Antibiotic Resistance Pattern of Bacterial Pathogens in Elderly Patients Admitted in the Intensive Care Unit

ANDREEA LOREDANA GOLLI[1#], FLOAREA MIMI NITU[1], MARIA BALASOIU[1], MARINA ALINA LUNGU[2], MADALINA OLTEANU[1#], ROXANA MARIA NEMES[3,4*], MARIA FORTOFOIU[1], ELENA RUSU[4], MIHAI OLTEANU[1]

[1] University of Medicine and Pharmacy Craiova, 2 Petru Rares Str., 200349, Craiova, Romania

[2] County Emergency Clinical Hospital Craiova, 1 Tabaci Str., 200642, Craiova, Romania

[3] Marius Nasta Institute of Pneumology, 90 Viilor Road, 050152, Bucharest, Romania

[4] Titu Maiorescu University, Faculty of Medicine, 67A Gheorghe Petrascu, 031593, Bucharest, Romania

To identify and to determine the resistance pattern of bacterial pathogens involved in infections of the elderly patients (≥ 65 years) admitted in the intensive care unit (ICU) at County Emergency Clinical Hospital Craiova, Romania. A retrospective study of bacterial pathogens was carried out on 463 elderly patients (≥ 65 years) admitted to the ICU, from January to December 2017. The analysis of the resistance patterns for the action of the appropriate antibiotics was performed using Vitek 2 Compact system and diffusion method. In this study there were analyzed 617 samples from 463 elderly patients (≥ 65 years). A total of 776 bacterial isolates were obtained, of which 175 strains of Klebsiella spp. (22.55%), followed by MRSA - Methicillin-Resistant Staphylococcus Aureus (108 -13.91%) and Escherichia coli (99 -12.75%). The most common isolates were from respiratory tract (572 isolates -73.71%). High rates of MDR were found for Pseudomonas (73.07%), MRSA (62.03%) and Klebsiella (44.57%). The study revealed an alarming pattern of antibiotic resistance in the majority of ICU isolates from elderly patients (≥65 years), which draws attention to the need for judicious use of antibiotics and for careful monitoring of the drug resistance of patients.

Keywords: elderly, antibiotic resistance, intensive care unit, bacterial pathogen

Elderly patients are more susceptible to infection and complications because the constant decline of physical function and compromised immune system, so the control of bacterial infections in hospitalized elderly patients is more important.

Hospital acquired infections (HAIs) have been shown to occur about 5 to 10 times more in the patients admitted in ICUs, which are critically ill patients [1]. Infections to which the elderly patients were particularly vulnerable are respiratory tract infections (RTIs, e.g., bronchitis, bacterial pneumonia and influenza), UTIs, intra-abdominal infections (particularly *C. difficile*), and acute bacterial skin and soft tissue infections.

A significant problem in intensive care units is constantly increasing resistance to these antibiotics, the emergence and spread of antimicrobial resistance (AMR) being now considered a global public health threat [2]

Starting from this reality, we analyzed the distribution and resistance patterns of the pathogens isolated from elderly patients hospitalized in ICU.

Experimental part

Materials and methods

The research is a retrospective study, which included the determination of pathogens involved in infections of the elderly patients (≥ 65 years) admitted to the intensive care unit (ICU) of County Emergency Clinical Hospital Craiova, Romania, a county hospital with 1518 beds (65 beds of ICU), which provides specialized healthcare to patients from Dolj county and Oltenia region. Data were collected from January 2017 to December 2017 from the clinical pathology databases of the hospital, including culture sensitivity reports of the elderly patients admitted to the ICU in the studied period. Samples included blood, urine, sputum/tracheal aspirate (respiratory secretion), pus/wound swabs, exudates, intravascular catheters, cerebrospinal fluid, sterile fluids. There were included in the study only those samples which were positive by culture.

