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RESEARCH REGARDING THE RISKS ASSOCIATED WITH THE EXPOSURE TO FREQUENTLY USED ANTIBIOTICS IN INTENSIVE CARE

SUMMARY

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"If a man does not know which port he wants to reach, no wind will favor him!" Seneca

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INTRODUCTION

Antibiotic resistance is a growing concern in the global medical community. This phenomenon has significant implications regarding the clinical evolution of patients, the efficiency of treatment, and the costs associated with medical care. The clinical relevance of the present work can be applied in intensive care units, where the most vulnerable patients are cared for. This unique patient population may benefit from understanding the dynamics of bacterial antibiotic resistance and the complex mechanisms that influence drug pharmacokinetics in the context of changes in the pathophysiology of critical illness.

The decision to address bacterial resistance to the most used antibiotics in intensive care reflects a combination of scientific, clinical, social, and interdisciplinary factors that significantly impact my professional development.

I chose to study the population of critical patients and the most used antibiotics in Intensive Care because I currently work as a specialist in Anesthesia and Intensive Care at the Sibiu County Emergency Clinical Hospital. In our daily work, we frequently face infections with multi-resistant bacteria and often run out of therapeutic options for these patients.

In the present study, we aim to conduct a descriptive analysis of adverse reactions related to the resistance and ineffectiveness of the antibiotics meropenem, colistin, and linezolid. These antibiotics are often used in intensive care units due to their broad spectrum and effectiveness in treating resistant bacteria. A review of pharmacovigilance reports determined the reporting frequency of adverse reactions related to drug resistance and drug ineffectiveness associated with meropenem, colistin, and linezolid. We then performed a disproportionality analysis, which compared the frequency of reporting adverse reactions related to drug resistance and ineffectiveness related to drug resistance and the performed a disproportionality analysis, which compared the frequency of reporting adverse reactions related to drug resistance and ineffectiveness for meropenem, colistin, and linezolid with the frequency of reporting these adverse reactions associated with other antibiotics or antifungals.

Another aspect that I wanted to study in this thesis is the impact of *Clostridioides difficile* infection. Although this anaerobic, Gram-positive bacterium has been identified for decades, it remains the leading cause of healthcare-associated infectious diarrhea. The development of this bacteria is frequently associated with the administration of antibiotics. The patient population in the Intensive Care Units is very vulnerable to this bacterium because approximately three-quarters of them are treated with antibiotics and also because of the fragility associated with critical illness.

Thus, in the second part of the present paper, we investigated the occurrence of *Clostridioides difficile* infection in patients who were administered antibiotics often used in critical illness. We performed a descriptive analysis of the reports uploaded to EudraVigilance. We compared the probability of reporting *Clostridioides difficile* infection for the evaluated antibiotics to other commonly used antibiotics.

In the last part of this doctoral thesis, I performed a retrospective analysis regarding the nosocomial infection with *Clostridioides difficile* from the data reported in 2022 in the Sibiu County Emergency Clinical Hospital. In this analysis, we considered demographic data, clinical course, type of infection detection, associated diseases, length of hospitalization, and prior exposure to antibiotics. We subsequently performed a descriptive analysis of the infection reported in 2022 in EudraVigilance as an adverse reaction correlated with the studied antibiotics. Finally, we conducted a comparison between both databases to determine the proportion of reports between the two databases.

Through the analyses performed, by determining the demographic trends, the clinical outcomes of the patients, and the frequency of reporting adverse reactions associated with antibiotic resistance and ineffectiveness, this work aimed to elucidate part of the complex interaction between the use of antibiotics and the risk of occurrence of bacterial resistance, the ineffectiveness of antibiotic therapy and the risk of *Clostridioides difficile* infection.





CURRENT STATE OF KNOWLEDGE

Starting from the fact that the administration of antibiotics in the intensive care unit is at the top of the statistics—about 71% of critically ill patients receive antibiotics as part of the therapeutic scheme—I chose to study this type of therapeutic substance (1).

The characteristics of the critically ill patient differ from those of other patients, so changes in the drug's pharmacokinetics are significant when it comes to adjusting the treatment to obtain an adequate and effective therapeutic response (2).

The absorption of orally administered drugs in this type of patient may be influenced by (i). delayed gastric emptying, (ii). intestinal ileus, (iii). administration of opioids, (iv). intestinal hypoperfusion, (v). therapeutic interventions such as nasogastric suction and (vi). changes in intraluminal pH (caused by administering antacids and antisecretory drugs) (3).

