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MEDICAL SCIENCES

EVALUATION OF COSTS RELATED TO ANTIMICROBIAL RESISTANCE OF PRIORITY GRAM-NEGATIVE BACILLI

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Introduction. *Antimicrobial Resistance (AMR) is one of the most serious threats to global public health, causing over 700 thousand deaths annually. In addition to the social burden, AMR generates high medical costs, and estimating these at the hospital level has been the subject of research in many international studies.*

Material and methods*. A comprehensive study was conducted, encompassing 172 cases of invasive infections recorded in patients hospitalized at the "Timofei Mosneaga" Republican Clinical Hospital, from which strains of antimicrobial-resistant E. coli, K. pneumoniae, A. baumannii, and P. aeruginosa were isolated in the years 2019-2021. Based on data regarding the duration of hospitalization, treatment costs, and expenses for investigations, indicators such as average cost, the median, minimum and maximum values of treatment, including the cost of antibiotics and laboratory analyses, were calculated.*

Results. *The economic impact indicators of AMR at the hospital level include: the duration of hospitalization, the total costs of a treated case, the costs of antibiotics, and the costs of laboratory analyses. In the structure of microorganisms isolated from the patients included in the study, K. pneumoniae predominates, accounting for 44.2%, and the total treatment cost for this organism was the highest at 202731.5 dollars. The maximum duration of hospitalization was recorded in patients from whom A. baumannii was isolated (27.7 days).*

Conclusions. *The resistance of strains isolated from patients has directly contributed to the extension of the hospitalization period. The resistance of A. baumannii and K. pneumoniae species has predominantly led to the increase in the economic burden of AMR.*

Cuvinte-cheie: *impact economic, rezistență la antimicrobiene, bacili Gram-negativi, infecții invazive, povara RAM.*

EVALUAREA COSTURILOR AFERENTE REZISTENȚEI LA ANTIMICROBIENE A BACILILOR GRAM-NEGATIVI PRIORITARI

Introducere. *Rezistența la antimicrobiene (RAM) reprezintă una dintre cele mai grave amenințări la adresa sănătății publice la nivel global, determinând anual peste 700 mii de decese. Pe lângă povara socială, RAM generează costuri medicale înalte, iar estimarea acestora la nivel de spital a constituit obiectul de cercetare a multor studii internaționale.*

Material și metode. *A fost realizat un studiu integral, care cuprinde 172 cazuri de infecții invazive, înregistrate la pacienții internați în Spitalul Clinic Republican „Timofei Moșneaga", de la care au fost izolate tulpini de E. coli, K. pneumoniae, A. baumannii și P. aeruginosa rezistente antimicrobiene, în anii 2019-2021. În baza datelor privind durata spitalizării, costurile tratamentului și cheltuielile pentru investigații, au fost calculați indicatorii: costul mediu, mediana, valorile minime și maxime ale tratamentului, inclusiv costul antibioticelor și al analizelor de laborator.*

Rezultate. *Indicatorii impactului economic al RAM la nivel de spital sunt: durata spitalizării, costurile totale ale unui caz tratat, ale antibioticelor și ale analizelor de laborator. În structura microorganismelor izolate de la pacienții incluși în studiu, predomină K. pneumoniae, cu o pondere de 44,2%, pentru care și costul total al tratamentului a fost maxim – 202731.5 dolari. Durata de spitalizare maximă s-a înregistrat la pacienții de la care s-a izolat A. baumannii (27,7 zile).*

Concluzii. *Rezistența tulpinilor izolate de la pacienți a contribuit în mod direct la extinderea duratei de spitalizare. Rezistența speciilor A. baumannii și K. pneumoniae au determinat în cea mai mare măsură creșterea poverii economice a RAM.*

INTRODUCTION

The burden caused by microorganisms resistant to antimicrobial agents is a very heavy one for all of humanity, and especially a daily challenge for doctors in intensive care units. In these units, multidrug-resistant Gram-negative bacteria are responsible for 45-70% of cases of ventilator-associated pneumonia, 20-30% of cases of bloodstream infections, and urinary tract infections associated with catheters (1).

Currently, there is a significant increase in the number of infectious diseases worldwide. The species *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Escherichia coli* are the most common pathogens involved in the etiology of infectious diseases. In 2017, they were included in the global surveillance list developed by the World Health Organization (WHO) (2).

Significant depleted stocks of antimicrobial agents, the rise of complex cases of infections with resistant microorganisms both in hospital and community settings have conditioned the urgent need for the development of new, effective antimicrobial agents against resistant microorganisms (2).

