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A Quantitative Study of Antibiotic Use Using ATC/DDD in the ICU (Intensive Care Unit) at Petala Bumi Hospital, Riau Province in 2018-2019

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Abstract:- Infectious diseases are still a problem crucial to public health, especially in countries develop. Reality shows that in developing countries, the country's order of the primary diseases is still occupied by various infectious diseases that require antibiotic therapy. Research on the quality of antibiotic use in multiple parts, the hospital found 30% to 80% not based on indications. Therefore, the judicious use of antibiotics is essential In addition to implementing good infection control to prevent the development of resistant bacteria in society. This study uses a cross-sectional descriptive design, using retrospective data with a qualitative approach using the Gyssens method and a quantitative approach using the DDD/100 patient-days method. This study uses secondary data retrospectively in the form of medical records of Intensive Care Unit (ICU) patients at the Petala Bumi Regional General Hospital, Riau Province, who were treated from January 1, 2018 to December 31, 2018, and January 1, 2019, to December 31, 2019. Where the percentage of accuracy or not administration of antibiotics. The data obtained will be analyzed quantitatively and presented in an analytical description.

Keywords— Antibiotics, ATC/DDD, Quantitative

I. INTRODUCTION

Infectious diseases are still one of the problems of public health, especially in developing countries. The fact shows that in developing countries, the country's order of the primary diseases is still occupied by various infectious diseases that require antibiotic therapy. Antibiotics are the most common drugs used for infections caused by bacteria. Multiple studies have found that about 40-62% of antibiotics are misused, among others, for diseases that do not require antibiotics. On research on the quality of antibiotic use in various parts hospitals found 30% to 80% not based on indications. Therefore, the judicious use of antibiotics is essential to implementing good infection control to prevent the development of resistant bacteria to society[2]. Bacterial resistance to antibiotics is a problem that still occurs in the Intensive Care Unit (ICU)[3]. Infection with antibiotic resistance in certain organisms can cause an increase in the duration of hospital stay, mortality, and patient costs. The data show that the pattern of antibiotics used affects the development of bacterial resistance. One way to overcome this is to use antibiotics rationally, monitor and evaluate the use of antibiotics in hospitals in a systematic, standardized and regular manner in hospitals and community health centers, and intervene to optimize these antibiotics. The wise use of antibiotics is essential in applying reasonable infection control to prevent the development of these resistant germs to the community[2].

According to WHO, rational use of medicine requires that patients receive treatments suitable for their clinical needs in doses that meet their individual needs for an adequate period and at a low cost. Irrational use of drugs can occur in all hospitals and the community[4]. This includes writing the wrong medicine, ineffective medicine, unnecessary medicine, unsafe medicine, not enough available medicine being used, and treatment being misused. As a result, it will negatively affect the possibility of adverse reactions to the patient's health and lack of patient confidence in the drug. Another negative effect is on the cost of health care and the quality of drug therapy and medical care[5].

Inappropriate use of antibiotics will have a negative impact, one of which is the increasing incidence of bacterial resistance to antibiotics, other negative impacts include increasing toxicity, side effects of these antibiotics, and increasing hospital costs. For this reason, the use of appropriate antibiotics is expected to have a positive impact, including reducing morbidity, mortality, economic losses, and reducing the incidence of bacterial resistance to antibiotics[6].

WHO declared the ATC/DDD system an international measurement standard for the study of drug use while establishing the WHO Collaborating Centre for Drug Statistics Methodology to maintain and develop the ATC/DDD system. This assessment can assess the use of antibiotics in hospitals to evaluate use, control usage, and plan drug purchases[7].

To reduce the misuse of antibiotics and promote the proper use of antibiotics, the role of pharmacists in assessing the use of antibiotics in the hospital environment is essential. The form of the study that can be carried out is by conducting an assessment of antibiotics use. In addition, to prevent the incidence of antibiotic resistance, it is also necessary to plan the use of antibiotics and control the incidence of antibiotic resistance. To determine the distribution of antibiotics used and in the context of preventing the occurrence of antibiotic resistance, data from studies on the use of antibiotics are

needed for several years. The increase in antibiotic resistance is a problem that requires special attention. Antibiotic resistance occurs due to inappropriate patterns of use or prescribing patterns of antibiotics, so it is necessary to use antibiotics to prevent the incidence of antibiotic resistance[8].

