The Characterization of Antibiotic Resistance of Bacterial Isolates from Intensive Care Unit Patient Samples in a University Affiliated Hospital in Romania

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To determine the resistance pattern of bacterial pathogens involved in infections of the patients aged between 18-64 years, admitted in a ICU from a 1518-bed university-affiliated hospital. A retrospective study of bacterial pathogens was carried out on 351 patients aged between 18-64 years admitted to the ICU, from January to December 2017. In this study there were analysed 469 samples from 351 patients (18-64 years). A total of 566 bacterial isolates were obtained, of which 120 strains of Klebsiella spp. (35.39%%), followed by Nonfermenting Gram negative bacilli, other than Pseudomonas and Acinetobacter (NFB) (75- 22.12%), Acinetobacter spp. (53 - 15.63%), Pseudomonas aeruginosa and Proteus (51 - 15.04%), and Escherichia coli (49 - 14.45%). The most common isolates were from respiratory tract (394 isolates – 69.61%). High rates of MDR were found for Pseudomonas aeruginosa (64.70%), MRSA (62.65%) and Klebsiella spp. (53.33%), while almost all of the isolated NFB strains were MDR (97.33%). There was statistic difference between the drug resistance rate of Klebsiella and E. coli strains to ceftazidime and ceftriaxone ($p<0.001$), cefuroxime ($p<0.01$) and to cefepime ($p<0.01$). The study revealed an alarming pattern of antibiotic resistance in the majority of ICU isolates.

Keywords: multidrug resistance (MDR), intensive care unit, bacterial pathogen

Antimicrobial resistance is a threat to all branches of medical and public health practice. In the European Union, about 25 000 patients die each year from infections caused by selected multidrug-resistant bacteria and the associated costs are estimated at about 1.5 billion euros per year [1].

Hospitals are a critical component of the antimicrobial resistance problem worldwide [2], in the condition in which 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 [3-8]. 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 [9].

According to the European Antimicrobial Resistance Surveillance Network (EARS-Net), Improving Patient Safety in Europe (IPSE) and ECDC data, Romania is one of the South-Eastern European countries with one of the highest prevalence rates of MDR pathogens [10,11].

Starting from this reality, we analysed the distribution and resistance patterns of the pathogens isolated from adult patients (18-64 years) hospitalized in ICU.

Experimental part

Materials and methods

The research is a retrospective study, which includes the determination of pathogens involved in infections of patients aged between 18-64 years, admitted to the intensive care unit (ICU) of Craiova Emergency Clinical County Hospital, 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 adult patients (18-64 years), 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 patients was carried out in the Hospital's Laboratory of Microbiology. The analyse 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 amoxicillin-clavulanic acid (20/10μg), cefazolin (30 μg), cefuroxime (30μg), ceftriaxone (30μg), cefotaxime (30μg) ceftazidime (30μg), cefepime (30μg), ciprofloxacin (5μg), teicoplanin (30μg), piperacillin-tazobactam (30μg), imipenem (10μg), meropenem (10 μg), ertapenem (10μg), linezolid (30μg), tetracycline (30μg) penicillin (10μg), erythromycin (15μg), clindamycin (2 μg), clarithromycin (15μg), doxycycline (30μg) and rifampicin (5μg). Interpretation was done according to Clinical Laboratory Standard Institute (CLSI) guidelines [12].

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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 [13].

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 analysed and expressed as percentages. The χ^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 469 samples from 351 patients aged between 18-64 years, hospitalized in ICU. The mean age of the patients was 47.28±13.21 years, 151 women (43.02%) and 200 men (56,98%). 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 positive samples by culture.

Distribution of subjects by age group reflects the largest proportion of patients over 35 years (79.48%) and 20.51% (72) between 18-34 years.

It is a retrospective study and the patients signed the informed consent for analysis and treatment.

A total of 566 bacterial isolates were obtained, excluding cases where it was more than one isolate of the same pathogen from the same patient. Among these, 339 isolates (59.89%) were Gram negative and 227 isolates (40.1%) were Gram positive bacteria. The most common isolate of the Gram negative pathogens was *Klebsiella* spp. (35.39%), followed by *nonfermenting Gram negative bacilli*, other than Pseudomonas and Acinetobacter (NFB) (22.12%), *Acinetobacter* spp. (15.63%), *Pseudomonas aeruginosa* and *Proteus* (15.04%), and *E.coli* (14.45%).