The identification of the isolated strains on the clinical specimens received from ICU elderly patients was carried out in the Hospital's Laboratory of Microbiology. The analysis of the resistance patterns for the action of the appropriate antibiotics was performed using Vitek 2 Compact system and diffusion method.

Antibiotics agents employed for susceptibility testing were ampicillin-clavulanic acid (20/10 μg), cefazolin (30 μg), cefuroxime (30 μg), ceftriaxone (30 μg), cefotaxime (30 μg) ceftazidime (30 μg), cefepime (30 μg), ciprofloxacin (5 μg), teicoplanin (30 μg), piperacillin-tazobactam (30 μg), imipenem (10 μg), meropenem (10 μg), ertapenem (10 μg), linezolid (30 μg), tetracycline (30 μg) penicillin (10 μg), erytromycin (15 μg), clindamycin (2 μg), clarithromycin (15 μg), doxycycline (30 μg) and rifampicin (5 μg). Interpretation was done according to Clinical Laboratory Standard Institute (CLSI) guidelines [3].

Information about gender and age of the patients, site of infection and antimicrobial resistance pattern were collected from Hospital's Information System and from the available hospital records, the whole process relying on effective communication with patients, the family and the medical team [4], observing ethical and ethical norms specific to medical research [5].

Data were entered and analysed using Microsoft Excel. Continuous variables like age are expressed as mean±STDEV. The pattern of micro-organisms and gender/sites of infections were analyzed and expressed as percentages. The $\chi 2$ test was used for count data, and $p<0.05$ meant the difference was statistically significant.

Results and discussions

From January to December 2017, there were analysed 617 samples from 463 elderly patients (≥ 65 years), hospitalized in ICU. The mean age of the patients was

* email: oxanamarianemes@gmail.com

#The authors contributed equally to the manuscript and thus share main authorship.

75.49±6.90 years, 212 women (45.78%) and 251 men (54.21%). Samples included blood, urine, sputum/tracheal aspirate (respiratory secretion), pus/wound swabs, exudates, intravascular catheters, cerebrospinal fluid, sterile fluids. There were included in the study only those samples which were positive by culture.

A total of 776 bacterial isolates were obtained, excluding cases where it was more than one isolate of the same pathogen from the same patient. Of these, 531 (68.42%) were Gram negative and 245 isolates (31.57%) were Gram positive bacteria. The most common isolate of the Gram negative pathogens was *Klebsiella* spp. (32.95%), followed by *E.coli* (18.64%) and *non-fermenting Gram negative bacilli*, other than Pseudomonas and Acinetobacter (NFB) (18.06%).

The most common isolates were from respiratory tract (572 isolates -73.71%), followed by 91 isolates from urine (11.73%, 59 (7.62%) isolates from pus/wound swabs, 33 (4.25%) isolates from blood (table 1).

According to our study, the most commonly isolated of all micro-organisms identified in the studied period was *Klebsiella* spp. (22.55%), followed by *MRSA - Methicillin-Resistant Staphylococcus Aureus (13.91%), Escherichia coli (12.75%), NFB* (12.37%), *CoNS* - Coagulase-negative staphylococci (11.21%), *Acinetobacter* spp. (7.34%) and *Pseudomonas aeruginosa* (6.70%).

Referring to the total number of samples collected by gender, isolation rates indicates a higher value for female patients for *MRSA* (50.92% compared to 49.07%), *Enterococcus* spp. (63.15% compared to 36.84%), *Enterobacter* spp. (70% compared to 30%) and *Streptococcus* spp. (66.66% compared to 33.33%) (table 2). Only one *Serratia* spp. strain was found in a male patient and one of *Haemophilus influenzae* in a female patient.

A similar percentage was highlighted for *Klebsiella* in other researchers' studies [6,7], but it was the second most frequent pathogen involved in infections of patients hospitalized in ICU, after *Acinetobacter* spp. [6,7] or *Pseudomonas* [7].