At the level of drug distribution, changes occur due to (i). decrease in tissue blood flow, (ii). alteration of capillary permeability, (iii). affecting pH, (iv). hypoproteinemia and (v). hyperhydration resulting from volume resuscitation of the critical patient. Thus, the plasma concentration of the administered drugs becomes unpredictable (4-7).

Drug metabolism in critically ill patients is also affected during critical illness. These changes occur as a result of liver dysfunction, which occurs in approximately 34%—46% of cases with sepsis, a pathology frequently treated in Intensive Care Units (8).

Another component of pharmacokinetics concerns drug elimination through the kidneys. In sepsis, acute renal injury often occurs, affecting the kidneys' normal capacity to eliminate drugs, which can be manifested by a reduction or an increase in excretion (9,10).

The changes mentioned above can contribute to antibiotic treatment failure. This phenomenon is characterized by the persistence of the pathogen despite the administration of appropriate antibiotic therapy, and, in addition to the survival of the infectious agent, it leads to the emergence of the phenomenon of antibiotic resistance (11).

The emergence and spread of antimicrobial resistance seriously affect their effectiveness and increase morbidity and mortality worldwide. Multidrug-resistant pathogens are found in hospitals and the community, posing a substantial challenge to clinicians and public health professionals (12,13).





PERSONAL CONTRIBUTIONS

STUDY 1 - ANALYSIS OF SPONTANEOUS REPORTS FROM THE EUROPEAN PHARMACOVIGILANCE DATABASE OF ADVERSE DRUG REACTIONS ASSOCIATED WITH MEROPENEM, LINEZOLID AND COLISTIN, WHICH ARE RELEVANT TO DRUG RESISTANCE AND EFFECTIVENESS.

Antimicrobial resistance is considered one of the significant threats to public health and is an essential factor influencing the clinical course of the patient admitted to the intensive care unit.

Pharmacovigilance can help raise awareness of potential drug resistance (R) or ineffectiveness (I) by reporting adverse drug reactions that are submitted to various spontaneous reporting systems.

The primary objective of the study was to determine the frequency of reporting drug resistance-related adverse reactions and their ineffectiveness associated with meropenem, colistin, and linezolid.

After the descriptive analysis, a disproportionality analysis was also performed. This analysis compared the reporting frequency of adverse reactions associated with drug resistance and ineffectiveness for meropenem, colistin, and linezolid with the reporting frequency of these adverse reactions associated with other antibiotics or antifungals. The research used this comparative method to identify notable differences in reporting adverse reactions. This would provide valuable information on the safety profiles of these antibiotics in terms of drug resistance and ineffectiveness.

These analyses were based on reports uploaded to the European pharmacovigilance database (EudraVigilance) regarding antibiotic resistance and ineffectiveness.

By 31 December 2022, 13,381 LIN-related individual safety reports had been uploaded to the European database (EV). MER was mentioned in 8,864 reports, and COL in only 986 reports.

Of the total adverse drug reactions reported for each antibiotic analyzed by 31 December 2022, 2.38–8.42% were linked to resistance, and 4.15–10.14% were related to ineffectiveness. The distribution of individual reports was also analyzed according to the age of the patient, the gender of the patient, the origin of the person who made the report, and according to the category of the reporters.

We subsequently performed a disproportionality analysis to assess the frequency of reporting adverse drug reactions relevant to the R and I of the analyzed antibiotics compared to other antimicrobials. The research used this comparative method to identify notable differences in reporting adverse reactions.

It is important to note that the statistics available in the EudraVigilance database only provide information on reported adverse reactions. The data presented in this database may be influenced by over-reporting, under-reporting, and reporting bias.

Based on the analysis of the collected data, this study highlights the importance of post-marketing drug safety monitoring in raising a warning signal of antimicrobial resistance, thereby potentially contributing to the reduction of antibiotic treatment failure in an intensive care setting.

Of the total adverse reactions reported for each antibiotic analyzed through December 31, 2022, between 2.38 and 8.42% of reports were related to drug resistance (2.38%—LIN, 3.56%—MER, and 8.42%—COL) and between 4.15% and 10.14% were related to drug ineffectiveness (4.15% - LIN, 9.45% - MER and 10.14% - COL, respectively). In addition, between 6 and 24% and 19 and 35% of reported adverse reactions relevant to resistance and ineffectiveness had a fatal outcome. The present study aims to raise awareness of the growing phenomenon of antibiotic resistance.

STUDY 2 - PHARMACOVIGILANCE STUDY ON THE RISK OF *CLOSTRIDIOIDES DIFFICILE* INFECTION ASSOCIATED WITH THE USE OF ANTIBIOTICS

Clostridioides difficile (CD), an anaerobic, Gram-positive bacterium, contributes to healthcare-associated infections and is the most common cause of infectious diarrhea.

