Treatment: A Systematic Review of Trends in Indonesia and Other Countries

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Abstract. One of the infectious diseases that is of particular concern in Indonesia is pneumonia. The trend in antibiotic use among pneumonia patients in long-term care facilities, as reported by Chae et al. in the Republic of Korea, shows an increase in both the number of pneumonia cases and antibiotic consumption. The WHO AWaRe system categorizes antibiotics, revealing a shift in prescribing patterns towards broad-spectrum antibiotics, which could potentially worsen microbial resistance. This systematic review aims to evaluate the use of antibiotics in hospitalized pneumonia patients in hospitals in Indonesia and other countries in addressing the issue of antibiotic resistance over the past 10 years. Inclusion criteria included studies on antibiotic use using the ATC/DDD method in pneumonia. Antibiotic consumption in Indonesia (24.51–185.36 DDD/100 patient-days) was higher compared to South Korea (15.5–18.67 DDD) and Hungary (11.41 DDD). Broad-spectrum antibiotics (ceftriaxone, levofloxacin, and meropenem) dominated, with the DU90% segment showing >50 % use of antibiotics in the "Watch" category. The high consumption was influenced by non-compliant clinical practices, excessive empirical use, and low public awareness. There is a need to improve adherence to pneumonia management guidelines, closely monitor antibiotic use, and educate healthcare workers and the community to reduce AMR.

Keywords: ATC; DDD; Evaluation; Antibiotic Consumption; Pneumonia

1 Introduction

Infectious diseases are one of the important health issues in developing countries, especially in Indonesia. One of the infectious diseases that is of particular concern in Indonesia is pneumonia. Pneumonia is an acute infection that attacks the lung tissue (alveoli) and can be caused by various microorganisms such as bacteria, viruses, fungi, and parasites [1]. Pneumonia is one of the leading causes of morbidity and mortality

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worldwide, especially among vulnerable populations such as children, the elderly, and individuals with comorbidities. The 2018 Riskesdas data shows that the incidence of pneumonia increases with age. In the age group <1 year, it reaches 2.1 %, in the age group 55 years – 64 years, it reaches 2.5 %, in the age group 65 years – 74 years, it reaches 3.0 %, and in the age group 75 years and older, it reaches 2.9 %. The high prevalence of pneumonia can also increase the use of antibiotics [1]. However, the irrational use of antibiotics has directly contributed to the emergence of antimicrobial resistance (AMR), which is now recognized as one of the greatest global health threats.

The average prevalence of resistance in Escherichia coli and Klebsiella pneumoniae in Indonesia is 26 % – 56 % [2]. Based on the results of the Antimicrobial Resistance in Indonesia (AMRIN) study in 2012, there was a decrease in the inappropriate use of antibiotics, but the prevalence of Extended-Spectrum B-Lactamase (ESBL) in K. pneumoniae (58 %) and E. coli (52 %) increased [2]. Antibiotic resistance can increase mortality and morbidity rates due to hard-to-treat infections, and it can also raise healthcare costs due to longer treatment periods and the use of more expensive second or third-line antibiotics. Bacterial resistance to antibiotics can be caused by several factors, including the lack of public awareness about the dangers of using antibiotics without a doctor's prescription and the improper use of antibiotics that does not adhere to guidelines in some healthcare facilities. Research in Yogyakarta shows that many individuals have misconceptions about the use of antibiotics, including the belief that antibiotics are effective in treating viral infections such as the flu [3]. This misunderstanding contributes to the inappropriate use of antibiotics. The trend in antibiotic use among pneumonia patients in care facilities in Korea shows an increase in both the number of pneumonia cases and antibiotic consumption [4]. The classification of antibiotics based on the WHO AWaRe system (Access, Watch, Reserve) helps understand the shift in prescribing patterns, with a tendency towards increased use of broad-spectrum antibiotics that could worsen microbial resistance.

In Indonesia, the control of antibiotic resistance in hospitals has become a government program under Minister of Health Regulation No. 8 of 2015 concerning the Antibiotic Resistance Control Program. This regulation aims to ensure more rational use of antibiotics in accordance with medical guidelines. One of the things that can be done is to monitor and evaluate the use of antibiotics. The evaluation of antibiotic use is conducted using the ATC/DDD method and DU 90 %. Strict monitoring of antibiotic use through methods such as Daily Defined Dose (DDD) is considered essential to identify usage trends and areas that require improvement [5].