After other researchers, *Coagulase-negative Staphylococci* (CoNS) and E coli were the most frequently isolated from patient samples [9]. According to Akter at al. [10], the predominant organism isolated from ICU were *E. coli* (28%), followed by *Klebsiella* spp. (27%) and *Acinetobacter* spp. (17.3%).

Similar prevalence of *S. aureus* in ICU was recorded in a study conducted in intensive care units in a university affiliated hospital in Shanghai, by Ruoming et al. (2014). [8]

The most frequently harvested samples originated from sputum/tracheal aspirate (73.71%) and *Klebsiella* was the most common isolated pathogen from respiratory tract (25%) (table 2), almost the same percentage revealed in the study conducted by Akter at al. [10].

From urine (11.73% from all samples), *E. coli* was the most frequently isolated organism (38.46%), consistent with other findings [9], while *MRSA* occupied, similar to the results of other researchers [11], first place among isolated pathogens from pus/wounds swabs (18.64%), and from blood (39.39%).

Consistent with our study, other investigators have reported also as the most common site of infection respiratory tract, urine and blood [3, 7, 12].

While antibiotics are considered the most effective method of treatment for bacterial infections, their empirical, indiscriminate, prolonged, or incorrect usage contributes significantly to the emergence of new infections by leading to the selection of resistant strains [13, 14].

Antimicrobial resistance (AMR) is a serious threat to public health and patient safety in Europe, leading to mounting healthcare costs, patient treatment failure, and deaths [15]. Several classes of bacteria have already exhibited multidrug resistance to antibiotics, such as *Klebsiella pneumoniae* and *E. coli* strains producing extended-spectrum beta-lactamase (ESBL), which hydrolyses the beta-lactam ring of penicillin, cephalosporins, and other related antibiotics, contributing to treatment failure [16-18].

According to the European Antimicrobial Resistance Surveillance Network (EARS-Net), the proportion of *Klebsiella pneumoniae* and *E. coli* resistant to fluoroquinolones, third generation cephalosporins, aminoglycosides and a combined resistance to the three antibiotic groups has been increased significantly between 2011-2014 [19]. This resistance is common in ESBL – producing strains [20], while the emergence of resistance in Enterobacteriaceae is considered an alarming health threat [21].

We have analyzed the percentage of multidrug-resistant (MDR) strains among the clinical isolates from ICU, by taking into consideration resistance to at least three different antibiotic groups: aminoglycosides, cephalosporins, carbapenems, tetracyclines and fluoroquinolones. Almost 55% from the *Acinetobacter* strains were MDR (resistant to cephalosporins, carbapenems and fluoroquinolones). High rates of MDR were found for *Pseudomonas* (73.07%), *MRSA* (62.03%) and *Klebsiella* (44.57%), much higher than those found in

Table 1
DISTRIBUTION OF ISOLATES AMONG SAMPLES FROM ELDERLY PATIENTS HOSPITALIZED IN ICU, COUNTY EMERGENCY CLINICAL HOSPITAL CRAIOVA, ROMANIA, BETWEEN JANUARY-DECEMBER 2017

Sample	Number of bacterial strains	%
Exudates	7	0.90
Intravascular catheters	4	0.51
Sterile fluids	7	0.90
Cerebrospinal fluid	3	0.38
Pus/wound swabs	59	7.62
Sputum/tracheal aspirate	572	73.71
Urine	91	11.73
Blood	33	4.25
Total	776	100

Table 2
DISTRIBUTION BY GENDER OF THE MICRO-ORGANISMS ISOLATED FROM SAMPLES FROM ELDERLY PATIENTS HOSPITALIZED IN ICU, COUNTY EMERGENCY CLINICAL HOSPITAL CRAIOVA, ROMANIA, BETWEEN JANUARY-DECEMBER 2017

