DEVELOPMENT AND IMPLEMENTATION OF AN ANTIMICROBIAL STEWARDSHIP PROGRAM THROUGH THE CONTROL OF ANTIMICROBIAL RESISTANCE AND THE RATIONAL USE OF ANTIBIOTICS

Jelena Micik
Acibadem Sistina, R.N. Macedonia, jelena.micikj@acibademsistina.mk
Evgenija Mihajloska
Faculty of Pharmacy, University "Ss. Cyril and Methodius", Skopje, R.N. Macedonia, emihajloska@ff.ukim.edu.mk
Aleksandar Dimkovski
Faculty of Pharmacy, University "Ss. Cyril and Methodius", Skopje, R.N. Macedonia, aleksandar.d@ff.ukim.edu.mk
Ljubica Shuturkova
Faculty of Pharmacy, University "Ss. Cyril and Methodius", Skopje, R.N. Macedonia ljsuturkova@ff.ukim.edu.mk
Aleksandra Grozdanova
Faculty of Pharmacy, University "Ss. Cyril and Methodius", Skopje, R.N. Macedonia, agrozdanova@ff.ukim.edu.mk

Abstract: Antimicrobial resistance is a serious threat to public health and patient safety globally, leading to increased medical costs, patient treatment failure, and increased mortality rates from infections. The objective is to slow down the development of resistance and maintain a balance between effective therapy and the inappropriate use of antibiotics, which contributes to resistance. An antimicrobial stewardship program is a coordinated effort to ensure that the use of antimicrobial drugs, such as antibiotics, is optimal in terms of effectiveness and safety, while minimizing the development of resistance. This evidence-based approach addresses the correct selection of antimicrobial agents, dosages, routes of administration, and duration of therapy. The antimicrobial stewardship program involves implementing strategies and guidelines for prescribing and using antimicrobials appropriately, monitoring their usage, and educating healthcare professionals and patients about their proper use. The goal is to promote responsible use of antimicrobials and prevent the emergence of antimicrobial-resistant infections. The significance of implementing an antimicrobial stewardship program in hospitals has been further highlighted by the COVID-19 pandemic.
For this purpose, a prospective study was conducted with the aim of analyzing the clinical results of the implemented program for antimicrobial management, by monitoring the trend of total antibiotic consumption, as well as monitoring the total number of approved justified/unjustified antibiotics from the intended control group: Meropenem, Imipenem/Cilastatin, Piperacillin/tazobactam, Colomycin, Moxifloxacin, Linezolid and Ertapenem, during the designated period before implementation (2021) and respectively after implementation (2022) of the program for antimicrobial management, in hospitalized patients at the Acibadem Sistina Clinical Hospital. After the implementation of the antimicrobial stewardship program, a decrease in the total consumption of the controlled group of antibiotics was observed, with the exception of linezolid. Moreover, there was a decline in the trend of unjustified approved antibiotics at the expense of an increase in justified approved antibiotics from the controlled group. To prevent antimicrobial resistance, a comprehensive early microbiological screening of patients was conducted, and a specific antibiotic regimen was chosen to reduce inappropriate empirical treatment. This monitoring enabled the tracking of the total number of pathogenic agents or isolates.
Continual monitoring of the AMS program's effectiveness and making necessary adjustments is essential to optimize its impact.
Keywords: antimicrobial resistance, antimicrobial stewardship, antibiotics, Acibadem Sistina Clinical Hospital.

1. INTRODUCTION

Antimicrobial resistance is a major threat to global public health. It is caused by the overuse and misuse of antibiotics, leading to the emergence and spread of drug-resistant pathogens. This results in the increasing ineffectiveness of antibiotics, making it more difficult to treat common infections and leading to more severe infections, complications, prolonged hospital stays, and mortality (Ventola, 2015).
The World Health Organization's recent report emphasized the prevalence of resistance in bacteria responsible for serious bloodstream infections and the growing resistance to treatment in several bacteria that cause commonly

occurring infections in the community. This report highlights the need for developing effective measures to prevent and treat drug-resistant infections, as well as for enhancing access to high-quality antimicrobial drugs, both existing and new (World Health Organization [WHO], 2023).