The evaluation of antibiotic use quantitatively can use the method established by the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) Classification and the measurement of antibiotic use with Defined Daily Dose (DDD) / 100 patient days. Define Daily Dose is the average daily dose of an antibiotic, and DDD is also a standard measurement unit that does not reflect the dose given to patients [6]. The DDD method is a method to determine the amount of antibiotic use expressed in DDD units per 100 inpatient days, which can then be further reviewed to produce Drug Utilization (DU) 90 %. Where DU 90 % can be used to ensure that the most frequently used antibiotics are in accordance with therapy guidelines or the National Formulary (Fornas). Therefore, this systematic review aims to evaluate the use of

antibiotics in hospitalized pneumonia patients in hospitals in Indonesia and other countries in addressing the issue of antibiotic resistance over the past 10 years.

2 Methods

2.1 The Classification of Anatomical Therapeutic Chemical (ATC) and Define Daily Dose (DDD)

The ATC classification system is arranged in a five-level hierarchy. There are fourteen primary anatomical/pharmacological categories, or first levels, in the system. The second levels of each ATC major group can be either therapeutic or pharmacological groupings. Chemical, pharmacological, or therapeutic subgroups make up the third and fourth levels, while the chemical substance itself makes up the fifth level. For example, in the ATC system, all plain ceftriaxone preparations are given the code J01DD04. It's a classification of ceftriaxone that illustrates the structure of the code:

J	Antiinfectives for systemic use (1st level, anatomical main group)
J01	Antibacterials for systemic use (2nd level, therapeutic subgroup)
J01D	Other beta-lactam antibacterials (3rd level, pharmacological subgroup)
J01DD	Third-generation cephalosporins (4th level, chemical subgroup)
J01DD04	Ceftriaxone (5th level, chemical substance)

Define Daily Dose (DDD) is the average maintenance dose assumed per day for a drug used for its primary indication in adults. DDD is a unit of measurement and does not always reflect the recommended daily dose or the prescribed daily dose. The therapeutic dose for individual patients and patient groups often differs from the DDD because it will be based on individual characteristics (such as age, weight, ethnic differences, type and severity of the disease) and pharmacokinetic considerations [7].

The ATC/DDD system is designed to be a tool for drug use monitoring and research in order to enhance the quality of drug usage. Therefore, a substance's classification in the ATC/DDD system does not indicate any evaluation of the relative or overall effectiveness of medications or drug groups, nor does it suggest a recommendation for their usage. In order to improve the quality of drug usage, one of the main goals of drug utilization is to track both rational and irrational drug use [7].

2.2 Study Design

This research is a systematic review of the evaluation of antibiotic use in hospitalized pneumonia patients in Indonesia and other countries using the ATC/DDD and DU90% methods.

2.3 Strategy Research

A systematic search was conducted in several databases, including SageJournal, Web of Science, PubMed, Scopus, and Garuda. This search used a combination of Boolean operators (AND, OR) and specific specifications (Title, Abstract) to ensure comprehensive coverage.The search terms used are as follows: "Antibiotic Evaluation," "ATC/DDD Method," "Pneumonia Patients," "Antibiotics Used," "Antibiotic Consumption," and "Drug Use."