Micro-organism	Females		Males		Total	
	n	%	n	%	n	%
Acinetobacter	27	47.36	30	52.63	57	100
NFB	42	43.75	54	56.25	96	100
Citrobacter	1	20	4	80	5	100
Enterobacter	7	70	3	30	10	100
E.coli	49	49.49	50	50.50	99	100
Haemophilus influenzae	1	100	-	-	1	100
Klebsiella	79	45.14	96	54.85	175	100
Proteus	14	40	21	60	35	100
Pseudomonas	23	44.23	29	55.77	52	100
Serratia	-	-	1	100	1	100
CoNS	35	40.23	52	59.77	87	100
S. aureus	10	50	10	50	20	100
MRSA	55	50.92	53	49.07	108	100
Streptococcus pneumoniae	1	12.5	7	87.5	8	100
Enterococcus	12	63.15	7	36.84	19	100
Streptococcus sp.	2	66.66	1	33.33	3	100
Total	358	100	418	100	776	100

NFB- Glucose-nonfermenting Gram-negative bacilli; *CoNS* -- Coagulase-negative staphylococci; *MRSA* - Methicillin-Resistant Staphylococcus Aureus;

other studies [12]. Less than one-third of *E. coli* strains were multidrug-resistant.

The antibiotic resistance rates of the isolates are summarized in tables 3-6. The combined resistance to multiple antimicrobial groups observed for *Klebsiella* spp. is consistent with European Centre for Disease Prevention and control (ECDC). The majority of infections caused by

Table 3
PATTERN OF PATHOGENS ISOLATED FROM DIFFERENT SPECIMEN TYPES IN ICU

Species	Sample							
	Sputum/tracheal aspirate	Urine	Pus/wound swabs	Blood	Intravascular catheters	Exudate	Sterile fluids	Cerebrospinal fluid
Acinetobacter	48		8					1
NFB	88	3	4	1				
Citrobacter	4	1						
Enterobacter	1	9						
E.coli	51	35	9	2			2	
Haemophilus influenza	1							
Klebsiella	143	16	8	4		3	1	
Proteus	25	1	7		1		1	
Pseudomonas	37	6	5		1		2	1
Serratia	1							
CoNS	72	1	2	12				
S. aureus	17		3					
MRSA	77	1	11	13	1	4	1	
Streptococcus pneumoniae	7							1
Enterococcus		18			1			
Streptococcus sp.			2	1				
Total	572	91	59	33	4	7	7	4

Table 4
ANTIMICROBIAL RESISTANCE PATTERN OF ENTEROBACTERIACEAE GNB (NUMBER AND PERCENTAGE)

Antimicrobial agent	*Klebsiella* (175)	*E.coli* (99)	*Enterobacter* (10)	*Proteus* (35)
Amoxicillin/clavulanic acid	53 (30.28%)	38 (38.38%)	4 (40%)	10 (28.57%)
Ceftazidime	106 (60.57%)	24 (24.24%)	-	23 (65.71%)
Ceftriaxone	117 (66.85%)	28 (28.28%)	6 (60%)	21 (60%)
Cefotaxime	75 (42.85%)	12 (12.12%)	-	10 (28.57%)
Cefuroxime	106 (60.57%)	48 (48.48%)	9 (90%)	23 (65.71%)
Cefazolin	144 (82.28%)	54 (54.54%)	8 (80%)	26 (74.28%)
Cefepime	107 (61.14%)	23 (23.23%)	3 (30%)	20 (57.14%)
Imipenem	44 (25.14%)	5 (5.05%)	-	11 (31.42%)
Ciprofloxacin	80 (45.71%)	32 (32.32%)	7 (70%)	18 (51.42%)
Meropenem	89 (50.85%)	16 (16.16%)	-	13 (37.14%)
Piperacillin/tazobactam	116 (66.28%)	-	-	21 (60%)
Ertapenem	74 (42.28%)	29 (55.77%)	-	10 28.57%)

* — not tested

Table 5
ANTIMICROBIAL RESISTANCE PATTERN OF GRAM POSITIVE COCI (NUMBER AND PERCENTAGE)

