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An Overview of Antibiotic Solubility Based on Reconstitution Time

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ABSTRACT

The reconstitution of parenteral antibiotics is the process of mixing antibiotic drugs with sterile solutions for intravenous use. According to Indonesian Nursing Law No. 38 of 2014, Article 33, nurses are authorized to provide limited pharmaceutical services, including assisting in drug reconstitution. Errors in the mixing process can lead to incorrect drug dosages or reduced efficacy. This study aims to describe the solubility of antibiotics based on the reconstitution time of antibiotics in the Medical Intermediate Care (MIC) unit at Dr. Hasan Sadikin General Hospital in Bandung. The research method used is quantitative descriptive correlational, utilizing frequency distribution to assess respondent characteristics, the antibiotics used, and their solubility. Central tendency measures are used to determine the mean solubility of antibiotics based on reconstitution time. A total of 66 samples were collected using accidental sampling techniques. The reconstitution procedure used *aquabidest* (distilled water) and NaCl. The duration of the reconstitution process affected the solubility of the antibiotics. It was concluded that the reconstitution and mixing procedures for parenteral preparations in the MIC unit did not fully meet Good Preparation standards. Antibiotics such as Cefepime, Vancomycin, Cefotaxime, and Meropenem had relatively longer reconstitution times compared to other antibiotics. Nurses should have the knowledge and skills to perform drug reconstitution according to standards. Hospitals should establish drug reconstitution standards to ensure the quality of medications

administered to patients, thus preventing an increase in antibiotic resistance.

Keywords
Antibiotics
Antibiotic Solubility
Drug Reconstitution
Nursing

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Introduction

The reconstitution of parenteral antibiotics involves mixing antibiotic drugs with a sterile solution for intravenous use. According to the Indonesian Pharmacist Competency Standards, pharmacists are responsible for ensuring that the preparation of sterile products in hospitals complies with Good Preparation Practices [1]. Indonesian Nursing Law No. 38 of 2014, Article 33, states that nurses are authorized to provide limited pharmaceutical services in the absence of pharmaceutical personnel [2]. These limited activities include storing and delivering medications to patients, which also involves assisting in drug reconstitution.

Collaboration among healthcare workers is crucial for the administration of medications to patients. According to Indonesian Health Law No. 36 of 2009 [3], healthcare workers are individuals who dedicate themselves to the health sector and possess the necessary knowledge and skills through education in specific health fields, requiring authorization to carry out health efforts. Healthcare workers include medical personnel, nursing staff, pharmaceutical staff, public health workers, nutritionists, physical therapists, and medical technicians. Medical personnel, primarily doctors, have the role of prescribing medications, especially antibiotics, which are then administered by nursing staff.

The pharmacy department is responsible for the provision, management, and dissemination of drug information, providing independent, accurate recommendations to doctors, nurses, and other healthcare professionals [4]. The process of reconstituting drugs from vials, as outlined by the Directorate of Community and Clinical Pharmacy Development, Ministry of Health, involves adding the appropriate solvent to the drug vial and gently rotating it until dissolved. The reconstitution time is the duration required to dissolve the active drug with the specified solvent.

Adequate knowledge among healthcare workers regarding antibiotic use can prevent ineffective treatments, increase patient safety, and curb the spread of resistance [5]. Antibiotics, derived from microorganisms, inhibit or kill other microorganisms and are used to treat specific infectious diseases [6]. A doctor must supervise their use to avoid unwanted effects. In

developing countries, antibiotics are still considered the most appropriate treatment for bacterial infections. However, uncontrolled use can lead to issues, such as the emergence of antibiotic-resistant bacteria, as seen with prolonged and increasing use of antibiotics [7].

Inaccuracies in the drug mixing process can result in incorrect or reduced drug dosages, affecting therapeutic efficacy, particularly in antibiotic therapy [5]. Bacterial resistance can occur with too short or too long antibiotic treatments at low doses, as bacteria may resist the antibiotic's action, reducing or nullifying its efficacy [7]. Studies at the Master Skill University College of Health Sciences in Malaysia revealed that nursing students' knowledge about antibiotic side effects is very low [8]; only 43% of nursing students could answer 5-6 out of 10 questions correctly, highlighting the need for better education. Other studies in other country show the same identification [9],[10].