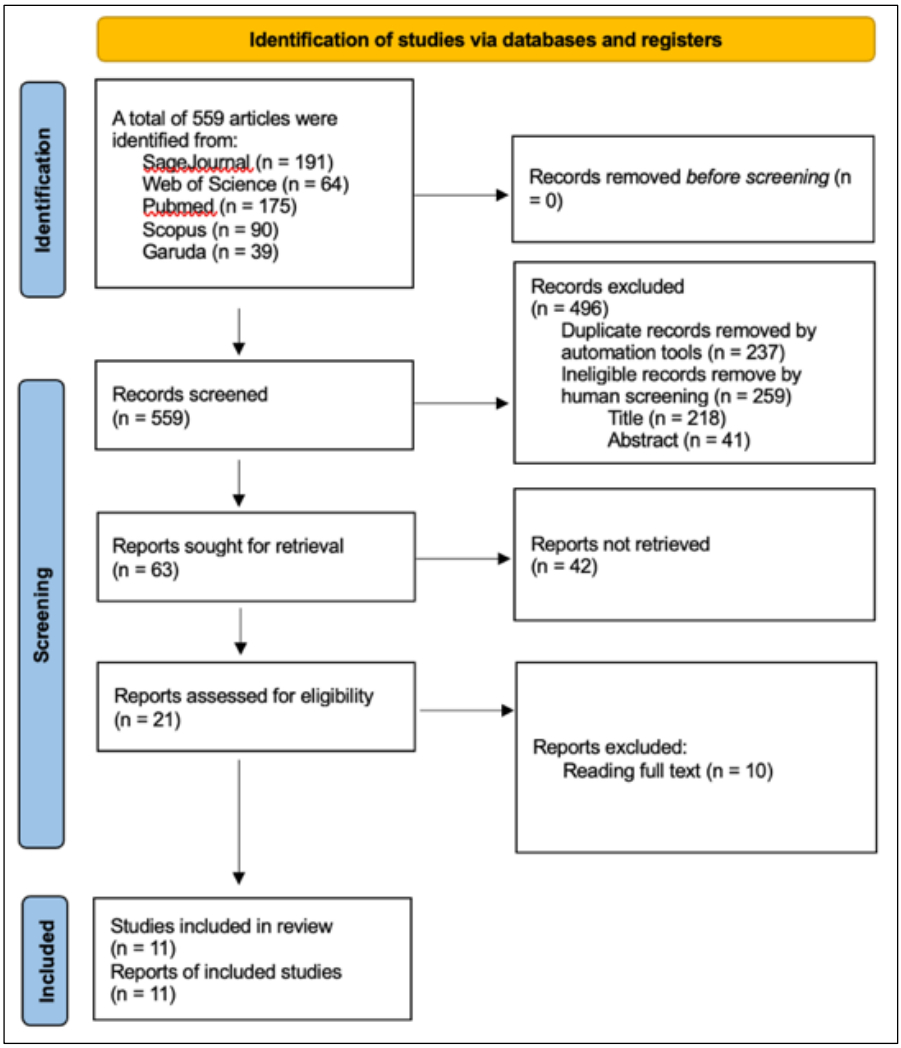

Fig. 1. PRISMA Flow Diagram.

2.4 Eligibility Criteria

The inclusion criteria for this systematic review are as follows: (1) discussing the use of antibiotics (WHO ATC/DDD) in pneumonia patients in Indonesia and various other countries; (2) published in English or Indonesian; (3) published between January 1, 2014, and October 31, 2024; and (4) having the full text available to the public. A total of eleven articles were selected for comparative analysis to gain insights into the evaluation of antibiotic use using the ATC/DDD method in pneumonia patients in Indonesia and other countries. This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to ensure a systematic and standardized approach.

2.5 Data Extraction

Data extraction was performed on full-text articles that met the inclusion criteria and were included in the review process. All articles were then characterized, including the title, authors, year, research timeframe, data collection methods, sampling methods, population, sample, and methods used to evaluate antibiotic use.

2.6 Data Analysis

This research follows the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to ensure a systematic and standardized approach. The process of identifying relevant literature is illustrated in a detailed flowchart, which can be seen in Fig. 1.

2.7 Study Quality Assesment

A total of 559 articles were found through the database search. The search was conducted in several international databases (SageJournal, Web of Science, PubMed, and Scopus) and one national database (Garuda [Digital Reference Garba]), published in English or Indonesian between January 2014 and December 2024. After being deemed eligible, the full-text articles (n=21) were reviewed and evaluated for inclusion in the study. Finally, 11 written between 2014 and 2024 were successfully included.

The articles selected based on inclusion and exclusion criteria were then assessed using the Joanna Briggs Institute (JBI) critical appraisal. The JBI critical appraisal is used to assess the quality of articles according to their research design, including qualitative studies and cross-sectional studies. The results of the valid assessment can provide information that the articles used in the systematic review can represent the needed information. In accordance with the assessment tool provided by the Joanna Briggs Institute (JBI), the researchers evaluated the methodological quality and risk of bias in the studies included in this systematic review. Based on that assessment, all eleven articles were deemed eligible for review because most items on the checklist received a "YES" answer.