Because of the reasons above, this study conducts to examine the use of antibiotics in patients treated in the ICU (Intensive Care Unit) of Petala Bumi Hospital, Riau Province, so that this research can be used in the end as material to increase the use of appropriate antibiotics.

II. RESEARCH METHODS

This study uses a cross-sectional descriptive design, using retrospective data with a qualitative approach using the Gyssens method and a quantitative approach using the DDD/100 patient-days method. This study uses secondary data retrospectively in the form of medical records of Intensive Care Unit (ICU) patients at the Petala Bumi Regional General Hospital, Riau Province, who were treated from January 1, 2018, to December 31, 2018, and January 1, 2019, to December 31, 2019.

Reviewers analyze antibiotics, namely doctors, pharmacists, and nurses in Petala Bumi Regional General Hospital, Riau Province. According to the Guidelines for Pharmaceutical Services for Antibiotic Therapy (Depkes RI., 2011), an assessment of the quality of antibiotic use should be carried out regularly prospectively by at least three reviewers (infection specialist, pharmacist, treating doctor).

The study population was all patient medical records in the Intensive Care Unit (ICU) Petala Bumi Hospital, Riau Province, during 2018 and 2019. In this study, the samples taken in this study were all patient medical records in the ICU room at the Petala Bumi Hospital in Riau Province during 2018 and 2019 who met the inclusion criteria and did not meet the exclusion criteria.

Data processing and analysis are carried out analytically quantitative. Quantitative evaluation of usage Antibiotics was analyzed using the ATC/DDD system set by WHO. Results show usage antibiotics in DDD/100 patient-days units indicating the percentage of accuracy or not administration of antibiotics. Data collection is carried out using the quantitative approach analysis using the ATC/DDD system established by WHO. The results show the use of antibiotics in DDD/100 patients/day units, where the percentage of results shows whether or not the accuracy administration of antibiotics. The data obtained will be analyzed quantitatively by the researcher and presented in an analytical description.

III. DISCUSSION

The study was conducted on antibiotic regimens prescribed by doctors in the ICU of the Petala Bumi Hospital in 2018 and 2019. The medical records of patients that can be included in this study are medical records completed data, including number, date and time of medical history, type of health insurance, patient identity, patient LOS, diagnostic results, physical and supporting examinations, clinical progress notes, and patient discharge summary.

This study collected 177 medical records of ICU patients. Of the 105 patient medical records in 2018, ten medical records could not be included in the quantitative research. Seven patients did not have complete medical records, while the other three were not given antibiotic therapy during treatment in the ICU. In addition, in 2019, it was known that 72 patients were being treated in the ICU of the Petala Bumi Hospital, eleven of whom could not be included in the quantitative study because six of them did not have complete medical records while the other five were not given antibiotics, during treatment in the ICU.

From the study results, the data studied in 2018 were 95 patients. In 2019 there were 61 ICU patients at the Petala Bumi Hospital would be assessed for quantitative use of antibiotics using the ATC/DDD formula. The assessment of the use of antibiotics will be calculated separately based on the grouping of years of the administration of antibiotics. The characteristics of patients receiving these antibiotics can be seen in Table 3.1 below:

Table 3.1 Patient Demographic Characteristics

Characteris-tics	2018		2019	
	Amount	%	Amount	%
Patient Status				
General	1	1.05	10	16.39
JKD Kampar	-	-	3	4.92
JKD City	29	30.53	3	4.92
Jampersal	-	-	1	1.64
KPS	-	-	8	13.11
BPJS	65	68.42	36	59.02
Age				
<20 years	2	2.11	4	6.56
20-40 years	9	9.47	13	21.31
41-50 years old	18	18.95	5	8.20
51-60 years old	17	17.89	15	24.59
>60 years old	49	51.58	24	39.34
Gender				
Man	43	45.26	35	57.38
Woman	52	54.74	26	42.62
Length of treatment				
1 - 5 days	71	74.74	44	72.13
6 - 10 days	20	21.05	8	13.11
11-20 days	4	4.21	9	14.75
Types of Antibiotics				
1 Type	56	58.95	41	67.21
2-3 Kinds	33	34.74	15	24.59
>3 Kinds	16	16.84	5	8.20

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From the demographic data above, it can be seen that in 2018 the status of most patients treated in the ICU was patients with BPJS insurance coverage as much as 68.42%, followed by city JKD patients as much as 30.53%. At the same time, 1.05% are patients with private financing status. From these data, it appears that most of the patients treated in the ICU are patients with insurance coverage. This is supported by the condition of ICU patients who require treatment at a reasonably high cost. Therefore patients without guaranteed funding for therapy will find it difficult to get treatment. ICU patients without health insurance have difficulty getting treatment due to cost constraints. However, it is possible that patients without health insurance can also be treated in the ICU.