The technique of adding solvent to powdered medication to prepare it for administration is called reconstitution. Nurses perform this process immediately before administering it to patients. Non-compliance with Good Preparation Practices in reconstituting antibiotics can lead to ineffective therapy and contribute to the development of antibiotic resistance. Bacterial resistance, particularly in nosocomial infections, has become a serious issue in Indonesian hospitals and needs to be controlled.

The World Health Organization (WHO) has identified antibiotic resistance as a global health problem [11]. Research by the Indonesia Ministry of Health's Research and Development Agency, in collaboration with WHO, shows an increase in deaths due to antimicrobial resistance in Indonesia [12]. It is estimated that antibiotic-resistant bacteria cause around 130,000 deaths annually in Indonesia.

The Medical Intermediate Care (MIC) unit at Dr. Hasan Sadikin General Hospital in Bandung, Indonesia is a high-care unit in the internal medicine department. One of the most common diseases treated in this unit is sepsis, which requires antibiotic therapy within an hour of diagnosis. This results in high antibiotic usage in the MIC unit. One of the roles of nurses is to ensure the safe and accurate administration of medications. Therefore, it is crucial for nurses to have comprehensive knowledge of drug preparation and administration. The scope of drug preparation includes the dissolution or reconstitution of sterile powders, and the preparation of simple and complex injections. This background forms the basis for our study on the solubility of antibiotics based on reconstitution time in the Medical Intermediate Care unit.

Methods

The research method used is descriptive analysis with frequency distribution to observe respondent characteristics, the antibiotics used, and their solubility. Central tendency measures are used to determine the mean solubility of antibiotics based on reconstitution time.

The study population includes all critically ill patients with sepsis and severe sepsis treated in the MIC unit at Dr. Hasan Sadikin General Hospital, Bandung. A total of 66 patients with severe sepsis who received antibiotics from June 1, 2018, to August 31, 2018, were included in the study. Accidental sampling was employed, with 66 patients as the sample size.

The independent variable in this study is the drug reconstitution process, while the dependent variables are the preparation time and drug solubility. This research inherently poses no risk to the subjects, but the researcher remains attentive to ethical issues while conducting the quantitative descriptive correlational study. The research is carried out within the unit adhering to the standard operational procedures for patient care at Dr. Hasan Sadikin General Hospital, Bandung.

Results

From the sixty-six samples collected, the respondent characteristics are presented in Table 1.

Table 1. Distribution of Antibiotic Use by Gender

Characteristics	Frequency	%
Gender		
• Male	18	27.3
• Female	48	72.7
Age group		
• < 20	5	7.6
• 20 – 40	24	36.4
• 40 – 60	18	27.3
• >60	19	28.7

From the 66 drug samples collected during the study period, the distribution of antibiotic use by age is as Table 2.

Table 2. Types of Antibiotics Used

Antibiotic	Frequency	%
Cefazoline	1	2
Cefepime	9	14
Cefoperazone	1	2
Cefotaxime	8	12
Ceftazidime	6	9
Ceftriaxone	9	14
Fosfomycine	1	2
Ertapenem	1	2
Imipenem	1	2
Meropenem	15	23
Tygacil	6	9
Vancomycin	5	8
Mycamin	1	2
Novellmycin	2	3
Total	**66**	**100**

Table 3 shows the antibiotic solubility based on reconstitution time. See also the Fig. 1 for the grouping of the results.