Antimicrobial stewardship (AMS) is a structured initiative that encourages the judicious utilization of antimicrobial agents, including antibiotics, to enhance patient outcomes, diminish microbial resistance, and contain the spread of infections caused by multi-resistant organisms (Roula, 2015; Benito, 2013). AMS program is effective in enabling healthcare providers to improve clinical outcomes and minimize negative effects by promoting better antibiotic prescription practices. AMS programs in hospitals have the potential to improve cure rates, decrease treatment failures, lower adverse effects, minimize antibiotic resistance, and reduce both hospital costs and stays (WHO, 2023). The WHO's AWaRe Classification Database, released in 2019, categorizes antibiotics according to their resistance potential into Access, Watch, or Reserve groups. This database serves as an interactive resource to enhance the monitoring and appropriate utilization of antibiotics (Center for Disease Control and Prevention [CDC], 2014). Antibiotics that fall under the Watch category, which are more susceptible to resistance, are of particular importance and should be prioritized as significant targets for stewardship programs and monitoring (WHO, 2021).

Antibiotic-resistant infections present one of the most significant obstacles for hospitals in delivering secure and efficacious healthcare. A critical measure in tackling and averting antimicrobial resistance in hospitals involves the adoption of AMS programs. These programs in hospitals comprise a set of initiatives designed to create, implement, and monitor interventions that promote the appropriate utilization of antimicrobial agents to enhance patient outcomes, avoid adverse effects, and limit the emergence of antibiotic resistance (CDC, 2021).

The Acibadem Sistina Clinical Hospital's Medicines Management Committee established a database to monitor the increased utilization of antibiotics. Upon examining past data from this database, it was discovered that antibiotics had been used irrationally from 2020 to 2021. The Medicines Management Committee at Acibadem Sistina Clinical Hospital developed an AMS program to address the problem of irrational antibiotic use and misuse. The strategy involves several critical activities, including the formation of an antimicrobial stewardship committee, the introduction of a policy for the use of antimicrobial stewardship programs, the active involvement of a multidisciplinary team in assessing antimicrobial treatment, the promotion of delayed strategies for prescribing antimicrobial therapy, the reduction of therapy duration where possible, personalized treatment based on pharmacokinetic and pharmacodynamic patient characteristics, and the implementation of pragmatic studies and internal processing of available databases for a precise approach to patient complications and clinical outcomes. This study provides an evaluation of the outcomes resulting from the strategy and activities undertaken as part of the AMS program.

2. MATERIALS AND METHODS

Study design

We conducted a prospective study to analyze the outcomes of the AMS program by comparing antimicrobial utilization of controlled group of antibiotics (meropenem, Imipenem/cilastatin, piperacillin/tazobactam colomycin, moxifloxacin, linezolid and ertapenem) for designated periods before (2021) and after (2022) implementation of AMS program in adult hospitalized patients at Acibadem Sistina Clinical Hospital.

Antimicrobial stewardship program

In December 2021, we established a strategy for implementing the AMS program as part of the global action plan for "optimizing the use of antimicrobial agents". The main focus in this program is optimized use of antibiotics which leads to better clinical patient outcomes, decreased antimicrobial resistance, a lower rate of nosocomial infections, and reduced health care costs.

Initially, we established a plan for intervention guided by the practical guide for Antimicrobial stewardship interventions provided by the World Health Organization (WHO, 2021). We also outlined the desired outcomes to assess the effectiveness of the intervention. We identified a AMS-Committee multidisciplinary team, including clinical infectologist, clinical microbiologist, hospital pharmacist and infection prevention and control nurses. The AMS-Committee implemented the following major interventions: education and training medical staff at the Acibadem Sistina Clinical Hospital in the prescription of antibiotic prophylaxis, empiric and definitive antibiotic therapy in accordance with the relevant protocols, creation of a standardized medical record with a form for daily monitoring of antibiotic therapy, and revision of the initial microbiological screening.