The most common isolates were from respiratory tract (394 isolates -69.61%), followed by 56 isolates from urine (9.89%), 52 isolates from pus/wound swabs (9.18%), 36 isolates from blood (6.36%) (table 1).

The most frequently isolated of all micro-organisms identified in the harvested samples was *Klebsiella* spp. (21.20%), followed by *MRSA - Methicillin-Resistant Staphylococcus Aureus (14,66%), NFB-* Glucose-nonfermenting Gram-negative bacilli (13.25%), *Acinetobacter* spp. (9.36%), *Pseudomonas aeruginosa* (9.01%) and *Proteus* spp. (9.01%). MRSA and *Enterococcus* spp. were the first and second predominant Gram positive bacteria, accounting for 17.31% from all isolates.

Referring to the total number of samples collected by gender, isolation rates indicates a higher value for male patients, double for *NFB, Acinetobacter* spp. *Pseudomonas aeruginosa* and more than three times higher for *CoNS* - Coagulase-negative staphylococci (table 2).

In terms of germ distribution by age group, there was a larger number in the case of patients between 35 and 64 years, the difference being statistically significant (table 3).

The most frequently harvested samples originated from sputum/tracheal aspirate (69.61%) and *Klebsiella* was the most common isolated pathogen from these samples (20.55%) (table 4).

From urine (9.89% from all samples), *E. coli* was the most frequently isolated organism (28.57%), while *Acinetobacter* spp. occupied the first place among isolated pathogens from pus/wound swabs (17.30%)., followed at a very short distance, with an equal percentage (15.38%), by *Pseudomonas aeruginosa* and *Klebsiella* spp.

Table 1

DISTRIBUTION OF ISOLATES AMONG SAMPLES FROM PATIENTS (18-64 YEARS) HOSPITALIZED IN ICU, COUNTY EMERGENCY CLINICAL HOSPITAL CRAIOVA, ROMANIA, BETWEEN JANUARY-DECEMBER

Sample	Number of bacterial strains	%
Exudates	5	0.88
Intravascular catheters	13	2.29
Sterile fluids	7	1.23
Cerebrospinal fluid	3	0.53
Pus/wound swabs	52	9.18
Sputum/tracheal aspirate	394	69.61
Urine	56	9.89
Blood	36	6.36
Total	776	100

Table 2

DISTRIBUTION BY GENDER OF THE MICRO-ORGANISMS ISOLATED FROM SAMPLES FROM PATIENTS (18-64 YEARS) HOSPITALIZED IN ICU, COUNTY EMERGENCY CLINICAL HOSPITAL CRAIOVA, ROMANIA, BETWEEN JANUARY-DECEMBER 2017

Micro-organism	Females		Males		Total	
	n	%	n	%	n	%
Acinetobacter	18	33.96	35	66.03	53	100
NFB	25	33.33	50	66.66	75	100
Citrobacter	2	25	6	75	8	100
Enterobacter	2	50	2	50	4	100
E.coli	25	51.02	24	48.97	49	100
Haemophilus influenzae	2	100	0	0	2	100
Klebsiella	42	35	78	65	120	100
Proteus	22	43.13	29	56.86	51	100
Pseudomonas	18	35.29	33	64.70	51	100
Serratia	0	0	1	100	1	100
CoNS	8	23.53	26	76.47	34	100
S. aureus	1	12.5	7	87.5	8	100
MRSA	31	37	52	62.65	83	100
Streptococcus pneumoniae	5	50	5	50	10	100
Enterococcus	6	40	9	60	15	100
Other Gram-positive bacilli	0	0	2	100	2	100
Total	207	100	359	100	566	100

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

Micro-organism	Females		Males		Total		p
	18-34 years	35-64 years	18-34 years	35-64 years	18-34 years	35-64 years	
Acinetobacter	5	13	7	28	12	41	<0.001
NFB	4	21	11	39	15	60	<0.01
Klebsiella	8	34	13	65	21	99	N.S
Proteus	2	20	7	22	9	42	<0.001
Pseudomonas	5	13	3	30	8	43	<0.001
E.coli	7	18	8	16	15	34	<0.001
MRSA	9	22	6	46	15	68	<0.05

*N.S-not significant

Table 3
DISTRIBUTION BY AGE GROUPS OF THE MOST COMMON MICRO-ORGANISMS ISOLATED FROM SAMPLES FROM PATIENTS (18-64 YEARS) HOSPITALIZED IN ICU, COUNTY EMERGENCY CLINICAL HOSPITAL CRAIOVA, ROMANIA, BETWEEN JANUARY-DECEMBER 2017