3 Result and Discussion

3.1 Study Characteristics

At the initial stage of the literature search, 559 articles were found, which were then filtered down to eleven articles for a systematic review. A total of eleven studies were analyzed in this review, covering research from Indonesia and other countries, with a focus on trends in antibiotic use among pneumonia patients. Seven studies originated from Indonesia, while four others came from South Korea and Hungary. The majority of the studies were conducted in hospital settings with a retrospective observational or cross-sectional design. The majority of articles in Indonesia come from the island of Java, specifically 5 articles (71,43 % [5], [8], [9], [10], [11]), followed by Nusa Tenggara Timur (14,28 % [12]) and Bali (14.28 % [13]), each with only 1 article. Overall, most studies use the ATC/DDD method to measure antibiotic consumption, while some additional studies incorporate the DU90% approach, the Gyssens method, or guideline adherence evaluation. Variations in patient populations, ranging from children to the elderly, as well as differences in study settings and evaluation methods, provide a comprehensive overview of antibiotic consumption trends and the challenges in pneumonia management across various countries. The characteristics of the studies are summarized in Table 1.

Table 1. Characteristics of Study

Author	Time of Study	Study Setting	Data Collection Methods	Population
In Indonesia				
Andarsari, M. R. et al. (2022)	January – December 2019	Hospital	Retrospective observational study	ICU patients aged >18 with CAP or HAP receiving antibiotics
Khairani, S. et al. (2023)	January – December 2019 and 2022	Hospital	Cross-sectional, retrospective	Adult inpatients with pneumonia diagnosis
Yulia, R. et al. (2020)	February – April 2018	Hospital	Descriptive observational study	Adults ≥18 years with pneumonia receiving antibiotics before culture
Prasetya, A. A. N. P. R. et al. (2023)	January – December 2022	Hospital	Cross-sectional, retrospective	Inpatients aged 18–65 with pneumonia receiving antibiotics
Nurkholis, F (2024)	January – December 2022	Hospital	Descriptive retrospective study	Pediatric pneumonia patients under age 5 with complete antibiotic records
Kresnawati, V et al (2021)	January-December 2019	Hospital	Retrospective observational study	Adult inpatients (≥18 years) diagnosed with community-

				acquired pneumonia (with or without comorbidities)
Sari, A (2016)	January–December 2014.	Hospital	Retrospective observational study	Pediatric inpatients (<18 years) diagnosed with pneumonia and receiving antibiotics
Other Countries				
Chae, J. et al. (2024)	January 2011 – December 2022	Hospital	Retrospective analysis using National Health Insurance claims	Inpatients diagnosed with pneumonia
Fan, C. et al. (2024)	May 2016 – April 2020	Hospital	Single-center retrospective comparative study	Children (29 days to 18 years) diagnosed with severe bacterial pneumonia
Kim, B. et al. (2020)	2010-2015	Hospital	Retrospective cohort analysis	Adults (≥18 years) hospitalized with community-acquired pneumonia (CAP)
Fésüs, A. et al. (2022)	January–December 2017	Hospital	Retrospective observational study	Adult inpatients (≥18 years) diagnosed with CAP and receiving empirical antibiotic therapy

3.2 Antibiotic Consumption

Most studies show variations in antibiotic consumption rates among pneumonia patients, both in Indonesia and other countries. In Indonesia, the total DDD/100 patient-days value varies quite widely, starting from 24.51 [11] to 185,36 [12]. A study in the intensive care unit reported a consumption of 73.64 DDD/100 patient-days, with the most commonly used antibiotics being levofloxacin, ceftriaxone, and meropenem [10]. In South Korea, a fluctuating trend in antibiotic consumption in long-term care hospitals has been reported, with the lowest consumption being 16.11 DDD per episode in 2016 and the highest being 18.67 DDD in 2021, particularly during the COVID-19 pandemic [4]. The average use of antibiotics for community-acquired pneumonia in Korean hospitals is 15.5 DDD per episode [13]. Meanwhile, in Hungary, the average antibiotic consumption is 11.41 DDD per community-acquired pneumonia patient [14]. One way to reduce the incidence of resistance is by limiting the use of antibiotics, allowing for the replacement of antibiotic use over a certain period [15]. The results of the eleven articles can be seen in Table 2.