During the daily audits for monitoring of antibiotic therapy, all hospitalized patients on antibiotic treatment were evaluated. The medical record used to track antibiotic therapy contains the following information: review of patients who are receiving antibiotic therapy for proper indication, review of patients who have been prescribed three or more broad spectrum antibiotics, overview of basic microbiological and laboratory parameters, review of the prescribed antibiotic dose according to the laboratory parameters. Compliance with the relevant protocols was assessed during the audits. The clinical pharmacists integrate the antimicrobial susceptibility data from all patients every month.

Outcomes

The outcomes of the study focused on two main measures: the difference in antibiotic consumption, measured in defined daily doses (DDDs) per 100 hospital days before and after the implementation of the AMS program, and the evaluation of approved justified and unjustified antibiotic prescriptions after the program's implementation. Prior to the implementation of the program, there were no restrictions or evaluations of antibiotic prescriptions. However, after the program's implementation, the approval of each antibiotic from the specified "controlled" group was carried out in consultation with the AMS Committee. The approved "controlled" antibiotics listed as "JUSTIFIED" corresponded to empirical therapy and confirmed microbiological reports of a positive isolate and certain antibiotic sensitivity. In contrast, the approved controlled antibiotics considered "UNJUSTIFIED" did not correspond with microbiological reports. For unjustified antibiotic prescriptions, empiric antibiotic therapy was continued despite negative microbiological reports, based on the patient's overall clinical condition and laboratory parameters. After stabilization of the patient's clinical condition and the level of inflammatory markers, the expansion of the antibiotic from the control group is followed by early de-escalation and reducing the duration of the antibiotic therapy.

Statistical analysis

We used a two-sample t-test to compare the means of two distinct groups, namely the antibiotic consumption before and after the implementation of an AMS program. The number of approved justified and unjustified antibiotic prescriptions was expressed in percentage and compare within year quartel.

Ethics approval

All methods used in the study were in accordance with the international guidelines, with the standards the Helsinki Declaration of 1975, revised in 1983 and approved by Ethics commission from Clinical Hospital Acibadem Sistina.

3. RESULTS

Antibiotic consumption before and after implementation of AMS program

The initial parameter that was observed involved assessing the number of detected pathogenic agents or isolates by conducting comparison between the years 2021 and 2022. The outcomes are documented in tables 1 and 2. Furthermore, charts 1 and 2 show a comparison between the overall count of isolates and the particular type of isolates during the specified period. The primary objective of conducting a thorough microbiological screening at an early stage is to minimize the unnecessary use of empiric therapy and prevent the emergence of antibiotic resistance by promptly identifying all potential pathogens and determining an appropriate antibiotic treatment plan. The findings suggest that in 2022, there were more confirmed cases of isolates compared to 2021, but at the same time, there was a decrease in the use of antibiotics (indicated by DDD per 100 hospital days). This can be attributed to the avoidance of empiric antibiotic therapies and the avoidance of making assumptions about possible pathogenic agents and incorrect prescription of antibiotic treatment.

Table 1. Total number of isolates (pathogenic agents) of hospital patients for 2021

Isolate (pathogen agent)	Total number of hospital patient isolates by specific type 2021	Percentage of hospital patient isolates by specific type 2021
Staphylococcus aureus	445	15,60%
Escherichia coli	308	10,80%
Klebsiella pneumoniae	334	11,70%
Acinetobacter baumannii	321	11,30%
Enterococcus spp.	280	9,80%
Pseudomonas aeruginosa	222	7,80%
Streptococcus pneumoniae	174	6,10%
Staphylococcus aureus (MRSA)	171	6,00%
Moraxella catarrhalis	139	4,90%
Proteus mirabilis	116	4,10%
Clostridium difficile	100	3,50%
Enterococcus faecium (VRE)	65	2,30%