Antibiotic resistance in Gram-negative bacilli involved in major infectious pathology significantly increases healthcare costs, the severity of infections, as well as death rates. According to studies, annually there are over 700 thousand deaths due to bacterial resistance, with the potential for a rapid increase in this figure to 10 million deaths in the next 30 years, accompanied by a cumulative cost of 100 trillion dollars, in the absence of effective measures for prevention and combating this phenomenon (3, 4).

The World Bank has estimated that without preventive and control measures, the global economic damages caused by infections from antimicrobial-resistant microorganisms could lead to a financial crisis equivalent to that of 2008-2009 by the year 2050. Additionally, by 2050, this phenomenon could annually decrease the global gross domestic product (GDP) by 1.1%, with its deficit exceeding 1 trillion dollars annually, starting as early as 2030 (5).

According to a study conducted by Nelson et al. (2017) in a hospital in the USA, the annual cost for treating patients with healthcare-associated infections (HAI) caused by *A. baumannii* was $39,787.0, including $74,306.0 for HAI treatment and $62,396.0 for community-acquired infections caused by the same species (6).

Thus, combating AMR is globally recognized as one of the priorities in public health due to its social impact and the economic harm it inflicts on the healthcare system. Measures for preventing and controlling this phenomenon should be based on the results of monitoring resistance to antimicrobial agents (1, 2).

Monitoring the consumption of antimicrobials among the population, both in the community and in hospital institutions, is a first step in the fight against the spread of antimicrobial resistance (AMR). These data will contribute to forming an overall picture of the prescription, dispensing, and use of antimicrobial agents (2).

According to research in the Republic of Moldova, Gram-negative bacilli isolated from patients with invasive infections also exhibit elevated resistance rates. It has been estimated that the highest resistance rates for strains of E. coli and K. pneumoniae were recorded for the penicillin group (73.9% and 91.8%, respectively), followed by the third-generation cephalosporin group with 56.5% and 94.1%, respectively, of resistant strains. For *P. aeruginosa* strains, there is alarming resistance to aminoglycosides (81.8%), as well as to last-resort drugs – carbapenems (72.7%). Strains of A. baumannii show resistance of over 90% of the isolated strains practically to all groups of antimicrobial agents (1, 5).

An important method for assessing the economic impact of AMR is evaluating the treatment costs at the hospital unit level, which has its own financial resources. These resources are directed towards the most rational use of the available budget, aiming to achieve efficiency both in terms of treatment and economically (6).

Numerous international studies highlight the main indicators for measuring the economic impact of treating patients with infections caused by resistant microorganisms within the hospital setting. These studies include a detailed analysis of the economic burden caused by AMR, reflected in the medical costs or the duration of hospitalization for patients (6, 7).

The study was conducted to assess the costs associated with the treatment of patients with infections caused by Gram-negative bacilli resistant to antimicrobials, who were hospitalized at the Republican Clinical Hospital during the years 2019-2021.

MATERIAL AND METHODS

According to the Regulation on the National System for Epidemiological Surveillance of Antimicrobial Resistance (SSERAM) approved by Order of the Ministry of Health, Labour and Social Protection (MSMPS) 711/2018, within the National System for Epidemiological Surveillance of Antimicrobial Resistance (SSERAM), strains of clinically significant Gram-negative bacilli, including *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Acinetobacter* spp., are reported in blood and cerebrospinal fluid (CSF).

A comprehensive study was conducted, encompassing all cases of invasive infections caused by strains of *E. coli, K. pneumoniae, P. aeruginosa*, and *A. baumannii* with resistance mechanisms, recorded during the period 2019-2021. Thus, 172 cases of invasive infections were studied during that period.

For the execution of this study, the records accompanying the strains of Gram-negative bacilli isolated in the Microbiological Laboratory of the *Timofei Mosneaga* Republican Clinical Hospital, which has been part of the National AMR Surveillance Network since 2018, were examined and sent to the national reference laboratory for AMR to confirm the resistance mechanisms. Additionally, the medical records of the hospitalized patients from whom these strains were isolated during the period 2019-2021 were also examined.

