

Evaluation of antibiotics using ATC/DDD and DU 90% methods on ICU patients at Universitas Sumatera Utara Hospital

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Abstract

Background: Evaluation of the use of antibiotics is the control of antimicrobial resistance. The ATC/DDD method was recommended to evaluate drug use quantitatively which can be used to compare the quantity of antibiotic use between hospitals and between countries. This research was a descriptive study with retrospective data collection cross-sectional. This research was conducted at the ICU of Universitas Sumatera Utara hospital in August–November 2022 from medical record data for the period January–December 2021 which included patient demographics, patient diagnoses, antibiotic dosage forms, routes of administration, types of antibiotics, dosage, duration of antibiotics use, and duration of treatment.

Methods: Evaluation of antibiotic doses using the ATC/DDD method. The results of the study from 57 medical records that met the inclusion criteria showed that the ICU patients who used the most antibiotics were male (59.7%), the age group was >56 years (56.14%), patient diagnoses with COVID-19 (33.33%), and the dosage form was injection with the intravenous route of administration. The most frequently used antibiotics were levofloxacin (48.54%) 45.61 DDD/100 patient-days and ceftriaxone (30.06%) 28.25 DDD/100 patient-days, and the average value of Length of Stay (LOS) is 5.4 ± 3.98 days with a total DDD/100 patient-days value of 93.96 (reference value of 51–67 DDD/100 patient-days). DU 90% segment namely levofloxacin (48.69%), ceftriaxone (30.16%) and meropenem (12.82%). The results of the study concluded that the use of antibiotics in ICU patients at Universitas Sumatera Utara Hospital showed a high DDD/100 patient-days rate. Therefore, it is necessary for hospital to continuously monitor and evaluated the rational use of antibiotics to prevent resistance of antibiotics.

Keywords

antibiotics, ATC/DDD method, ICU, DU 90%

Background

Infectious diseases are caused by the entry and multiplication of microorganisms, such as bacteria, viruses, fungi, prions, and protozoa, into the body, causing organ damage. Most infections are caused by bacteria (Novelni et al. 2021). Antibiotic therapy is used to treat patients with bacterial in-

fections. Antibiotics are typical chemical compounds produced by living organisms, including derivative compounds and structural analogs, which are synthesized synthetically and at low levels and are capable of inhibiting important processes in the life of one or more species of microorganisms. Antibiotics are the drugs most widely used in bacterial infections caused by bacteria (Muntasir et al. 2022).

The Intensive Care Unit (ICU) is an organizational unit for special clinical services that is separate from other units and operates in an integrated manner with other departments in a hospital (Rehatta et al. 2019). Evaluation of antibiotic use is an indicator of the quality of antimicrobial resistance control programs in hospitals, aimed at providing information on patterns of antibiotic use in hospitals, both in quantity and quality (Kementerian Kesehatan Republik Indonesia 2015). DDD is defined as the assumed average maintenance dose per day for a drug used as its main indication in adults. The Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) method is recommended to quantitatively evaluate drug use (WHO Collaborating Centre for Drug Statistics Methodology. [accessed on 13 October 2022]). This method is performed by calculating the DDD per 100 patient-days, which aims to evaluate the type and amount of antibiotics used (Kementerian Kesehatan Republik Indonesia 2011). The high DDD value of antibiotics, which is higher than the WHO standard, indicates that there is still the possibility of irrational antibiotic use. The smaller the DDD value, the more selective is the use of antibiotics. This non-selectivity in the prescription and use of antibiotics may lead to many inappropriate prescriptions, and the use of antibiotics will affect the irrational use of antibiotics (Effendi et al. 2020). The Drug Utilization (DU) 90% method shows the grouping of drugs that enter the 90% usage segment, which is often used in conjunction with the analysis of ATC/DDD drug use. Research on drugs that are categorized into the 90% segment is needed to emphasize the drug segment related to drug evaluation, control, and procurement (Mahmudah et al. 2016). This study aimed to determine the demographic profile of patients and evaluate antibiotic utilization by ATC/DDD methods in ICU patients at Universitas Sumatera Utara hospital.