Streptococcus beta-hemolyticus gr.A	32	1,10%
Haemophilus influenzae	29	1,00%
Stenotrophomonas maltophilia	22	0,80%
Streptococcus agalactiae	20	0,70%
Enterococcus faecium	19	0,70%
Staphylococcus epidermidis	19	0,70%
Enterobacter spp.	9	0,30%
Enterobacter aerogenes	8	0,30%
Enterococcus faecalis	3	0,10%
Serratia marcescens	3	0,10%
Enterococcus faecalis (VRE)	2	0,10%
Streptococcus alfahaemolyticus	1	0
Citrobacter freundii	1	0
Pseudomonas spp.	1	0
Streptococcus beta-haemolyticus gr. C	0	0

Table 2.Total number of isolates (pathogenic agents) of hospital patients for 2022

Isolate (pathogen agent)	Total number of hospital patient isolates by specific type 2022	Percentage of hospital patient isolates by specific type 2022
Staphylococcus aureus	629	17,70%
Escherichia coli	422	11,90%
Klebsiella pneumoniae	471	13,3
Enterococcus spp.	321	9,10%
Acinetobacter baumannii	235	6,60%
Pseudomonas aeruginosa	232	6,50%
Staphylococcus aureus (MRSA)	225	6,30%
Moraxella catarrhalis	209	5,90%
Streptococcus pneumoniae	171	4,80%
Clostridium difficile	140	3,90%
Proteus mirabilis	115	3,20%
Haemophilus influenzae	115	3,20%
Streptococcus beta-hemolyticus gr.A	95	2,70%
Stenotrophomonas maltophilia	46	1,30%
Streptococcus agalactiae	33	0,90%
Staphylococcus epidermidis	15	0,40%
Enterobacter aerogenes	15	0,40%
Enterococcus faecium (VRE)	15	0,40%
Enterococcus faecium	10	0,30%
Enterococcus faecalis	10	0,30%
Streptococcus alfahaemolyticus	10	0,30%
Serratia marcescens	4	0,10%
Klebsiella oxytoca	3	0,10%

Citrobacter freundii	3	0,10%
Streptococcus beta-haemolyticus gr. C	3	0,10%
Pseudomonas spp.	1	0,00%

Chart 1. Comparison of the total number of isolates 2021/2022

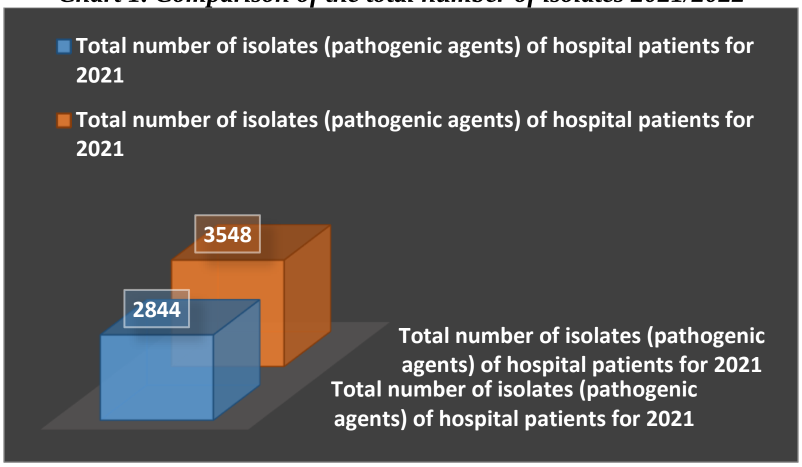
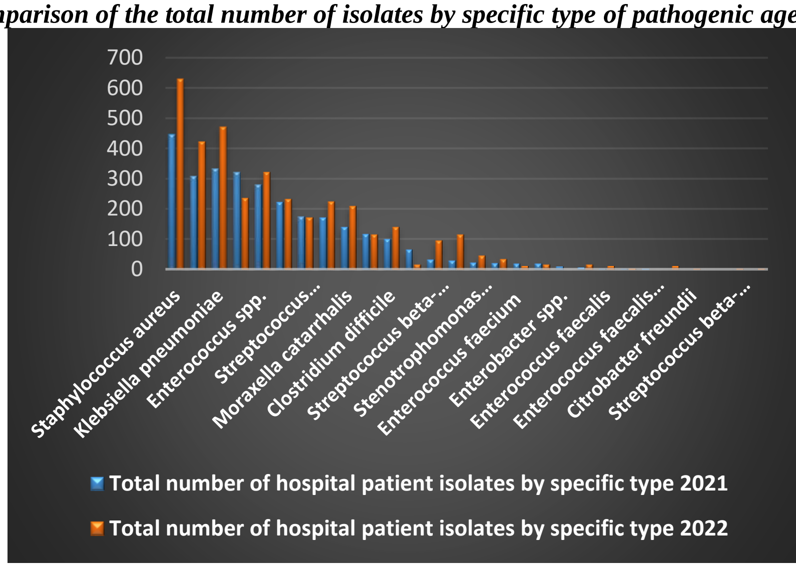