Table 4
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	38		9	2	1	-	2	1
NFB	67	1	4	3	-	-	-	-
Citrobacter	5	1	-	2	-	-	-	-
Enterobacter	2	1	-	1	-	-	-	-
E.coli	25	16	6	1	-	-	1	-
Haemophilus influenza	2	-	-	-	-	-	-	-
Klebsiella	81	17	8	5	6	1	2	-
Proteus	33	8	4	1	4	1	-	-
Pseudomonas	38	3	8	-	2	-	-	-
Serratia	-	-	-	1	-	-	-	-
CoNS	27	-	3	2	-	-	-	2
S. aureus	6	-	1	-	-	1	-	-
MRSA	60	3	4	13	-	2	1	-
Streptococcus pneumoniae	10	-	-	-	-	-	-	-
Enterococcus	-	6	5	3	-	-	1	-
Streptococcus sp.	-	-	-	-	-	-	-	-
Other Gram-positive bacilli	-	-	-	2	-	-	-	-
Total	394	56	52	36	13	5	7	3

The first place among the pathogens isolated from blood was held by MRSA (36.11%).

In our study we have analysed 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.83% from the *Acinetobacter* spp. strains were MDR. High rates of MDR were found for *Pseudomonas aeruginosa* (64.70%), *MRSA* (62.65%) and *Klebsiella* spp. (53.33%), while almost all of the isolated *NFB* strains were MDR (97.33%).

The antibiotic resistance rates of the isolates are summarized in tables 5, 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 *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 [14].

Around 85% from the *Klebsiella* spp. strains isolated in our study were resistant to first generation cephalosporins, 70-80% to second-generation, almost half to third-generation and over 70% to fourth-generation cephalosporins. About 50% of the *Klebsiella* spp. strains were resistant to meropenem and ertapenem, and almost a third to imipenem, consistent to CDC analysis which places Romania between the three countries with the highest carbapenems resistance [14]. Also half of the strains were resistant to ciprofloxacin and amoxicillin/clavulanic acid (table 5).

Around 40% of *E. coli* isolates were resistant to amoxicillin/clavulanic acid and almost 60% to first-generation cephalosporins. Less than 20% of *E. coli* strains were resistant to cabapenems.

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 ($p<0.001$), cefuroxime ($p<0.01$) and to cefepime ($p<0.01$).

In the Gram-positive group, MDR *MRSA* strains were identified in our research, in the conditions in which this pathogen 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 [14].

A higher degree of resistance of *MRSA* was found to be against penicillin (90.36%), clindamycin (83.13%), erythromycin (77.10%), tetracycline (73.49%), oxacillin (74.69%) and ciprofloxacin (65.06%). Almost all MRSA strains (80 - 96.38%), were susceptible to linezolid (table 6).

Over 80% from the isolated strains of *coagulase-negative staphylococci* (CoNS) were resistant to penicillin and

Antimicrobial agent	Klebsiella (120)	E.coli (49)	Proteus (51)
Amoxicillin/clavulanic acid	55 (45.830%)	19 (38.77%)	18 (35.29%)
Ceftazidime	84 (70%)	12 (24.48%)	37 (72.55%)
Ceftriaxone	97 (80.83%)	19 (38.77%)	39 (76.47%)
Cefotaxime	59 (49.16%)	9 (18.36%)	21 (41.17%)
Cefuroxime	83 (69.16%)	18 (36.73%)	38 (74.51%)
Cefazolin	103 (85.83%)	28 (57.14%)	21 (41.17%)
Cefepime	86 (71.66%)	13 (26.53%)	33 (64.70%)
Imipenem	34 (28.33%)	4 (8.16%)	12 (23.53%)
Ciprofloxacin	59 (49.16%)	12 (24.48%)	27 (52.94%)
Meropenem	62 (51.66%)	9 (18.36%)	12 (23.53%)
Piperacillin/tazobactam	86 (71.66%)	11 (22.44)	22 (43.13%)
Ertapenem	59 (49.16%)	6 (12.24%)	11 (21.56%)

Tabl 5
ANTIMICROBIAL RESISTANCE PATTERN OF ENTEROBACTERIACEAE GNB (NUMBER AND PERCENTAGE)