Methods

This was a descriptive study with retrospective cross-sectional data collection. The medication records of all patients in the ICU used antibiotics at the Universitas Sumatera Utara hospital period January and December 2021. This study included patients who met the inclusion criteria. Medication record sheets were reviewed to gather necessary information (sex, age, diagnosis, dosage forms, route of administration, LOS, type of antibiotic, dosage, and duration of antibiotic use). The inclusion criteria were as follows:

- ICU patients at Universitas Sumatera Utara hospital that used antibiotics during the January- December 2021 period,
- Aged ≥ 18 years, and
- Prescription of antibiotics in a single composition.

Quantitative evaluation of antibiotics using the ATC/DDD method from the collected data is then grouped by type antibiotics, dosage forms, dose, ATC code classifica-

tion, and the DDD value set by the WHO Collaborating Center for Drugs Statistics Methodology via the website (<http://www.wwhocc.no/atc-ddd-index>). The number of uses was then calculated (frequency multiplied by the number of days of hospitalization when the patient received antibiotics), total strength of antibiotics used (strength \times number usage), total per group, total days of stay, or Length of Stay (LOS) during ICU treatment. Quantitative analysis was performed using the Defined Daily Dose (DDD) method unit DDD/100 patient-days using the following formula:

$$\text{DDD}/100 \text{ patient-days} = \frac{\text{quantity of dosage antibiotic used by the patient(gram)}}{\text{WHO DDD of dosage standard (gram)}} \times \frac{100}{\text{quantity of LOS}}$$

(WHO Collaborating Centre for Drug Statistics Methodology. [accessed on 13 October 2022]).

Evaluation of the use of antibiotics using the DU 90% method of the ATC/DDD calculation results was entered into the formula:

$$\text{DU } 90\% = \frac{\text{value}_{100}^{\text{DDD}} \text{ patient-days antibiotik}}{\text{Total value}_{100}^{\text{DDD}} \text{ patient-days}} \times 100\%$$

Drug utilization (DU) of 90% was obtained by dividing the number of DDD/100 patient-days of antibiotics by the total DDD/100 patient-days of all antibiotics used in ICU patients, and then multiplying by 100%. The percentage of antibiotic use is then accumulated and sorted from the highest to the lowest percentage (WHO Collaborating Centre for Drug Statistics Methodology. [accessed on 13 October 2022]). Antibiotic utilization was based on the ATC code issued by the WHO. The choice of antibiotic code was based on the diagnosis of the disease (WHO Collaborating Centre for Drug Statistics Methodology. [accessed on 13 October 2022]).

Statistical analysis

The data are presented in the form of percentage tables, and average values were processed using Microsoft Excel.

Results

Patients characteristics

This study included 57 medical records that met our inclusion criteria. The patient characteristics included sex, age, diagnosis, comorbidity, and LOS, as shown in Table 1.

Discussion

During the study period, the total population comprised 102 medical records, and 57 medical records were samples that met the inclusion criteria. Table 1 shows that male patients were more frequent than female patients. This result is similar to that of Fathin and Kusumawati (2022) at Universitas Sumatera Utara hospital, who reported patients using antibiotics (male 52% and 48% female). This condition

Table 1. Characteristics of ICU Patients at USU Hospital Period January-December 2021.

Gender	Total
Male	34 (59.7%)
Female	23 (40.3%)
Age (years)	
18–25	1 (1.8%)
26–35	5 (8.8%)
36–45	10 (17.5%)
46–55	9 (15.8%)
>56	32 (56.14%)
Diagnosis	
Covid-19	19 (33.33%)
Decreased awareness of various causes	12 (21.05%)
Post-surgical	12 (21.05%)
Respiratory failure	2 (3.50%)
Acute lung edema	1 (1.75%)
Antibody dependent enhancement	1 (1.75%)
Pleural effusion	1 (1.75%)
Chronic kidney failure	1 (1.75%)
Hematoma	1 (1.75%)
Massive haemoptysis	1 (1.75%)
Uterine myoma	1 (1.75%)
Head bleeding	1 (1.75%)
Chronic obstructive pulmonary disease (COPD)	1 (1.75%)
Status epilepticus	1 (1.75%)
Hemorrhagic stroke	1 (1.75%)
Ischemic stroke	1 (1.75%)
Comorbidity	
Community acquired pneumonia	9 (52.95%)
Sepsis	5 (29.41%)
Hospital-acquired pneumonia	2 (11.76%)
Tuberculosis	1 (5.88%)
Length of stay (days)	
≤4	30 (52.63%)
5–9	18 (31.57%)
≥10	9 (15.78%)

is related to heavier physical activity by males, thus causing a rapid decrease in the immune system quickly (Azyenela et al. 2022) and the patient becomes vulnerable to infection.