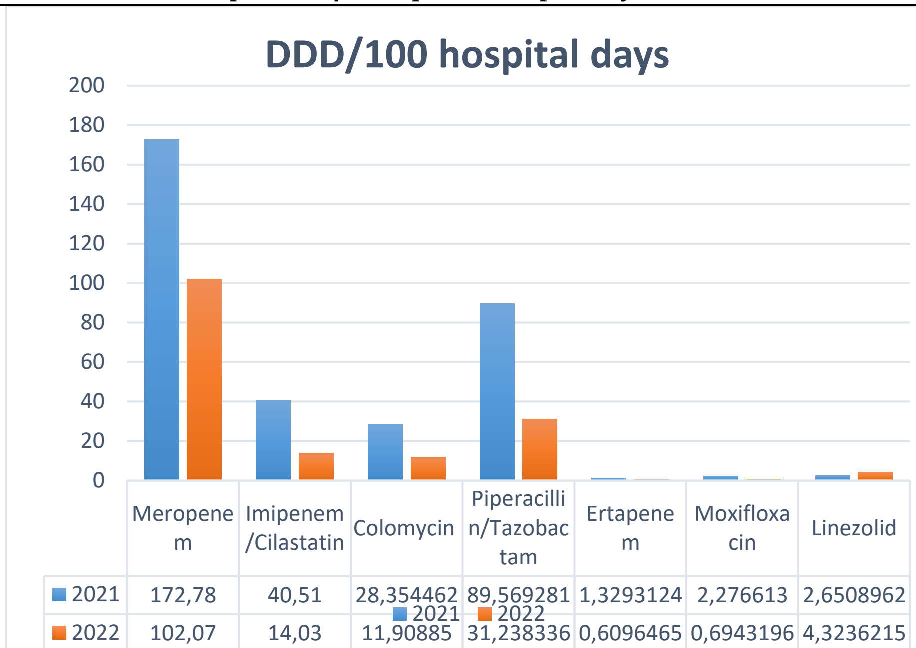
Chart 2. Comparison of the total number of isolates by specific type of pathogenic agents 2021/2022



The defined daily dose is a commonly used measure of antibiotic consumption, which is endorsed by the World Health Organization (WHO) and is frequently utilized in antimicrobial stewardship programs (WHO Collaborating Centre for Drug Statistics Methodology, 2013). In this study, DDDs were calculated per 100 hospital days using WHO guidelines for each antibiotic. Chart 3 represent the difference between DDDs per 100 hospital days in 2021 and 2022. The findings indicate that the controlled group's use of antibiotics has decreased over time (p=0.3709). However, there has been an increase in the use of linezolid, mostly because of more patients with acute renal insufficiency switching from vancomycin to linezolid to avoid vancomycin's potential harmful effects on the kidneys.