Antimicrobial agent	MRSA (83)	CoNS (34)	Enterococcus (15)
Ciprofloxacin	54 (65.06%)	26 (76.47%)	13 (86.66%)
Clindamycin	69 (83.13%)	28 (82.35%)	2 (13.13%)
Clarithromycin	50 (60.24%)	12 (35.29%)	1 (6.66%)
Doxycycline	25 (30.12%)	17 (50%)	5 (33.33%)
Erythromycin	64 (77.10%)	26 (76.47%)	2 (13.33%)
Linezolid	3 (3.61%)	2 (5.88%)	1 (6.66%)
Penicillin	75 (90.36%)	30 (88.23%)	5 (33.33%)
Rifampicin	35 (42.16%)	23 (67.64%)	-
Tetracycline	61 (73.49%)	25 (73.53%)	7 (46.66%)
Teicoplanin	16 (19.27%)	1 (2.94%)	2 (13.33)
Oxacillin	62 (74.69%)	26 (76.47%))	-

* – not tested

Table 6
ANTIMICROBIAL RESISTANCE PATTERN OF GRAM POSITIVE COCI (NUMBER AND PERCENTAGE)

clindamycin, around 75% to ciprofloxacin, erythromycin, tetracycline and oxacillin (table 6).

The *Enterococci* isolates were found resistant to ciprofloxacin (86,66%) and only one strain was resistant to linezolid.

A high resistance to the cephalosporins (around 70%), has been highlighted in the case of *Pseudomonas aeruginosa* strains. Half of the strains were resistant also to carbapenems and almost 60% to ciprofloxacin.

A very high level of resistance was found for the tested strains of other *nonfermenting Gram negative bacilli* (other NF-GNB) (between 70-95%), to all generations of cephalosporins, piperacillin/tazobactam, carbapenems. (table 7).

According to our study, for the *Acinetobacter* strains it was found a high resistance to the carbapenems (70-77%) and to third and fourth-generation cephalosporins (cefotaxime - 90.56%, ceftazidime - 84.90%, cefepime - 79.24%), and also to ciprofloxacin (79.24%).

Around 75% of the *Proteus* strains were resistant to ceftazidime, cefrtriaxone and cefuroxime, 65% to cefepime and more than a half to ciprofloxacin.

Our study included patients hospitalized in ICU, aged between 18-64 years, with the aim of highlighting the MDR strains which caused infections in the active people which did not belong to the risk groups. We excluded from this study children under the age of 18 and elderly people (over 65 years), vulnerable age groups with particularities of the evolution of infection [15, 16] and response to antibiotic therapy [17].

The research revealed that the most common isolated pathogen was *Klebsiella* spp. (21,20%), followed by MRSA and *NFB*- Glucose-nonfermenting Gram-negative bacilli. The first two germs were also identified in the samples collected from elderly patients hospitalized in the same period in ICU. [18] *Klebsiella* ranks first among isolated germs in other researchers' studies [19], while a similar percentage was also highlighted for this pathogen [20,21], but occupying the second, third or fourth place in the hierarchy of the most frequent pathogens involved in infections of patients hospitalized in ICU, after *Acinetobacter* spp. [20, 22], *Pseudomonas* [21] or *E. coli* [23].

Antimicrobial agent	Acinetobacter spp. (53)	Pseudomonas spp. (51)	Other NF-GNB (75)
Amoxicillin/clavulanic acid	5 (9.43%)	19 (37.25%)	35 (46.66%)
Ceftazidime	45 (84.90%)	37 (72.55%)	65 (86.66%)
Ceftriaxone	28 (52.83%)	32 (62.74%)	66 (88%)
Cefotaxime	48 (90.56%)	21 (39.62%)	53 (70.66%)
Cefuroxime	7 (13.20%)	23 (45.09)	54 (72%)
Cefazolin	8 (15.09%)	35 (66.62%)	71 (94.66%)
Cefepime	42 (79.24%)	36 (70.58%)	61 (81.33%)
Ertapenem	7 (13.20%)	25 (49.01%)	62 (82.66%)
Imipenem	37 (69.81%)	21 (41.17%)	49 (65.33%)
Ciprofloxacin	42 (79.24%)	30 (58.52%)	37 (49.33%)
Meropenem	41 (77.35%)	26 (50.98%)	59 (78.66%)
Piperacillin/tazobactam	46 (86.79)	25 (49.02%)	69 (92%)
Tetracycline	-	9 (17.64%)	17 (22.66%)

* –not tested

Table 7
ANTIMICROBIAL RESISTANCE PATTERN OF NON-FERMENTING GNB (NUMBER AND PERCENTAGE)

After other researchers, *Coagulase-negative Staphylococci* (CoNS) and E coli were the most frequently isolated from patient samples [24].