The group of patients who received the most antibiotics was the group aged more than 60 years, which was 51.58%. This is because elderly patients can have more than one disease, which is generally chronic degenerative (multi pathology). Second, there is a decline in organ function that causes elderly patients to fall into a failure to thrive condition easily. So this condition happens very often. Most of the elderly patients who are hospitalized are very susceptible to falls and have the potential to become chronic. Critically elderly patients are usually transferred to the intensive care unit by the treating physician. This will increase the demand for intensive care unit (ICU) use. Comorbidities in the elderly also often use various types of drugs,

The most extended length of stay of patients in the ICU ranged from 1-5 days (74.74%). Then, the length of treatment is 6-10 days (21.05%), followed by the length of stay > 10 days (4.21%). In contrast, the number of antibiotics received by patients ranged from 1-3 antibiotics. One patient may be prescribed a combination of antibiotics. Where the antibiotic used empirically in this hospital is ceftriaxone.

Table 3.2 The most common diseases in the ICU of Petala Bumi Hospital

Type of diagnosis	**2018**		**2019**	
	Amount	**%**	**Amount**	%
Post major surgery	15	15.79	9	14.75
Cardiovascular disorders	16	16.84	13	21.31
Loss of consciousness	31	32.63	13	21.31
Severe respiratory failure	15	15.79	18	29.51
Chronic kidney failure, liver function, diabetes mellitus and acute complications	6	6.32	5	8.20
Septic shock	12	12.63	3	4.92
TOTAL	95	100.00	61	100.00

Viewed from table 3.2, it can be seen that the diagnosis of the most disease cases in the ICU of Petala Bumi Pekanbaru Hospital in 2018 was a case of decreased consciousness (32.63%). Still, in 2019 data, there was a decrease in the number of instances to (21.31%). Then followed by cases of cardiovascular disorders (16.84%), post-major surgery, and severe respiratory disorders (15.79%), while septic shock (12.63%), and organ disorders only (6.32%)). However, compared to cases in 2019, there appears to be a significant decrease in the number of cases. It can be seen in cases of septic shock only a number (4.92%). However, the number of cases caused by severe respiratory disorders seemed to increase compared to the previous year, which amounted to (29.51%). Patients admitted to the ICU are generally due to an unstable condition and require intensive therapy. The goal of intensive therapy treatment in patients in the ICU is to prevent severe complications in patients.

Table 3.3 Distribution of Diseases by Age in the ICU of Petala Bumi Hospital

Type of diagnosis	**2018**			**2019**		
	40	**41-60**	**>60**	**40**	**41-60**	**>60**
Post major surgery	5	5	3	7	1	2
Cardiovascular disorders	-	3	9	3	8	6
Loss of consciousness	3	14	13	1	6	-
Severe respiratory failure	3	10	6	2	9	9
Chronic kidney failure, liver function, diabetes mellitus and acute complications	2	3	1	1	-	-
Septic shock	2	8	6	2	-	-
TOTAL	15	43	38	16	24	17

Based on the table above, it can be seen that most of the patients treated in the ICU of Petala Bumi Hospital ranged in age from 41-60 years, either in 2018 or 2019. The proportion of patients aged 41-60 years was primarily patients with decreased consciousness and impaired patients, heavy breath. This was followed by septic shock and post-major surgery. Meanwhile, the proportion of cardiovascular disorders and organ disorders was the same in 2018. Meanwhile, if you look at disease data in 2019, there were no case reports of organ disorders and septic shock in patients aged 41-60 years or an age range > 60 years. Most cases were found in severe respiratory disorders, followed by cardiovascular disorders, decreased consciousness, and cases after major surgery.