Table 3. Overview of Antibiotic Solubility Based on Reconstitution Time

Antibiotic	N	Mean of time	Solubility
Cefazoline	1	0:40:00	Soluble
Cefepime	9	3:10:00	Soluble
Cefoperazone	1	1:30:00	Soluble
Cefotaxime	8	2:11:15	Soluble
Ceftazidime	6	1:50:40	Soluble
Ceftriaxone	9	1:45:53	Soluble
Fosfomycine	1	1:40:00	Soluble
Ertapenem	1	1:27:00	Soluble
Imipenem	1	0:30:00	Soluble
Meropenem	15	2:06:24	Soluble
Tygacil	6	0:41:20	Soluble
Vancomycin	5	2:24:00	Soluble
Mycamin	1	0:30:00	Soluble
Novellmycin	2	0:45:00	Soluble

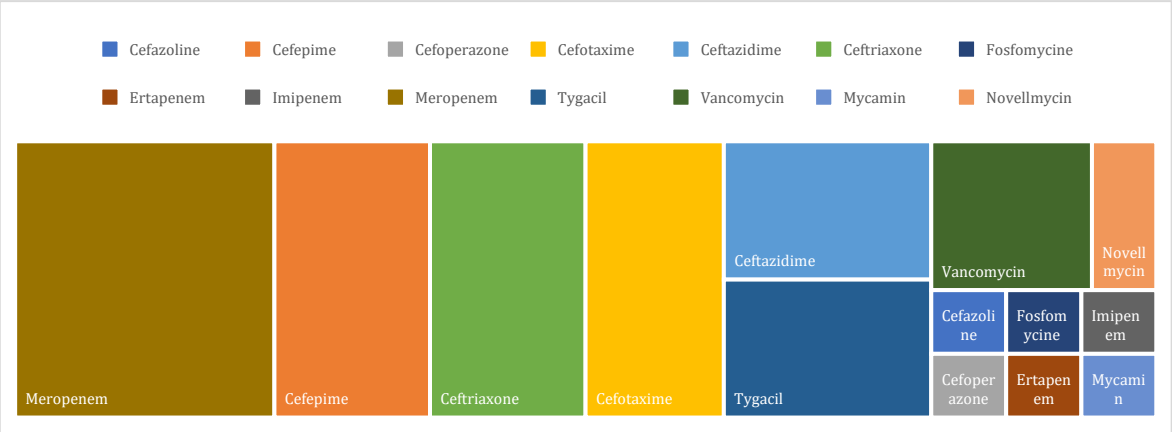


Fig. 1. Grouping of the Antibiotic Solubility Based on Reconstitution Time

From Table 4, in patients with severe sepsis receiving antibiotic therapy, the reconstitution time significantly impacts the solubility of antibiotic drugs. Some types of antibiotics come with ready-to-use solvent solutions, which facilitate the reconstitution process.

Table 4. Analysis of Types of Antibiotics Based on Dispensing Time

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	124.293[a]	96	.028
Likelihood Ratio	93.792	96	.545
N of Valid Cases	58		

However, for antibiotics that do not come with pre-prepared solvent solutions, nurses or pharmacists must carefully follow the product recommendations to ensure the appropriate drug concentration for patients. Antibiotics such as Cefepime, Vancomycin, Cefotaxime, and Meropenem require relatively longer reconstitution times compared to other antibiotics. The technique of mixing, sterility, and precision of healthcare staff also greatly influence the final

drug product prepared for patient administration. The better the reconstitution process, measured time, and precision of staff, the lower the rate of drug resistance in hospitals.

Discussion

The observations across all types of antibiotics indicate that the reconstitution and mixing processes of parenteral preparations have not adequately adhered to aseptic techniques to prevent microbial contamination during dissolution/mixing. There are four factors determining whether the sterility of parenteral preparations can be maintained during the mixing process [13]: a room with minimal microbial contamination, sterile materials and equipment, trained nurses, and the application of aseptic techniques. Therefore, dissolving injection preparations on a trolley in patient care rooms is not an appropriate choice because the vial caps and intravenous needles can become contaminated.

Upon reviewing the reconstitution methods, some nurses shake vials with needles left inside, while others remove the needle during shaking. Some shake vigorously without positioning the vial at 90 degrees, resulting in powder residue on the vial cap, and in some cases, undissolved powder at the vial bottom. Ideally, the needle should remain inside the vial during shaking to prevent contamination. Shaking should occur at a 90-degree angle to maximize contact between the substance and solvent, ensuring thorough dissolution. Vigorous shaking should be avoided to prevent powder from settling at the vial's cap bottom.