Since the p-value is 0.3709, which is not statistically significant, it may be essential to perform further analysis over a more extended period to verify the findings and ascertain the clinical importance of any observed alterations.

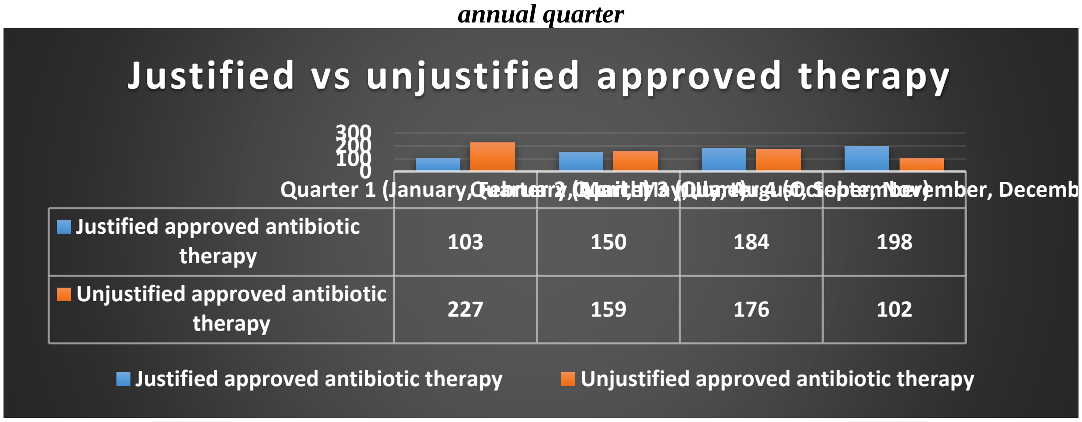
Chart 3. Comparison of DDD per 100 hospital days in 2021 and 2022



Justified and unjustified approved antibiotic prescription

Following the implementation of the AMS program, there was a significant increase in the proportion of justified antibiotic therapies as compared to unjustified therapies for the control group of antibiotics. Chart 4 provides an overview of the justified and unjustified approved antibiotic therapies from the controlled group of antibiotics in each annual quarter.

Chart 4. Justified and unjustified approved antibiotic therapies from the controlled group of antibiotics in each annual quarter



4. DISCUSSION

To our knowledge this is the first AMS program in the Republic of North Macedonia within the tertiary healthcare framework.

Our results are similar to other studies that have reported reduction in the total consumption of controlled group antibiotics after implementation of AMS program (Roberto, 2015). Based on the revised protocols and conclusions drawn, there was a confirmed improvement in the prescription of antibiotic therapy, with an increased trend of justified versus unjustified therapies, leading to a reduced trend of total consumption of antibiotics in 2022 compared to 2021. Based on the data presented, we can deduce that performing a thorough and timely microbiological screening allows us to identify the pathogens at the outset, prior to using empiric antibiotic treatment. This approach is often misguided in cases where the pathogenic agent and its sensitivity have not been confirmed. Specifically, a comprehensive microbiological screening at the outset, which includes all potential sources of infection and existing infections, enables us to accurately determine the appropriate antibiotic treatment regimen. This approach ensures that we administer the correct duration of treatment, eliminate the unnecessary use of empiric therapy and its associated costs, and repeat the relevant parameters during the definitive antibiotic therapy. This approach typically differs from empiric therapy, which is only used before the pathogenic agent and antibiotic sensitivity have been determined.

It is important to highlight the impact of COVID-19 on hospitalization rates in 2021, particularly at the infectious disease unit of the "Acibadem Sistina" Clinical Hospital where there has been an increase in the number of days patients spend there. Throughout 2021 and 2022, hospital-acquired infections have been identified, with a particular emphasis on 2022 due to a higher number of clinically confirmed cases. This confirms that COVID-19 is not the sole factor leading to a surge in the consumption of specific antibiotics. An additional reason for implementing an antimicrobial management program was the need to prevent the early escalation of antibiotic therapy without taking into account the clinical condition and evidence of a pathogenic agent, particularly in light of the COVID-19 pandemic. This would ensure a more rational and effective prescription of antibiotic therapy.