Excluded from the study were:

- patients with invasive infections from whom strains of *Escherichia coli* have been isolated from blood and/or CSF, resistant to one or more drugs from the beta-lactam group;
- patients with invasive infections from whom strains of *Klebsiella pneumoniae* have been isolated from blood and/or CSF, resistant to one or more drugs from the beta-lactam group;
- patients with invasive infections from whom strains of *Acinetobacter baumannii* have been isolated from blood and/or CSF, resistant to one or more drugs from the beta-lactam group;
- patients with invasive infections from whom strains of *Pseudomonas aeruginosa* have been isolated from blood and/or CSF, resistant to one or more drugs from the beta-lactam group;

Excluded from the study were:

- patients from whom strains of Gram-positive microorganisms were isolated;
- patients from whom strains of Gram-negative bacilli sensitive to all groups of antimicrobial agents were isolated;
- patients from whom strains of Gram-negative bacilli, not included in the global surveillance list, were isolated;
- patients from whom strains of Gram-negative bacilli were isolated from biosubstrates other than blood and cerebrospinal fluid.

The collected patient data, based on the personal records in the Archive of the *Timofei Mosneaga* Republican Clinical Hospital, focused on the duration of hospitalization, the total cost of treatment within the hospital, the cost of antimicrobial agents used for treatment, and the cost of laboratory analyses for each treated case.

A database was created in Excel, organizing the obtained information, and subsequent calculation of respective statistical indices, such as mean values, the median, minimum, and maximum values for the costs of each parameter. The indicators were calculated cumulatively for all three years and individually for each isolated resistant pathogen.

The normality of the data distribution was tested using the Shapiro-Wilk and d'Agostino-Pearson methods. To determine the statistical significance of the observed differences, the non-parametric Kruskal-Wallis test was conducted. When obtaining a p-value less than 0.05, the null hypothesis was rejected, concluding that there is a statistically significant difference between the observed variables.

RESULTS

The processing of the respective data collected within the *Timofei Moşneaga* Republican Clinical Hospital (RCH) allowed for the evaluation of cases of infections with resistant microorganisms concerning the costs associated with AMR. Figure 1 presents data on the general characteristics of resistant pathogens isolated from 172 patients hospitalized during the period from 2019 to 2021.

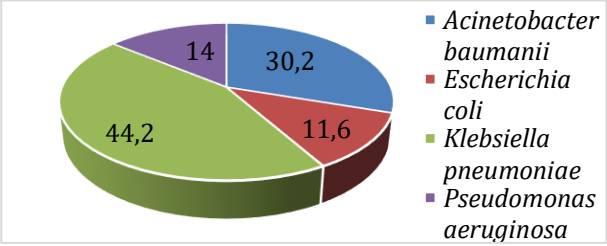

Figure 1. The cumulative percentage share (%) of resistant pathogens isolated from blood and CSF from patients hospitalized in the RCH during the years 2019-2021.

Based on the data presented in figure 1, it is observed that the majority of Gram-negative bacterial infection cases reported by the RCH during the period from 2019 to 2021 are caused by *K. pneumoniae* – 44.2±7.6%, followed by *A. baumannii* with a share of 30.2±7.0%, *P. aeruginosa* with 14.0±5.2%, and *E. coli* with 11.6±4.8%.

As a result of the analysis, no statistically significant differences (p>0.05) were determined regarding the duration of hospitalization based on the isolated Gram-negative bacterial species. The median value of this indicator varied from 19 days (min=4, max=98 days) for *P. aeruginosa* to 24 days (min=3, max=66 days) for *A. baumannii* (tab. 1).

The total costs for the treatment of a patient during hospitalization included: expenses for antimicrobial agents used, expenses for other types of medications besides antimicrobial agents, expenses for clinical and paraclinical investigations, as well as expenses for laboratory investigations.

Based on the costs recorded for the patients included in the study, the median cost of a case of infection with the isolated resistant microorganism was calculated using the SPSS software. Thus, it was found that the total treatment cost, estimated through the Kruskal-Wallis test, was higher for patients affected by *A. baumannii* strains compared to *E. coli* (p=0.0004) and *P. aeruginosa* (p=0.0123), while the observed difference compared to *K. pneumoniae* was not statistically significant (p=0.0571). Similarly, the difference in treatment costs for patients with *E. coli* compared to those from whom *P. aeruginosa* was isolated was not significant (p=0.2385).

The median value of the total cost varied from 1,328 thousand dollars (min=0,100 thousand dollars; max=12,109 thousand dollars) for *E. coli* to 2,841 thousand dollars (0,406-13,187 thousand dollars, respectively) for *A. baumannii* (tab. 2).

Table 1. The duration of hospitalization for patients with infections caused by antimicrobial-resistant microorganisms, years 2019-2021 (days).