The reconstitution process of Meropenem with half the recommended Aqua Pro Injection volume demonstrates varying concentrations and affects its solubility in the final preparation. Meropenem is moderately soluble in water with a solubility range of 1:30-100, thus not fully dissolving when 1 g is dissolved in 10 mL of sterile water or 500 mg in 5 mL. However, dissolution in 20 cc or 100 cc of solvent, as conducted in the MIC room, results in clear and soluble solutions. Inadequate solubility affects drug concentration in the bloodstream, impacting the effectiveness of treating patient infections. Optimal Meropenem concentration is cited in the literature as 50 mg/mL, suitable for storage for 8 hours at 25°C and 48 hours at 4°C [14],[15]. Hence, the volumes used in the MIC room do not always meet minimum volume recommendations to ensure safe administration to patients.

Analysis of dissolved substance concentrations in reconstituted antibiotic preparations meets requirements when solvent types and volumes match those listed on labels or in literature. However, halving the solvent volume results in inadequate drug levels (<90%), rendering it unsuitable for injection doses. Ceftriaxone injection preparation involves dissolving 1 g dry powder in a vial with 10 mL Aqua Pro Injection (per manufacturer's instructions), with the same method applied for 2 g administration by dissolving two 1 g vials in 10 mL each, discarding the remaining portion. For multiple 500 mg doses, alternating preparation is advisable. Correct reconstitution ensures concentrations of approximately 100

mg/mL. Ceftriaxone reconstituted with Aqua Pro Injection, yielding a 100 mg/mL concentration, can be stored for a maximum of 6 hours at temperatures below 25°C or 24 hours in a refrigerator (manufacturer's instructions). Reconstitution with Dextrose 5% or NaCl 0.9% maintains stability for 2 days at room temperature (25°C) [16].

Cefotaxime injection preparation involves dissolving 1 g dry powder in a vial with 5 mL Aqua Pro Injection (as per literature and manufacturer's instructions), and for 2 g administration, two 1 g doses are dissolved in 5 mL Aqua Pro Injection each. Cefotaxime 500 mg, 1 g, and 2 g doses can be reconstituted with 10 mL Aqua Pro Injection to achieve concentrations of approximately 50, 95, and 180 mg/mL [17]. Antibiotic injection administration following reconstitution results in clear drug solutions, ensuring correct patient dosage.

Thus, trained staff are essential for reconstituting drugs to provide appropriate patient care. Regular training for nurses and pharmacists is necessary to maintain the quality of medications administered. Standards should be established to regulate drug reconstitution processes by staff other than pharmacists.

Conclusion and Recommendation

Based on the findings and discussion of this study, several conclusions can be drawn. Reconstitution procedures were conducted using Aquabidest and NaCl solutions, with the duration of reconstitution affecting the solubility of antibiotic drugs. Proper reconstitution techniques are essential skills that healthcare personnel, especially those handling antibiotics, must possess. It was also found that the reconstitution and mixing procedures of parenteral preparations in the MIC room do not fully meet Good Preparation Practice (GPP) criteria. Therefore, nurses need to be equipped with training and standard operating procedures for reconstituting and mixing powdered preparations, and ideally, this process should be performed by pharmacy staff. Based on these conclusions, several recommendations are proposed. Nurses should acquire expertise and skills in drug reconstitution to ensure that these tasks are performed according to established standards. Given that the study found deficiencies in the reconstitution and mixing procedures in the MIC room, it is crucial to establish standardized guidelines for drug reconstitution to ensure medication quality and prevent antibiotic resistance. Regular evaluation systems should be implemented to monitor staff compliance with these standards. Additionally, nurses should receive adequate training and standard operating procedures for handling powdered preparations, with pharmacy staff ideally overseeing or conducting these processes. By implementing these recommendations, hospitals can improve patient safety, enhance the effectiveness of antibiotic therapies, and mitigate the risks associated with inadequate preparation practices.

Conflict of Interest

The authors declare that there is no conflict of interest.

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