The study revealed that patients aged >56 years were the most frequently used antibiotics. This is similar to Widya (2018) at Dr. Moewardi Surakarta hospital. The risk of developing a disease in the elderly can increase because there has been a decrease in the function of various organs of the body due to damage to cells caused by the aging process, which reduces the production of hormones, enzymes, and substances needed for immunity. Therefore, the elderly are more susceptible to infection and more likely to suffer from more than one type of disease (Maryam et al. 2008).

The most common diagnosis that warranted admission to the ICU was COVID-19, followed by decreased awareness of various causes and post-surgical patients. The patient's ICU also had comorbid illnesses, community pneumonia, sepsis, hospital pneumonia, and tuberculosis. The most common disease is COVID-19 because in the January-December 2021 period, the coronavirus, which can be transmitted, is spreading. According to Adimara et al. (2021), COVID-19 in severe cases can cause damage

to organ function, which can cause other diseases such as pneumonia, sepsis, acute respiratory syndrome, kidney failure, and even death.

Decreased consciousness often occurs in ICU patients because it is an indication of failure of the function of the integrity of the brain from organ failure such as heart, respiratory, and circulatory failure, which will lead to brain failure with consequent death. This is related to the post-surgery experience of ICU patients (Indra et al. 2020).

LOS is the length of time that each patient is hospitalized, which is obtained by dividing the number of days of stay by the number of patients. The LOS is calculated from the time the patient enters the ICU until he/she leaves the ICU. The length of hospital stay was 308 days and the average LOS was 5.4 ± 3.98 days. The most common duration of antibiotic administration to patients during treatment in the ICU was 3 days. If the patient's condition improved, the patient was transferred to the inpatient room and antibiotics were administered according to the clinical pathway of the patient's diagnosis. In general, patients with bacterial infections are hospitalized for 7–10 days, but this depends on comorbidities, the development of complications, and the severity of the disease. The duration of therapy for each individual may differ depending on the clinical response and comorbidity, as in the treatment of pneumonia caused by Methicillin-Resistant *Staphylococcus aureus* (MRSA), the duration of therapy can reach 7–21 days depending on the level of infection (Menendez et al. 2001).

Table 2 showed there were 252 antibiotics used alone, with the most widely prescribed drugs being third-generation quinolones (fluoroquinolones), namely levofloxacin (38.8%) and third-generation cephalosporin class ceftriaxone (34.5%). This is not much different from Muhammad's research (2018) at Dr. In Moewardi in Surakarta hospital, antibiotics were used alone, with the most commonly prescribed drug being levofloxacin (35.42%), followed by ceftriaxone (29.86%) (Muhammad and Mutmainah 2018). Levofloxacin is a third-generation fluoroquinolone class of broad-spectrum antibiotics that is more effective against bacteria, and is a third-generation broad-spectrum cephalosporin antibiotic that is active against gram-positive, gram-negative, aerobic, or anaerobic bacteria (Kresnawati et al. 2021).

Nine types of antibiotics were administered alone and 16 types of antibiotics were administered in combination. Antibiotics were then classified based on the ATC code according to the WHO Collaborating Center for Drug Statistics Methodology Guideline in 2022. In this study, only a single administration of antibiotics was associated with an ATC code. The use of antibiotics based on the ATC codes is shown in Table 3.

As shown in Table 3, intravenous antibiotics were most commonly administered. The majority of gifts in ICU patients are parenteral; this is done to maintain the concentration of the drug in the blood and in critically ill patients (Bertsche 2008). Intravenous administration of antibiotics aims for antibiotics to react immediately and enter blood vessels. This route provides a rapid effect and good control

Table 2. Antibiotics Used in ICU Patients at USU Hospital Period January-December 2021.