Bacterium	Duration of hospitalization				
	n	mean (SD)	the median	min	max
Acinetobacter baumannii	1441	26.9 (14.9)	24	3	66
Escherichia coli	458	23.2 (24.5)	20	1	91
Klebsiella pneumoniae	2446	26.5 (18.2)	23	1	118
Pseudomonas aeruginosa	614	25.6 (21.3)	19	4	98

Table 2. The total costs incurred by the hospital for the treatment of cases of infections with resistant microorganisms isolated from patients during the period 2019-2021 (thousands of dollars).

Bacterium	Cost of treatment				
	n	mean	median	min	max
Acinetobacter baumannii	165.435	3.181	2.841	0.406	13.187
Escherichia coli	396.430	1.972	1.328	0.100	12.109
Klebsiella pneumoniae	202.732	2.668	2.291	0.191	10.997
Pseudomonas aeruginosa	50.761	2.115	1.679	0.525	6.613

In addition to the total treatment costs, the cost specifically for antimicrobial agents was also estimated, using the Kruskal-Wallis test.

The antimicrobial agents used for the treatment of patients included ciprofloxacin, levofloxacin, vancomycin, ceftazidime, meropenem,

ertapenem, imipenem, erythromycin, amoxicillin, amoxicillin clavulanic-acid, ceftriaxone, cefoperazon, cefoperazon-sulbactam, ceftazidim, ceftriaxon, cefuroxim, piperacillin-tazobactam, colistin, metronidazole, gentamicin, amikacin. The doses and duration of administration varied depending on the patient.

The highest expenses for antimicrobial agents used for a case of infection were recorded in patients with infections caused by *A. baumannii*, compared to infections caused by *E. coli* (p=0.0008) and *K. pneumoniae* (p=0.0003). However, the difference in the median cost between the treatment of infections caused by *A. baumannii* and those caused by *P. aeruginosa* was not statistically significant (p=0.0505).

The median cost value for antimicrobial agents varied from 0,112 thousand dollars (min=0.001 thousand dollars; max=1,002 thousand dollars) for *E. coli* infections to 0,453 thousand dollars (0,008-1,720 thousand dollars, respectively) for *A. baumannii* infections (tab. 3).

The data obtained for the indicators calculated in the SPSS statistical software, based on the expenses for laboratory investigations, using the same Kruskal-Wallis test, indicate higher median values for infections caused by *A. baumannii* with 0,661 thousand dollars (min=0,194 thousand dollars; max=2,625 thousand dollars). The lowest median values were recorded for investigations of infections caused by *E. coli* – 0,445 thousand dollars (min=0,056 thousand dollars; max=3,522 thousand dollars). As a result of the analysis, no statistically significant differences (p>0.05) were determined regarding the costs of laboratory analyses based on the isolated agent (tab. 4).

Table 3. The cost of antimicrobial agents used in cases of infections caused by resistant bacteria during the period 2019-2021 (thousands of dollars).

Bacterium	Cost of antibiotics				
	***n* (%)**	**mean**	**the median**	**min**	**max**
Acinetobacter baumannii	26.022 (15.7)	0.500	0.453	0.008	1.720
Escherichia coli	4.445 (1.1)	0.222	0.112	0.001	1.002
Klebsiella pneumoniae	27.377 (13.5)	0.360	0.193	0.009	3.298
Pseudomonas aeruginosa	8.793 (17.3)	0.366	0.280	0.031	1.772

Table 4. The costs related to expenses for laboratory analyses conducted on patients during hospitalization, 2019-2021 (thousands of dollars).

Bacterium	Cost of investigations				
	***n* (%)**	**mean (SD)**	**the median**	**min**	**max**
Acinetobacter baumannii	41.213 (24.9)	0.793	0.661	0.194	2.625
Escherichia coli	13.559 (34.4)	0.678	0.445	0.056	3.522
Klebsiella pneumoniae	58.374 (28.8)	0.775	11.128	0.065	3.560
Pseudomonas aeruginosa	14.111 (27.8)	0.588	8.9905	0.106	1.274

The extensive number of studies aiming to quantify the costs associated with AMR at the hospital level either focuses on the overall hospital expenditures or on department-specific expenses. These studies concentrate on indicators such as the duration of hospitalization, antibiotic costs, laboratory analysis costs, total costs per treated case, which are also the focal points of the present study (8 - 11).

The Gram-negative bacilli included in the research were isolated from blood samples taken from patients with invasive infections, similar to the studies conducted by Dos Santos et al. and Lashari et al. These patients were in critical condition and admitted to intensive care units (12, 13).