Predominantly Gram-negative germs, found in our study, is consistent with the results of other researchers [19].

Consistent with our study, other investigators have reported also as the most common site of infection respiratory tract, urine and blood [3,19, 25-27].

Although antibiotics are considered to be the most effective method of fighting against infections, their empirical, indiscriminate, prolonged, or incorrect usage contributes significantly to the selection of MDR strains [28, 29, 30]. 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 [14].

A worrying phenomenon in Romania is also the existence of the MDR-TB and XDR-TB cases in socio-economic conditions (malnutrition, agglomeration, stress), with the doubling of number of cases of XDR-TB in the last years [31,32], including the cases of extrapulmonary tuberculosis which originates from the hematogenous metastatic affects developed during the prime TB infection period [33].

Our study revealed that over half of the strains of *Klebsiella* spp. are MDR, in the conditions in which, according to the European Antimicrobial Resistance Surveillance Network (EARS-Net), more than one third (34,5%) of the *Klebsiella pneumoniae* isolates reported in 2016 were resistant to at least one of the antimicrobial groups under regular surveillance (fluoroquinolones, third generation cephalosporins, aminoglycosides and carbapenems). Another study conducted by us it was observed also combined resistance to multiple antimicrobialgroups for *Klebsiella spp.*, isolated strains from of urine specimens [34].

In a research conducted by Radji et al [35]**,** *K. pneumoniae* was also found to be multidrug resistant to the third generation cephalosporins and quinolone antibiotics. An increasing carbapenem resistance rate for *Klebsiella, Acinetobacter and Pseudomonas* was reported in their study by Akter et al [24].

A small percentage of *E. coli* strains have been carbapenem resistant, consistent with EARS-Net. The results are consistent with analyses from the European Centre for Disease Prevention and Control [14].

For preventing transmission of resistant enterobacteriaceae the screening for carriers with subsequent isolation of those identified is effective. Infection prevention and control relies on the consistent application of some measures as hand hygiene, appropriate use of personal protective equipment, and ensuring a clean and well-maintained care environment [36].

More than two-thirds of MRSA strains have been MDR. The percentage is almost identical to the one identified in a prospective study performed in Romania by Licker at al, (66.51% MDR and 20.18% XDR *S.aureus* strains) [37]. The results are consistent also with other findings [3, 22], while *MRSA* remains a major cause of healthcare-associated infections worldwide, with higher percentages in the southern and south-eastern parts of Europe [38, 39].

In our research, both *Coagulase-negative Staphylococci* (CoNS) and *MRSA* showed resistance to penicillin in almost all patients, which is similar to another study conducted by Bathia et al**.** [19].

Although there were significant decreases of the mean percentages for fluoroquinolone resistance, aminoglycoside resistance and carbapenem resistance during the period 2013 to 2016 [34], our study found more than half of the *Pseudomonas* strains resistant to carbapenems and fluoroquinolones, outcomes consistent with other findings [3, 40-43].

In our study it was found a very high level of resistance of *Acinetobacter* strains to the carbapenems, cephalosporins, piperacillin-tazobactam and ciprofloxacin, which is consistent with the results from other studies [3, 44-46]. Antimicrobial resistant *Acinetobacter* spp is a public health concern due to the severe limitation of treatment and infection control options [38].

Our study draws attention to the very high percentage of NFB strains resistant to cephalosporins and carbapenems, almost all strains being MDR. Axente et al. [41]**,** in a study conducted also in Romania, revealed 69.95% resistant strains to penicillins (less frequently prescribed in ICUs in present).

This study only refers to infections in patients aged between 18-64 years, a category belonging to the active population, admitted to ICU, considering that they have high risk of acquiring HAIs, with highly resistant bacterial pathogens.

Conclusions

The study revealed an alarming pattern of antibiotic resistance in the majority of ICU isolates from patients aged between 18-64 years, with the risk as a part of these resistant strains to spread outside the hospital causing infections in the community.

To prevent the proliferation of MDR strains, the surveillance of antibiotic prescription and monitoring studies are necessary, together with direct communication between clinicians and microbiologists for adopting individual therapeutic measures and using appropriate antibiotics based on antibiogram.

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