	Type of antibiotic	Total number of antibiotic prescription
Single	Levofloxacin	98 (38.8%)
	Ceftriaxone	87 (34.5%)
	Meropenem	41 (16.5%)
	Cefoperazone	10 (3.9%)
	Azithromycin	7 (2.7%)
	Ciprofloxacin	5 (1.9%)
	Cefazolin	2 (0.8%)
	Cefotaxime	1 (0.4%)
	Ampicillin sulbactam	1 (0.4%)
	Total	252 (100%)
Combination	Levofloxacin + Cefotaxime + Ampicillin Sulbactam	9 (15.25%)
	Ceftriaxone + Levofloxacin	8 (13.55%)
	Doxycycline + Clindamycin + Metronidazole + Tazam	6 (10.16%)
	Ceftriaxone + Ciprofloxacin	5 (8.47%)
	Meropenem + Amikacin	5 (8.47%)
	Ceftriaxone + Gentamicin	5 (8.47%)
	Ceftriaxone + Meropenem + Levofloxacin	5 (8.47%)
	Rifampicin + Pyrazinamide + Streptomycin + Meropenem	4 (6.77%)
	Ceftriaxone + Metronidazole	2 (3.38%)
	Meropenem + Metronidazole	2 (3.38%)
	Ceftriaxone + Gentamicin + Metronidazole	2 (3.38%)
	Meropenem + Ceftriaxone + Ciprofloxacin + Doxycycline	2 (3.38%)
	Meropenem + Levofloxacin + Ceftriaxone + Metronidazole	1 (1.69%)
	Meropenem + Ciprofloxacin	1 (1.69%)
	Azithromycin + Levofloxacin	1 (1.69%)
	Ciprofloxacin + Ceftazidime	1 (1.69%)
	Total	59 (100%)

of circulating drug levels. The route of oral antibiotic administration was also assessed in this study. The oral route of antibiotic administration is economical, convenient, and safe for treating infections. However, parenteral antibiotics can be considered for moderate-to-severe infections (Departemen Kesehatan Republik Indonesia 2011).

Inpatient conditions typically require intravenous drug therapy. Intravenous drug administration requires complex procedures and special preparation (Leal et al. 2016). Intravenous drugs are generally used in hos-

Table 3. ATC Code.

Classification of antibiotic	Name of antibiotic	ATC code	Route of administration
3 rd Generation Quinolones (Fluoroquinolon)	Levofloxacin	J01MA12	Intravenous
3 rd Generation Cephalosporins	Ceftriaxone	J01DD04	Intravenous
Carbapenem	Meropenem	J01DH02	Intravenous
3 rd Generation Cephalosporins	Cefoperazone	J01DD12	Intravenous
Macrolides	Azithromycin	J01FA10	oral
2 nd Generation Quinolones (Fluoroquinolon)	Ciprofloxacin	J01MA02	Intravenous
1 st Generation Cephalosporin	Cefazolin	J01DB04	Intravenous
Penicillin	Cefotaxime	J01DD01	Intravenous
3 rd Generation Cephalosporins	Ampicillin Sulbactam	J01CA01	Intravenous

pitals because they are very important for patients requiring a pharmacological effect quickly or if a patient cannot receive oral medication (Marsilio et al. 2016).

Table 4 show that the results of evaluating the use of antibiotics from 57 medical records of ICU patients at Universitas Sumatera Utara hospital for the January-December 2021 period were carried out using the DDD/100 patient-days method which describes the number of patients receiving the definitive daily dose (DDD) for certain indications or in this study for patients ICU. In this study, the total use of antibiotics in ICU patients at Universitas Sumatera Utara hospital for the January-December 2021 period was 93.96 DDD/100 patient-days. This is different from the study of Scholze et al (2015) in a German hospital that revealed the total use of antibiotics by sepsis and pneumonia patients was 51.00–67.1 DDD/100 patient days. According to Sari et al. (2016), the greater the total value of DDD/100 patient-days, the higher the level of antibiotic use in 100 days of hospitalization. The small quantity of antibiotics used shows that doctors are more selective in choosing therapy for patients, so that it is closer to the principle of wise use of antibiotics because if the administration of antibiotics is based on certain indications, it indicates the use of antibiotics is more appropriate, so the quantity of antibiotic use will decrease. The number of prescriptions and use of antibiotics with inappropriate indications will also affect the accuracy of the use of antibiotics in patients (Laras et al. 2012). This comparison of val-

Table 4. DDD/100 patient-days value.