Based on spontaneous reports from EudraVigilance (EV), we performed a descriptive analysis of cases of *Clostridioides difficile* (ICD) infection reported as a spontaneous adverse reaction related to the use of ceftriaxone, colistin, ciprofloxacin, gentamicin, linezolid, meropenem, and piperacillin/tazobactam. Following the descriptive analysis, we assessed the likelihood of reporting ICDs for the evaluated antibiotics compared to other antibiotics. The individual case safety reports included in the study did not contain personal patient information, so ethics committee approval was not required for the present study.

Most reports of adverse reactions in EVs that were related to ICDs were associated with ceftriaxone (33%), ciprofloxacin (28%), and piperacillin/tazobactam (21%).

Also, based on these reports, an analysis of the clinical evolution of the cases was performed for each antibiotic, and a forecast of the number of individual safety reports correlated with the ICD for 2023-2025.

In addition, a disproportionality analysis was performed, which showed that all the antibiotics studied had a lower probability of reporting than clindamycin. A causal relationship between a drug and the occurrence of an adverse reaction cannot be established from EV data alone, as the phenomena of under-reporting, over-reporting, and reporting bias can affect the results.

Based on the analysis of the collected data, this study emphasizes the importance of surveillance and monitoring programs for antibiotic use. In addition, standardized laboratory tests are essential to define the nature of ICD accurately. To prevent this infection, specialists should collaborate and strictly adhere to antibiotic administration schedules, hygiene practices, and isolation protocols.

STUDY 3. ANALYSIS OF CLINICAL CHARACTERISTICS, CLINICAL EVOLUTION OF PATIENTS, AND THE RELATIONSHIP BETWEEN EXPOSURE TO ANTIBIOTICS IN CLOSTRIDIOIDES DIFFICILE INFECTION

Clostridioides difficile is a Gram-positive bacterium that causes nosocomial infections, significantly impacting public health.

In the present study, we aimed to describe the clinical characteristics, clinical course, and relationship between antibiotic exposure and the occurrence of *Clostridioides difficile* (ICD) infection based on reports from two different databases.

Thus, we conducted a retrospective study with the data of patients diagnosed with nosocomial ICD admitted to the Sibiu County Clinical Emergency Hospital (SCCEH) in Romania, followed by a descriptive analysis based on the spontaneous reports submitted to the EudraVigilance (EV) database. The approval of the ethics committee of the institution was obtained before the initiation of this study (no. 26995/13.11.2023)

Between January 1 and December 31, 2022, we included 111 patients hospitalized in SCCEH, with a nosocomial ICD diagnosis. In parallel, 249 EV reports were analyzed.

According to data collected from SCCEH, ICD was most commonly reported in patients aged 65–85 (66.7%) and women (55%). In total, 71.2% of all patients showed positive clinical evolution. Most cases were reported in the departments of internal medicine (n = 30, 27%), general surgery (n = 26, 23.4%), and infectious diseases (n = 22, 19.8%). Patients were most frequently exposed to ceftriaxone (CFT) and meropenem (MER).

Subsequently, following the descriptive analysis of spontaneous reports recorded in the EV database (n = 249) between January 1 and December 31, 2022, it was observed that the majority of adverse reactions reported in EV related to the occurrence of ICDs were reported for CFT, PIP/TAZ (piperacillin/tazobactam), MER and CPX (ciprofloxacin).

Understanding the association between prior antibiotic exposure and ICD risk may help update antibiotic administration protocols and reduce the incidence of ICD by decreasing exposure to high-risk antibiotics. This study is notable for using a unique approach, comparing results from two data sets collected from a clinical setting and the European reporting system. This methodology helps us better understand antibiotic use's clinical characteristics and effects on ICD occurrence, providing a more accurate representation of real-world outcomes. The present study provides valuable insights to the scientific community, emphasizing the need for responsible antibiotic use and effective infection prevention and control.

GENERAL CONCLUSIONS

The results of this work are essential for enriching the knowledge about the risks of antibiotics used in the Intensive Care Unit. They can contribute to increasing the safety of patients through the reporting mechanisms of adverse reactions.

A retrospective analysis of adverse reactions reported for meropenem, colistin, and linezolid based on spontaneous reports in EudraVigilance up to 31 December 2022 suggested the following:

- between 2.38 and 8.42% of reports were related to drug resistance (2.38%—LIN, 3.56%—MER, and 8.42%—COL, respectively);
- between 4.15% and 10.14% were related to drug inefficiency (4.15% LIN, 9.45% MER, and 10.14% COL, respectively);
- between 6 and 24% and between 19 and 35% of reported adverse reactions relevant to resistance and ineffectiveness, respectively, had a fatal outcome;

The data analyzed showed that males reported adverse reactions to the three antibiotics more frequently than females.