The high consumption of antibiotics in Indonesia can be influenced by several factors. First, the use of broad-spectrum antibiotics such as ceftriaxone, levofloxacin, and meropenem is more dominant in Indonesia compared to other countries. The most commonly used antibiotics in various studies are third-generation cephalosporins

(especially ceftriaxone), followed by fluoroquinolones such as levofloxacin and beta-lactam/beta-lactamase inhibitors. In Indonesia, ceftriaxone and levofloxacin dominate in various studies ([10], [12], [16], [5]). In a study in South Korea, it was also found that third-generation cephalosporins are the most commonly prescribed antibiotics for CAP, followed by macrolides and a combination of beta-lactam/beta-lactamase inhibitors [13]. Pediatric studies in Indonesia show a tendency to use cefotaxime and azithromycin as the primary choices for children with pneumonia [9][11]. The high consumption of antibiotics in Indonesia can be influenced by several factors. First, the use of broad-spectrum antibiotics such as ceftriaxone, levofloxacin, and meropenem is more dominant in Indonesia compared to other countries. Studies by Yulia et al. and Khairani et al. show that these antibiotics are often used even for cases of community-acquired pneumonia that could actually be treated with narrow-spectrum antibiotics [5][12]. This raises concerns about the risk of faster microbial resistance selection, as warned by the WHO in the AWaRe classification framework, that the use of antibiotics from the "Watch" and "Reserve" categories should be limited to reduce resistance selection [17].

Four studies in Indonesia used the DU90% method to evaluate the antibiotic profile [12][16][9][5]. Consistently, ceftriaxone and levofloxacin dominate the DU90% segment, showing a high preference for broad-spectrum antibiotics. The Gyssens method was used by Yulia et al. to evaluate the appropriateness of antibiotic therapy with clinical diagnosis. The application of evaluation methods such as ATC/DDD and DU90% in Indonesian studies provides a quantitative picture of antibiotic usage patterns. However, the use of clinical appropriateness evaluation methods such as the Gyssens method is still limited. Quality-based evaluation is very important to ensure that the antibiotics used are not only in the correct dosage but also in accordance with clinical indications and microbiological data.

The results of the study by Fésüs et al. underscore a fundamental issue in clinical practice, namely the low level of adherence to the management guidelines for community-acquired pneumonia (CAP) in Hungary [14]. Poor adherence to guidelines, both national and international, has serious impacts on clinical outcomes, including increased mortality rates. In the management of CAP, the selection of appropriate and timely empirical antibiotics is a key factor in determining the success of therapy. Non-compliance with recommendations, such as the unnecessary use of broad-spectrum antibiotics or delays in starting empirical therapy, worsens the patient's prognosis [18]. Therefore, routine audits and feedback, guideline-based training, and the implementation of antibiotic use control are important strategies to improve clinical compliance. Meanwhile, Fan et al. showed that the implementation of the Antimicrobial Stewardship Program (ASP) in pediatric intensive care units in China contributed to a 17.2% reduction in antibiotic consumption during the intervention period, although this result was not statistically significant ($p=0.562$) [19]. The downward trend still holds clinical significance, particularly in the context of reducing selective pressure on microbial resistance. The lack of statistical significance may be due to several factors, such as a limited sample size, variation in clinical practices between units, or the intervention duration not being long enough to show significant changes.