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Table 3.4 Use of ICU antibiotics at Petala Bumi Hospital

Giving time	2018		2019	
	n	%	n	%
1-5 days	81	84.38	49	80.33
6-10 days	15	15.63	7	11.48
11-15 days	0	0	5	8.20

The administration of antibiotics to patients in the ICU of Petala Bumi Pekanbaru Hospital can be seen from the table above, and it appears that most antibiotics are given in the ICU is 1-5 days. In 2018 it was known that as many as (83.38%) were given antibiotics during treatment in the ICU. While in 2019, it decreased to (80.33%). Then followed by 6-10 days of administration (15.63%) in 2018, but decreased to (11.48%) in 2019. In 2018 there was no antibiotic administration more than ten days of treatment, but in 2018 2019, found as many as (8.20%) cases of antibiotic administration during the 11-15 day treatment period. The duration of antibiotic therapy is based on clinical indications and the infecting bacteria. Then antibiotic treatment can be replaced or discontinued according to the condition of the infection.

Quantitative assessment of antibiotic use was carried out by calculating DDD (Defined Daily Doses) per 100 days of hospitalization according to WHO recommendations. This can be done by collecting data on antibiotic use from patient medical records. Data on the use of antibiotics treated in the ICU was obtained from the calculation of DDD/100 days of hospitalization. The smaller the quantity of antibiotics used can be used as a parameter indicating that doctors are more selective in prescribing antibiotics to be closer to the principle of rational use of antibiotics.

Table 3.5 Types of antibiotics in the ICU of Petala Bumi Hospital in 2018

NO	DDD CODE	NAME ANTIBIOTICS	TOTAL DDD	%
1	JO1GB06	Amikacin	30.00	5.70
2	J01CA01	Ampicillin	44.25	8.41
3	J01FA10	Azithromycin	15,16	2.88
4	J01DD01	Cefotaxime	5.50	1.05
5	J01DD04	Ceftriaxon	168.00	31.93
6	J01DD12	Cefoperazon	8.00	1.52
7	J01DD02	Caftazidim	20.25	3.85
8	J01MA02P	Ciprofloxacin	20.66	3.93
9	J01XX01	Fosfomicin	15.00	2.85
10	JO1GB03	Gentamicin	1.60	0.30
11	J01DH51	Imipenem	4.50	0.86
12	J01MA12	Levofloxacin	37,00	7.03
13	J01DH02	Meropenem	93.50	17.77
14	J01XD01	Metronidazole	62.66	11.91

Based on the data in table 3.5, it can be seen that the most widely used antibiotic in the ICU room of Petala Bumi Pekanbaru Hospital during 2018 was ceftriaxone (31.93%) and followed by meropenem (17.77%) and metronidazole (11.91%). Ceftriaxone is the most commonly prescribed antibiotic because ceftriaxone has a broad spectrum and is effective for treating infections caused by various gram-positive and gram-negative bacteria. (Mc Evoy, 2008). Guidelines for the Use of Antibiotics mention the choice of ceftriaxone as prophylactic therapy because of its high concentrations in tissue and blood (90-120 ug/ml). Based on the Drug Information literature, the second and third-generation cephalosporin antibiotics are not better than the first generation. Due to cost considerations and concerns about the potential emergence of resistance due to broad-spectrum antibiotics[9].

The high use of ceftriaxone as a definitive therapy is contrary to the regulations of the Minister of Health of the Republic of Indonesia. The use of antibiotics for traditional treatment should prioritize the selection of narrow-spectrum antibiotics. Frequent use of the same antibiotics should be avoided. The use of advanced antibiotics such as third-generation cephalosporins, fluoroquinolones, aminoglycosides should not be used too often for routine purposes to maintain the availability of effective antimicrobials when retention problems arise[10].

Table 3.6 Types of Antibiotics at Petala Bumi Hospital in 2019

NO	DDD CODE	NAME ANTIBIOTICS	TOTAL DDD	%
1	J01DD01	Cefotaxime	3.49	1.10
2	J01DD04	Ceftriaxon	138.50	43.59
3	J01DD12	Cefoperazon	1.50	0.47
4	J01DD02	Caftazidim	31.50	9.91
5	J01MA02P	Ciprofloxacin	4.00	1.26
6	JO1GB03	Gentamicin	4.26	1.34
7	J01MA12	Levofloxxacin	61.50	19.35
8	J01DH02	Meropenem	64	20.14
9	J01XD01	Metronidazole	9	2.83

The data on antibiotics in 2019 also showed results that were not much different from the previous year. The highest number of antibiotic use was found in the use of ceftriaxone (43.59%), followed by meropenem (29.14%) and levofloxacin (19.35%).