Antimicrobial agent	MRSA (108)	CoNS (87)	Enterococcus (19)
Ciprofloxacin	71 (65.74%)	64 (73.56%)	14 (73.68%)
Clindamycin	85 (78.70%)	69 (79.31%)	-
Clarytromicin	71 (65.74%)	31 (35.63%)	-
Doxicicline	52 (59.77%)	40 (45.97%)	-
Erytromycin	86 (79.62%)	67 (77.01%)	-
Linesolid	2 (1.85%)	1 (1.15%)	1 (5.26%)
Penicillin	103 (95.37%)	85 (97.70%)	13 (68.42%)
Rifampicin	51 (47.22%)	60 (68.96%)	-
Tetracycline	76 (70.37%)	70 (80.46%)	12 (63.15%)
Teicoplanin	13 (12.03%)	6 (6.89%)	-

* —not tested

Table 6
ANTIMICROBIAL RESISTANCE PATTERN OF NON-FERMENTING GNB (NUMBER AND PERCENTAGE)

Antimicrobial agent	Acinetobacter spp. (57)	Pseudomonas spp. (52)	Other NF-GNB (96)
Amoxicillin/clavulanic acid	6 (10.52%)	19 (36.53%)	41 (42.70%)
Ceftazidime	30 (66.66%)	39 (75%)	84 (37%)
Ceftriaxone	31 (17.71%)	34 (65.38%)	6 (60%)
Cefotaxime	49 (85.96%)	19 (36.53%)	63 (65.62)
Cefuroxime	3 (5.26%)	-	68 (70.83%)
Cefazolin	7 (12.28%)	27 (51.92%)	87 (90.62%)
Cefepime	43 (75.43%)	39 (75%)	79 (82.29%)
Ertapenem	4 (7.01%)	29 (55.77%)	75 (78.12%)
Imipenem	42 (73.68%)	19 (36.53%)	53 (55.20%)
Ciprofloxacin	44 (77.19%)	29 (55.77%)	43 (44.79%)
Meropenem	42 (73.68%)	31 (59.61%)	77 (80.20%)
Piperacillin/tazobactam	-	-	83 (86.45%)
Tetracycline	-	-	23 (23.95%)

K. pneu-moniae are healthcare-associated and the most common resistance phenotype was combined resistance to three key antimicrobial groups: fluoroquinolones, third-generation cephalosporins and aminoglycosides [15].

60-80% from the *Klebsiella* strains isolated in our study were resistant to cephalosporins, a third to amoxicillin/clavulanic acid and 66.28% to piperacillin/tazobactam. A quarter of the *Klebsiella* strains were resistant imipenem and around 50% to other carbapenems, consistent to CDC analysis, which places Romania between the three countries with the highest carbapenems resistance. [15]. *K. pneumoniae* was also found to be multidrug resistant to the third generation cephalosporins and quinolone antibiotics in a research conducted by Radji et al. (2014) [22].

An increasing carbapenem resistant rate for *Klebsiella, Acinetobacter and Pseudomonas* was reported in their study by Akter et al (2014) [10]**.**

Arround 40% of *E. coli* isolates were resistant to amoxicillin/clavulanic acid. Almost 95% of the tested strains were susceptible to imipenem and 70% to ertapenem, around 75% to third and fourth-generation cephalosporins. The results are consistent with analyses from the European Centre for Disease Prevention and Control [15].

In our study, the results showed that there was statistic difference between the drug resistance rate of *Klebsiella* and *E. coli* strains to ceftazidime and ceftriaxone ($p<0.001$) and to ciprofloxacin ($p<0.05$).

A study conducted by Zheng et al. (2017) [23], on pathogenic bacteria and antibiotic resistance of Enterobacteriaceae in hospitalized elderly patients, but not in ICU, revealed a high drug resistance rate of *Escherichia coli* and *Klebsiella pneumoniae* to sulfamethoxazole, followed by ciprofloxacin and levofloxacin.