In the etiological spectrum of invasive infections, the species *K. pneumoniae* predominates with a percentage of 44.2%, followed by *A. baumannii* with 30.2%. This finding is in line with studies conducted by Lashari et al. and Nelson et al. (11, 13).

A study conducted in 10 hospitals in Korea estimated that the hospitalization duration of patients who contracted an infection with resistant *A. baumannii* was the highest compared to patients from whom other Gram-negative microorganisms were isolated (14). Similarly, in the current research, it was found that the hospitalization duration was longer for patients with infections caused by *A. baumannii.*

A shorter duration of hospitalization was observed for patients with infections caused by *E. coli*, as found by Hernandez-Pastor et al. in a study based on the PINC AI Healthcare US database. This reduced duration of hospitalization was also recorded in that particular study (15).

The majority of the analyzed studies included patients from whom strains of Gram-negative bacilli resistant to antimicrobial agents were isolated, a criterion that the present study also focused on, evaluating the costs associated with these bacilli during the patient's hospitalization (16, 17, 18).

Another calculated indicator for assessing the economic impact determined by AMR was the total cost of treatment during a patient's hospitalization. This indicator had maximum values for patients from whom antimicrobial-resistant *A. baumannii* was isolated, followed by patients with infections caused by resistant *K. pneumoniae*. Similar findings were also observed in the studies conducted by Lashari et al., Huang et al., and Wilson et al. (8, 13, 19).

In the case of costs for antibiotics used in treatment, as well as expenses for laboratory investigations, patients who contracted infections with *A. baumannii* are at the forefront with the highest expenditures, results similar to those observed in the research. After *A. baumannii*, the highest antibiotic costs were recorded for patients from whom *P. aeruginosa* was isolated, a finding also noted by Blanchette et al. and Zhen et al (7, 20).

Values dissimilar to the studies by Tabak et al., Zhen et al., and Kim et al. were determined for the costs of laboratory investigations, which placed *P. aeruginosa* in the second position, and the current research found higher values for this indicator for *K. pneumoniae* after *A. baumannii* (7, 14, 21).

The duration of hospitalization, as well as all treatment-related costs for patients with infections caused by resistant pathogens, have consistently been higher for patients with infections caused by antimicrobial-resistant *A. baumannii* (11, 14).

The study conducted by us has the following limitations:

- it is based on data collected over a period of 3 years. To conduct a more comprehensive investigation, data over a longer period, adjusted for annual inflation, is needed;
- lack of a control group to perform comparative calculations of hospitalization duration, treatment cost, and investigations for patients with infections caused by resistant and sensitive microorganisms, respectively, to determine incremental cost;
- patients were not separated into those with community-acquired infections and those with healthcare-associated infections;
- 47.7% of the patients died during hospitalization, which influenced the estimated costs for the treatment of patients with infections caused by antimicrobial-resistant Gram-negative bacilli.

Taking these aspects into account, further research in this field could develop the estimation of the economic impact of AMR and perform more complex calculations.

CONCUSIONS

The application of the methodology for estimating the economic impact of AMR based on the data collected during the period 2019-2021 has revealed the following:

1. In the etiological structure of infections caused by resistant microorganisms, the species *K. pneumoniae* predominates with a share of 44.2%.
2. The hospitalization period for patients with infections caused by antimicrobial-resistant *A. baumannii* proved to be the longest, with the median value of infection cases being 24 days.
3. The highest costs were recorded for the treatment of patients with infections caused by resistant *A. baumannii*, with the median cost of treatment being 2,841 dollars.

4. The median cost of antibiotics for an infection case was higher for the treatment of patients with infections caused by resistant *A. Baumannii* – 0,453 dollars. Similarly, the median value of laboratory analysis costs was highest for infections caused by this pathogen.

Based on the above, it is observed that antimicrobial resistance in K. pneumoniae and A. baumannii species largely contributes to the increased economic burden of AMR. Therefore, it is imperative to pay attention and allocate sufficient resources to preventive and control measures for infections caused by these bacteria.

Following the conducted research on assessing the costs related to antimicrobial resistance of priority Gram-negative bacilli, it can be concluded that as a logical next step, comparative studies on diseases caused by other microbial agents would be welcomed.

CONFLICT OF INTEREST

No author reported any conflicts of interest.

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ETHICAL APPROVAL

Favorable opinion of the Research Ethics Committee of the Nicolae Testemițanu State University of Medicine and Pharmacy, No. 1, dated September 27, 2022.

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