Giving antibiotics in the ICU must consider many things, such as de-escalation strategies, critically ill patients, organ function, especially the liver and kidneys, global and local bacterial patterns, and the possibility of microbial resistance. The de-escalation strategy requires empirical broad-spectrum antibiotics and then narrowing the spectrum after the results of microbial cultures and antibiotic sensitivity tests are obtained. Most of the patients admitted to the ICU come from various health care centers around the hospital. This patient had received empiric antibiotics, but his

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condition worsened. One of the possible causes of this incident is the resistant occurrence in the causative microbe to the antimicrobial antibiotics that have been given.

Meanwhile, most of the patients admitted to the ICU experienced disturbances in the respiratory system, hemodynamics, fluid regulation, and metabolism. This causes a decrease in peripheral perfusion, which results in impaired distribution of antibiotics in peripheral tissues. The concentration of antibiotics cannot reach the minimum inhibitory concentration (MIC), thereby increasing the potential for bacterial strains that are resistant to certain antimicrobials11.

Based on table 3.7, in general, the use of antibiotics in quantity in the ICU of Petala Bumi Pekanbaru Hospital in 2018 was higher than the WHO DDD standard. Of the 14 types of antibiotics used, nine types had higher usage than the WHO standard. In contrast, as many as five other types have lower usage than WHO standards. The highest use of antibiotics in the ICU in 2018 was ceftriaxone and meropenem. The use of ceftriaxone as much as 26.05 DDD/100 days of hospitalization showed that ceftriaxone was 0.26 DDD per day. The use of meropenem as much as 14.50 DDD/100 days of hospitalization showed that the use of meropenem was 0.145 DDD per day.

Meanwhile, data from table 3.8 shows that there is no significant change in the quantity of antibiotic use in the ICU room at Petala Bumi Hospital Pekanbaru. In general, it can be judged that the use of antibiotics in the ICU of Petala Bumi Pekanbaru Hospital is higher than the WHO standard. Of the nine types of antibiotics used during 2019, six types of antibiotics were found to have higher usage than the WHO standard. In comparison, the other three types of antibiotics have lower usage. The highest use of antibiotics in 2019 was the use of ceftriaxone (26.53%) followed by meropenem (12.26%) and levofloxacin (11.78%). The use of ceftriaxone as much as 26.53 DDD/100 days of hospitalization showed that ceftriaxone was 0.265 DDD per day. While the use of meropenem 0,

Based on research in 2010, it was found that in the use of antibiotics in the ICU, it was found that ceftriaxone was the most widely used drug, amounting to 62.2 DDD/100 patients. Likewise, in a study in 2011 in the pediatric ward, antibiotics came from the cephalosporin group, namely ceftriaxone, with total use of 39.4 DDD/100. While the 2017 tofu research by Andriani in the operating room, internal medicine, and gynecology at RSU, Dr. M. Djamil Padang, the quantitative evaluation of antibiotics, found that cefoperazone was the most widely used antibiotic, namely 16.04 DDD/100 patient-day. These values become a reference that the use of antibiotics in the Petala Bumi Hospital in the ICU is still very high compared to the WHO standard of antibiotic use.

If this occurs in critically ill patients, hemodynamic control may be difficult or it may become resistant to positive inotropic drugs and vasoconstrictors. The patient's deterioration was not due to the ineffectiveness of antibiotics as bactericidal but due to shock. And there are many cases of worsening of critical patients in the ICU not due to infection. Patients in the ICU are challenging to differentiate according to their primary origin, e.g., orthopedic cases, digestive surgery, lung disease, urological disease, and so on. However, empiric antibiotics in primary care (before ICU) will improve outcomes[12].

Table 3.7 Quantitative Evaluation of Antibiotic Use in 2018

NO	DDD CODE	NAME OF ANTIBIOTIC	TOTAL DDD	DDD WHO	DDD/100 PATENT	Patient DDD/ WHO DDD
1	JO1GB06	Amikacin	30.00	1	4.65	Higher
2	J01CA01	Ampicillin	44.25	6	6.86	Higher
3	J01FA10	Azithromycin	15,16	0.5	2.35	Higher
4	J01DD01	Cefotaxime	5.50	4	0.85	Lower
5	J01DD04	Ceftriaxon	168.00	2	26.05	Higher
6	J01DD12	Cefoperazon	8.00	4	1.24	Lower
7	J01DD02	Caftazidim	20.25	4	3.14	Lower
8	J01MA02P	Ciprofloxacin	20.66	0.8	3.20	Higher
9	J01XX01	Fosfomicin	15.00	8	2.33	Lower
10	JO1GB03	Gentamicin	1.60	0.24	0.25	Higher
11	J01DH51	Imipenem	4.50	2	0.70	Lower
12	J01MA12	Levofloxxacin	37,00	0.5	5.74	Higher
13	J01DH02	Meropenem	93.50	3	14.50	Higher
14	J01XD01	Metronidazole	62.66	1.5	9.71	Higher