Notably, a significant proportion of resistance-relevant reports have been recorded for colistin. The World Health Organization includes it in the Reserve group, which confirms this.

All three antibiotics were more likely to report drug resistance-relevant adverse reactions than MOX, PIP/TAZ, VAN, AMF, and ISA.

Analyzing adverse reactions associated with Clostridioides difficille infection reported in EudraVigilance, ceftriaxone (33%), ciprofloxacin (28%), piperacillin/tazobactam (21%) and meropenem (11%) were found to have a high incidence of adverse reactions associated with Clostridioides difficille infection. These antibiotics were responsible for an average of 40.5, 32.0, 25.3, and 13.6 yearly reports. In addition, an increase in ICDs related to some of the most commonly used antibiotics in intensive care has been predicted. A disproportionality analysis showed that all the antibiotics studied had a lower probability of reporting than clindamycin. Although a higher incidence of ICDs was reported for CFT, accounting for 2.38% of all adverse reactions, severe adverse reactions were still found to have a lower frequency than other antibiotics.

The latter part of the present work uses a unique approach, comparing results from two data sets collected from a clinical setting and the European reporting system.

A significant proportion (77.5%) of all patients admitted to SCCEH and diagnosed with ICD in 2022 were represented by the population over 65 years of age,

and 55% of those affected by ICD were women. Regarding ICD-related adverse reactions recorded in EV, no significant differences were observed between women (50.4%) and men (49.6%).

The results of the present study showed that, on average, ICD is detected 9.2 days after admission to SCCEH. Furthermore, after the detection of ICD, the average length of hospital stay after diagnosis is 11.03 days.

Reports from EV showed that COL, PIP/TAZ, MER, CFT, and CPX were associated with prolonged hospitalization in a high proportion (100%, 92.3%, 91.7%, 80%, and 83, respectively, 3%).

A pattern was observed when the comorbidity index, age categories, and clinical course of patients diagnosed with ICD were correlated. Thus, elderly patients with a higher comorbidity score have a higher risk of developing unfavorably from a clinical point of view.

Also, some significant differences were identified, especially when comparing different age groups within favorable and unfavorable clinical evolution categories. These differences underscore the importance of considering demographic and comorbidity factors in ICD. In addition, for all analyzed antibiotics except CFT, exposure to other antibiotics was increased in SCCEH reports compared to EV.

This methodology helps us better understand clinical characteristics and the effects of antibiotic use on the emergence of antibiotic resistance, antibiotic ineffectiveness, and risk of *Clostridioides difficile* infection, providing a more accurate representation of real-world outcomes.

This paper provides valuable insights to the medical community, emphasizing the need for responsible antibiotic use, effective infection prevention and control, assessment of antimicrobial resistance, and implementation of public health programs to monitor antibiotic use and adverse reactions.

ORIGINALITY AND INNOVATIVE CONTRIBUTIONS OF THE RESEARCH

The topic addressed in the present work is integrated into the current context of health systems worldwide regarding the strict supervision of the administration of antibiotics. The present study provides valuable insights to the scientific and medical community, emphasizing the need for responsible antibiotic use, prevention, and effective infection control, providing complex information on the safety profiles of these antibiotics in terms of antibiotic resistance, ineffectiveness, and risk of Clostridioides infections.

The originality of the thesis consisted in the analysis of some real situations reported in the European database of registration of adverse reactions, Eudravigilance, as well as at the level of a sanitary unit with beds in Romania, regarding specific adverse effects associated with exposure to antibiotics, frequently used in Intensive Care. Following the descriptive analysis, the evaluation of the probability of reporting some of the observed adverse reactions consisted of the disproportionality analysis of their signals registered in Eudravigilance. The prediction of reports in EudraVigilance during the period 2023-2025 of the evolution of infections with Clostridiodes difficile associated with exposure to certain antibiotics was another element of originality of the study.

Also, a particularity of this study is represented by the unique approach of comparing the results regarding the risk of Clostridioides difficile infections associated with antibiotic exposure from the two data sets collected from a clinical setting and a system of spontaneous reporting of adverse reactions.

This study reminds and encourages the need to implement personalized drug dosing strategies and knowledge of patient characteristics, which can only be achieved through a holistic approach by a multidisciplinary team consisting of intensive care physicians, infectious disease physicians, clinical pharmacologists, pharmacists, and laboratory staff.

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