Table 2. Result of Study

Author	Result	
	DDD/100 patient-days	DU 90%
In Indonesia		
Andarsari, M. R et al (2022)	Total DDD/100 patient-days: 73,64 DDD/100 patient-days. The Highest DDD/100 patient-days: Levofloxacin inj 21,92 DDD/100 patient-days; Ceftriaxone inj 20,45 DDD/100 patient-days; Meropenem inj 14,29 DDD/100 patient-days	NA
Khairani, S et al (2023)	Total DDD/100 patient-days: 185,36 DDD/100 patient-days. The Highest DDD/100 patient-days: Ceftriaxone inj 104,00 DDD/100 patient-days; Levofloxacin inj 22,56 DDD/100 patient-days; Meropenem inj 15,88 DDD/100 patient-days	Segmen DU 90%: Ceftriaxone: 56,11%; Levofloxacin: 12,17%; Meropenem: 8,56%; Cefoperazone: 6,17%
Yulia, R et al (2020)	Total DDD/100 patient-days: 35,53 DDD/100 patient-days. The Highest DDD/100 patient-days: Levofloxacin inj 15,22 DDD/100 patient-days; Ceftriaxone inj 9,23 DDD/100 patient-days; Meropenem inj 4,34 DDD/100 patient-days	NA
Prasetya, A.A.N P R et al (2023)	Total DDD/100 patient-days: 171,85 DDD/100 patient-days. The Highest DDD/100 patient-days: Levofloxacin inj 79,88 DDD/100 patient-days; Ceftriaxone inj 40,52 DDD/100 patient-days; Azithromycin tab 8,14 DDD/100 patient-days	Segmen DU 90%: Levofloxacin inj: 46,51%; Ceftriaxone inj: 23,6%; Azithromycin tab: 4,74%; Cefoperazone inj: 4,18%; Meropenem inj: 4,06%; Ciprofloxacin inf: 3,59%; Levofloxacin tab: 3,59%
Fiqih Nurkholis (2024)	Total DDD/100 patient-days: 79,99 DDD/100 patient-days. The Highest DDD/100 patient-days: Azithromycin 52,14 DDD/100 patient-days; Ceftriaxone 17,74 DDD/100 patient-days; Cefotaxime 3,29 DDD/100 patient-days	Segmen DU 90% Azithromycin 65,22%; Ceftriaxone 22,17%
Kresnawati, V et al (2021)	Total DDD/100 patient-days: 77,25 DDD/100 patient-days. The Highest DDD/100 patient-days: Ceftriaxone 38,79 DDD/100 patient-days; Cefotaxime 28,88 DDD/100 patient-days; Levofloxacin 3,29 DDD/100 patient-days	NA
Sari, A (2016)	Total DDD/100 patient-days: 24,51 DDD/100 patient-days. The Highest DDD/100 patient-days: Cefotaxime 14,64 DDD/100 patient-days; Ampicillin 4,06 DDD/100 patient-days; Ceftazidime 1,84 DDD/100 patient-days	NA
Other Countries		
Chae, J. et al. (2024)	The amount of antibiotic consumption per episode among patients with pneumonia in LTC hospitals was 17.14 DDD in 2011 and 16.11 DDD in 2016, which had the lowest antibiotic consumption. Since 2016, antibiotic consumption increased to 18.67 DDD in 2021 and decreased again to 18.11 DDD in 2022	NA

Fan, C. et al. (2024)	The consumption of total antibiotics has also decreased, with a 17.2 decrease in DDD values during the intervention period	NA
Kim, B. et al. (2020)	Third-generation cephalosporins (4.9 DDD/episode, 31.4%) were the most prescribed, followed by macrolides (2.7 DDD/episode, 17.1%) and beta-lactam/beta-lactamase inhibitors (2.1 DDD/episode, 13.6%). Average antibiotic consumption per CAP episode was 15.5 DDD	NA
Fésüs, A. et al. (2022)	Average antibiotic consumption was 11.41 ± 8.59 DDD/patient (range: 1–44.5). Amoxicillin-clavulanic acid (29.07% monotherapy, 54.09% combination) and ceftriaxone (29.07% monotherapy) were the most used	NA

4 Conclusion

The consumption of antibiotics in pneumonia patients in Indonesia tends to be higher compared to other countries, with a dominant use of broad-spectrum antibiotics such as ceftriaxone, levofloxacin, and meropenem. This has the potential to worsen antimicrobial resistance (AMR), especially due to the use of antibiotics in the "Watch" and "Reserve" categories in the WHO AWaRe classification, which has not yet aligned with the guidelines. A study in Indonesia shows a variation in DDD/100 patient-days between 24.51 and 185.36, while countries like South Korea and Hungary report lower figures (11.41–18.67 DDD). Factors contributing to the high consumption in Indonesia include public misunderstandings about antibiotic use, clinical practices that do not adhere to guidelines, and a lack of evaluation of the quality of antibiotic therapy. The Antibiotic Resistance Control Program and the implementation of monitoring methods such as ATC/DDD and DU90% are crucial for improving the rational use of antibiotics. Recommendations include routine clinical audits, guideline-based training, and strengthening antimicrobial stewardship programs.

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