In the Gram-positive group, a higher degree of resistance of *MRSA* was found to be against penicillin (95.37%), erythromycin (79.62%), clindamycin (78.70%), tetracycline (70.37%) and ciprofloxacin (65.74%), consistent with other findings [1,10]. A prospective study performed in Romania by Licker at al, identified 66.51% MDR and 20.18% XDR *S.aureus* strains [24]**,** in the conditions in which *MRSA* has been the most important cause of antimicrobial-resistant healthcare-associated infections worldwide, with higher percentages in the southern and south-eastern parts of Europe [15]. The most active antibiotic against MRSA (table 5) was linezolid, with almost all strains (105) being susceptible (table 5).

Almost all the tested strains of *coagulase-negative staphylococci* (CoNS) were resistant to penicillin, arround 80% to clindamycin, tetracycline and erytromycin, 70% to rifampicin (table 5).

The *Enterococci* isolates were resistant to ciprofloxacin (73.68%), penicillin (68.42%), and tetracycline (63.15%), and almost all strains were susceptible to linezolid.

All the tested strains of *Pseudomonas aeruginosa* (36.53% from all strains) were resistant to amoxicillin/clavulanic acid, 75% to ceftazidime and cefepime. 36.53% from the strains were resistant to imipenem and between 55-605% to ciprofloxacin, meropenem and ertapenem (table 6). The resistance to ceftazidime and cefepime observed in our study was similar to that of a previous report on multidrug-resistant *Pseudomonas aeruginosa*, which also revealed that 80% of *P. aeruginosa* were resistant to carbapenem antibiotics such as imipenem and meropenem [25, 26]**.** 26.27% of the *Pseudomonas* strains have been found to be resistant to carboxypenicillins and ureidopenicillins in a study conducted by Axente et al. [27]**.**

A very high level of resistance was found for the tested strains of other *non fermenting Gram negative bacilli* (other NF-GNB) (between 90-99%), to amoxicillin/clavulanic acid, to all generations of cephalosporins, ciprofloxacin, piperacillin/tazobactam, imipenem, tetracycline [28, 29]. Only one strain was found resistant to linezolid (table 6).

A high resistance to the carbapenems (73%) was found for the *Acinetobacter* strains, which were also resistant to cefotaxime (86%), cefepime (75.43%), ciprofloxacin (77.19%) and ceftazidime (66.66%). In another research conducted in Saudi Arabia on multidrug resistance Acinetobacter species at the intensive care unit, it was found a much higher percentage -over 90% - of resistant strains to the same antibiotics [30].

In our study, for all the other NF-GNB strains, a high degree of resistance has been observed on cephalosporins, carbapenems and ureido-penicillins, consistent with other findings [1].Moolchandani K. et al have reported concordance resistance pattern to various classes of antimicrobials for Acinetobacter and Pseudomonas [1]

Another study conducted in Romania by Axente et al. evidenced an increased resistance (69.95% resistant strains) to penicillins (presently less frequently prescribed in ICUs) found in GNB [27].

This study only refers to infections in elderly patients (over 65 years of age) admitted to ICU, because there are very few studies reported only for this vulnerable age group, with particularities of response to antibiotic therapy (especially if is correlated with other substances intake) [31] . Comparisons of the prevalence of isolated germs and their antibiotic resistance were made with the results obtained in studies that took into account all age groups, considering the fact that the elderly represent the majority of the cases admitted to the ICU.

Conclusions

The study revealed an alarming pattern of antibiotic resistance in the majority of ICU isolates from elderly patients ($\geq$65 years). The detection of bacterial resistance is an important way to observe the clinical rational use of drugs, in which the laboratory plays a very important role.

Surveillance of antibiotic prescription and monitoring studies are required to reduce the risk of resistance, together with direct communication between clinicians and microbiologists for adopting individual therapeutic measures and using appropriate antibiotics based on antibiogram. It is also necessary to collaborate with the epidemiologist in order to apply the measures for the control hospital acquired infections.

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