Table 3.8 Quantitative Evaluation of Antibiotic Use in 2018

NO	DDD CODE	NAME OF ANTIBIOTIC	TOTAL DDD	DDD WHO	DDD/100 PATENT	Patient DDD/ WHO DDD
1	J01DD01	Cefotaxime	3.49	4	0.67	Lower
2	J01DD04	Ceftriaxon	138.50	2	26.53	Higher
3	J01DD12	Cefoperazon	1.50	4	0.29	Lower
4	J01DD02	Caftazidim	31.50	4	6.03	Higher
5	J01MA02P	Ciprofloxacin	4.00	0.8	0.77	Lower
6	JO1GB03	Gentamicin	4.26	0.24	0.82	Higher
7	J01MA12	Levofloxxacin	61.50	0.5	11.78	Higher
8	J01DH02	Meropenem	64	3	12.26	Higher
9	J01XD01	Metronidazole	9	1.5	1.72	Higher

IV. CONCLUSION

The amount of antibiotic use in a hospital can be calculated using the DDD method with DDD/100 patient-day units, which describes the number of patients receiving the definitive daily dose (DDD) for specific indications or in this study for ICU patients.

Antibiotics are drugs that have an essential role in the medical management of critically ill patients in the ICU. Determining the choice of a particular antibiotic for a patient must be considered a lot. Guidelines from the ministry of health for the use of antibiotics (Permenkes No. 2406/MENKES/PER/2011 mentions in table 20. Antimicrobial Stewardship supporting strategies. Strategy: Streamlining or de-escalation therapy, how to implement it: after the results of microbiological examinations and sensitivity tests of empirical antibiotic therapy are available, change to a more sensitive, narrower spectrum; safer; and cheaper.

Empirical antibiotics are often appropriate for initial antibiotic administration or given first to primary care physicians. In contrast, patients in the ICU primarily refer to patients who have received empiric therapy and have not improved. However, the patient's condition worsens not necessarily due to the causative bacteria. The infection is not eradicated.

To increase the effectiveness of empiric bactericidal antibiotics, it can be done by combining with other classes of antibiotics such as macrolides or combining them with other groups. It is necessary to consider an ICU-specific empiric that takes into account the local evidence base. A map of bacteria and sensitive antibiotics should be available in every ICU, used for consideration in determining the choice of specific empiric antibiotics. Subsequent administration of

antibiotics followed the guidelines of the Ministry of Health according to the results of culture and sensitivity tests.

In many critically ill patients, there is a decrease in organ functions, especially the liver and kidneys, which must be considered in administering antibiotics. Patients with low liver function, such as patients with cirrhosis of the liver, which are highly susceptible to infection, should be considered for their low metabolic capacity and susceptibility to overdose13. Some critically ill patients have hypoalbuminemia, so antibiotics with high plasm protein binding can cause overdose and patients with insufficiency or even kidney failure. There is the potential for overdose due to impaired elimination. In critically ill patients, many have decreased blood perfusion to cells throughout the body, including to the muscles or subcutaneous tissue as well as to the digestive tract, so that the route of drug administration through the muscle (intramuscular) or the subcutaneous (e.g., insulin), or through the digestive tract (orally or by enteral/NGT) is inefficient, and must use the intravenous route. Thus the selected antibiotic is the one that is prepared for intravenous administration. Even with the intravenous route of administration, it cannot reach all body compartments, so that in certain places (in organs/places with the low volume of distribution), germs can be "hidden," resulting in antibiotic resistance. Critical patients with "stress ulcers" due to poor blood perfusion to the intestinal mucosa, usually accompanied by the poor intestinal mucosal barrier, and translocation of bacteria from the intestinal lumen (mainly E. coli) into the systemic circulation causing sepsis, which may be these bacteria are not sensitive to the empiric antibiotics received by the patient. Multi-drug resistance (MDR) E. coli bacterial infections that do not receive appropriate and adequate antibiotics have a poor prognosis[12].

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