This study confirms how the implementation of an AMS program in a tertiary hospital carried out by a team of professionals was associated with a reduction in consumption of antimicrobials and decreased unjustified approved antibiotic therapy. However, there is still a persistent problem with a large number of unjustified therapies. Therefore, a decision was made to continue the AMS program in 2023 and on a long-term basis until the goal of complete reduction of unjustified therapies is achieved, along with the trend of reduced total consumption of antibiotics and the elimination of abuse in the daily prescription of antibiotics.

Encouraging constant communication between healthcare professionals has proven to be effective in reducing the inappropriate use of antibiotics. This is expected to result in a reduction of various indirect expenses, such as those associated with antibiotic side effects and resistance, earlier transition to oral therapy, discontinuation of unnecessary antimicrobial agents, increased length of hospital stay and readmission, and hospital-acquired infections. These factors should be considered to support the implementation of AMS programs.

5. CONCLUSION

Although decreasing antibiotic consumption and promoting judicious use are beneficial outcomes, it is crucial to evaluate the long-term effects of the AMS program on patient outcomes. Establishing an AMS policy at the hospital level and organizing seminars to promote AMS activities can contribute to the ongoing improvement of antibiotic prescribing practices, ultimately resulting in better patient outcomes. It is vital to maintain oversight of the effectiveness of the AMS program and make any required adjustments to maximize its impact.

REFERENCES

Benito, B.A., José, G.M., Jerónimo, J.P., Álvaro, A.P., & Jesús, R.B. (2013). Scientific evidence and research in antimicrobial stewardship. *Enfermedades Infecciosas y Microbiología Clínica*, 31(Suppl 4), 56-61. doi:10.1016/S0213-005X(13)70134-4

Centers for Disease Control and Prevention, CDC. (2021). Core Elements of Hospital Antibiotic Stewardship Programs. Retrieved from https://www.cdc.gov/antibiotic-use/core-elements/hospital.html

Centers for Disease Control and Prevention, CDC. (2019). The Core Elements of Hospital Antibiotic Stewardship Programs. Retrieved from https://www.cdc.gov/antibiotic-use/healthcare/pdfs/hospital-core-elements-H.pdf

Roberto, R.C., Juan, E.L., Elena, A.A., Piedad, P.T., Leonor, L.M., & Montserrat, M.P. (2015). Measurement of antimicrobial consumption using DDD per 100 bed-days versus DDD per 100 discharges after the implementation of an antimicrobial stewardship program. *Rev Esp Quimioter*. 317-21. PMID: 26621177

Roula, R.B., Marquetta, M.F., Eddie, E.G., & Danny, D.Z. (2015). The importance of an Antimicrobial stewardship program *Fed Pract*.32(9): 20–24. PMID: 30766084

Ventola, C.L. (2015). The antibiotic resistance crisis: part 1: causes and threats. *P T*. 40(4):277-83. PMID: 25859123

World Health Organization, WHO (2021). Antimicrobial resistance. https://www.who.int/newsroom/fact-sheets/detail/antimicrobial-resistance

World Health Organization, WHO (2021). Antimicrobial stewardship interventions: a practical guide. Retrieved from https://apps.who.int/iris/handle/10665/340709

World Health Organization, WHO (2021). AWaRe classification. Retrieved from https://www.who.int/publications/i/item/2021-aware-classification.

World Health Organization, WHO. DDD Indicators. Retrieved from https://www.who.int/tools/atc-ddd-toolkit/indicators

World Health Organization Collaborating Centre for Drug Statistics Methodology (2023). Guidelines for ATC classification and DDD assignment. https://www.whocc.no/filearchive/publications/2023_guidelines_web.pdf