ATC code	Name of antibiotic	Total dose used (mg)	DDD default value (mg)	DDD usage	DDD 100/patient-days	Percentage (%)
J01MA12	Levofloxacin	70250	500	140.5	45.61	48.54
J01DD04	Ceftriaxone	174000	2000	87	28.25	30.06
J01DH02	Meropenem	111000	3000	37	12.01	12.78
J01DD12	Azithromycin	3500	300	11.7	3.8	4.04
J01FA10	Ciprofloxacin	4600	800	5.75	1.87	1.99
J01MA02	Cefoperazone	20000	4000	5	1.62	1.72
J01DB04	Ampicillin sulbactam	6000	6000	1	0.32	0.34
J01CA01	Cefazolin	3000	3000	1	0.32	0.34
J01DD01	Cefotaxime	2000	4000	0.5	0.16	0.17
Total DDD/100 patient-days					93.96	100

ues can be used as a reference that the use of antibiotics in the Universitas Sumatera Utara hospital for ICU patients is still very high, so that in the future it can be taken into consideration for prescribing antibiotics to prevent resistance.

The current high use of antibiotics is due to infectious diseases, which still predominate in Indonesia. Infectious diseases caused by the growth of microbes in the body due to internal and external factors that must be considered include maintaining cleanliness, using personal protective equipment, carrying out septic and aseptic actions, and the ability to prevent infection transmission in hospitals are actions that provide quality services (Izza et al. 2021).

Based on the results of this study, the most widely used antibiotic was levofloxacin, with a total use of 45.61 DDD/100 patient-days (48.54%). In Muhammad's (2018) study, the DDD/100 patient-day levofloxacin value was 53.88 (48.16%). The use of levofloxacin at Universitas Sumatera Utara hospitals is still low when compared to Muhammad's study, but in Rahmah's (2022) study at Wawa Huasada Kepanje hospital, the DDD/100 patient-days levofloxacin value was 33.52 (33.33%). Differences in DDD/100 patient-day values in the use of antibiotics can be caused by differences in etiology. Culture results and clinical responses can be considered when determining therapy. According to Liu et al. (2020), levofloxacin is very active against pathogenic respiratory system infections and has a good therapeutic success rate; thus, it can be used as the first-line treatment for COVID-19, pneumonia, and sepsis. Levofloxacin is a third-generation fluoroquinolone class of broad-spectrum antibiotics that is effective against gram-negative and gram-positive bacteria (Melarosa et al. 2019).

The second most commonly used antibiotic was the third-generation cephalosporin, ceftriaxone, with a total DDD/100 patient-days of 28.25 (30.06%). In a study by Prasetyo and Kusumaratni (2018) at the DKT hospital in Kediri, the DDD/100 patient-days value for ceftriaxone was 23.86. The use of ceftriaxone was higher at the USU hospital than at the DKT Kediri Hospital. Ceftriaxone is a broad-spectrum third-generation cephalosporin antibiotic that is active against gram-positive, gram-negative, aerobic or anaerobic bacteria. Ceftriaxone is an active antibiotic against pneumococcal bacteria, which is an empiric therapy option for infectious diseases caused by this group of bacteria, one of which is pneumonia (Kresnawati et al. 2021). This is in accordance with Universitas Sumatera Utara hospital guidelines for administering ceftriaxone antibiotics to patients with pneumonia.

The evaluation of drug use by determining DU 90% can be used in conjunction with the ATC/DDD method for control purposes in drug planning and procurement. As shown in table 5, the antibiotics included in the DU 90% segment were levofloxacin (48.69%), ceftriaxone (30.16%), and meropenem (12.82%), and the antibiotics included in the 10% segment were azithromycin (4.05%), ciprofloxacin (1.99%), cefoperazone (1.72%), ampicillin sulbactam (0.34%), cefazolin (0.34%), and cefotaxime (0.17%). This is different from the study by Azyenela et al. (2022) at Solok hospital, it was found DU 90% segment was cefixime (49.77%), ceftriaxone (18.39%), cefotaxime

Table 5. DU 90%.

ATC code	Name of antibiotic	DDD/100 patient-days	DU 90%	Segment DU
J01MA12	Levofloxacin	45.61	48.69	
J01DD04	Ceftriaxone	28.25	30.16	90%
J01DH02	Meropenem	12.01	12.82	
J01FA10	Azithromycin	3.8	4.05	
J01MA02	Ciprofloxacin	1.87	1.99	
J01DD12	Cefoperazone	1.62	1.72	
J01CA01	Ampicillin Sulbactam	0.32	0.34	10%
J01DB04	Cefazolin	0.32	0.34	
J01DD01	Cefotaxime	0.16	0.17	

(14.78%), metronidazole (8.76%) and the 10% segment, namely ciprofloxacin (5.07%), azithromycin (1.32%), levofloxacin (0.39%), cefadroxil (0.23%) and meropenem (0.07%). This condition can occur because the 90% DU method is performed simultaneously with the analysis of drug use using the ATC/DDD method. Drugs included in the DU 90% segment are included in the accumulated use of 90% (Fazriyah 2017).

Antibiotics included in the 90% segment indicate that these antibiotics are most widely used, and antibiotics included in the 10% segment indicate that these antibiotics are used little in prescribing antibiotics (WHO 2022). A DU value of 90% is the reference data for examining the quality of prescription and adherence to guidelines and formularies. Knowing the DU value of 90% can be used for drug evaluation, drug use control, and appropriate interventions if non-compliance with the formulary (Pratama et al. 2019).

This study revealed that 90% namely levofloxacin (48.69%), ceftriaxone (30.16%), and meropenem (12.82%). The results of the study were the same as those of the study by Andarsari et al. (2022) on the first and third ranks of antibiotics, which were the three most used antibiotics, levofloxacin, ceftriaxone, and meropenem, with a total of all antibiotics 73.64 DDD/100 patients-days. Most useful is parenteral Levofloxacin at 21.92 DDD/100 patient-days, ceftriaxone at 20.45 DDD/100 patient-days and meropenem at 14.29 DDD/100 patient-days (Andarsari et al. 2022).

Based on the WHO Access, Watch, Reserve (AWaRe) classification of antibiotics for evaluation and monitoring of use (2021), the three antibiotics were included in the Watch group antibiotics, which included antibiotic classes that have higher resistance potential and include most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. Priority should be given to these medicinal products as key targets for management programs and monitoring. Selected Watch Group antibiotics, listed as individual medicinal products in the WHO Model List of Essential Medicinal Products for a limited number of specific infectious diseases, are recommended as first- or second-choice empirical therapy options. Therefore, stakeholders must be careful in using antibiotics by evaluating the utilization implemented strictly and continuously (2021 AWARe classification (who.int)).

Conclusions

The study revealed the average value of LOS was 5.4 days with a total DDD/100 patient-days value of 93.96 and DU 90% namely levofloxacin (48.69%), ceftriaxone (30.16%), and meropenem (12.82%). It can be concluded that the DDD/100 patient-day value remained high. This condition indicates the need for further studies to ensure that antibiotic utilization is rational to achieve the outcome of the therapy and increase the quality of life of the patient.

Abbreviations

ATC/DDD, The Anatomical Therapeutic Chemical/Defined Daily Dose; DDD, Defined Daily Dose; ICU, the Intensive Care Units; LOS, Length of Stay; MRSA, by Methicillin-Resistant *Staphylococcus aureus*; DU, Drug Utilization; COVID-19, Corona Virus 19; and AWaRe, WHO Access, Watch, Reserve.

Ethics approval and consent to participate

Ethics approval was issued by the Universitas Sumatera Utara Health Research Ethics Committee number 748/KEPK/USU/2022 on 12 August 2022.

Not applicable for consent to participate because the data was taken from medical records.

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Availability of data and materials

All datas and software used for supporting the conclusion of this article are available from the public data respiratory at the website of <https://bit.ly/3PLgoTR> and to access the ATC code at https://www.whocc.no/atc_ddd_index/.

Authors' contributions

ESN designed, coordinated this research and drafted the manuscript. IP carried out the experiment and data analysis. HRT conceived of the study, and participated in research coordination. The authors read and approved the final manuscript.

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