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

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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), ceftazidime (30 µg), cefepime (30 µg), piperacillin-tazobactam (30 µg), imipenem (10 µg), meropenem (10 µg), ertapenem (10 µg), linezolid (30 µg), tetracycline (30 µg) penicillin (10 µg), erythromycin (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±STDDEV. The pattern of micro-organisms and gender/sites of infections were analyzed and expressed as percentages. The χ² 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
The predominant organism isolated from ICU were E. coli isolated from patient samples [9]. According to Akter et al. Staphylococci (CoNS) and E. coli were the most frequently isolated organism. 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 (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 et al. [10], the predominant organism isolated from ICU were E. coli (28%), followed by Klebsiella spp. (27%) and Acinetobacter spp. (17.3%).

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...
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 resistant Staphylococcus Aureus;

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     | %     |
| Acinetobacter      | 27      | 47.36 | 30    | 52.63 |
| NFB                | 42      | 43.15 | 54    | 56.85 |
| Citrobacter        | 1       | 20    | 4     | 80    |
| Enterobacter       | 7       | 70    | 3     | 30    |
| E. coli            | 49      | 49.49 | 56    | 50.50 |
| Haemophilus influenza | 1     | 100   | -     | -     |
| Klebsiella         | 79      | 45.14 | 96    | 54.85 |
| Pseudomonas        | 13      | 44.25 | 28    | 55.77 |
| Serratia           | 10      | 50    | 10    | 50    |
| CONS               | 10      | 50    | 10    | 50    |
| S. aureus          | 10      | 50    | 10    | 50    |
| MRSA               | 55      | 50.92 | 55    | 49.07 |
| Streptococcus pneumonia | 1  | 12.5  | 7     | 87.5  |
| Enterococcus       | 12      | 63.15 | 7     | 36.84 |
| Streptococcus sp.  | 2       | 66.66 | 1     | 33.33 |
| Total              | 388     | 100   | 418   | 100   |

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

| Sample                | Sputum/tracheal aspirate | Urine | Pur/wound swabs | Blood | Intravascular catheters | Exudate | Sterile fluids | Cerebrospinal fluid |
|-----------------------|---------------------------|-------|----------------|-------|-------------------------|---------|----------------|---------------------|
| Acinetobacter         | 48                        | 8     |                |       |                         |         |                |                     |
| NFB                   | 98                        | 3     | 4              | 1     |                         |         |                |                     |
| Citrobacter           | 4                         | 1     |                |       |                         |         |                |                     |
| Enterobacter          | 1                         | 9     |                |       |                         |         |                |                     |
| E. coli               | 51                        | 35    | 9              | 2     |                         |         |                |                     |
| Haemophilus influenza | 1                         |       |                |       |                         |         |                |                     |
| Klebsiella            | 143                       | 16    | 8              | 4     |                         | 3       | 1              |                     |
| Pseudomonas           | 25                        | 1     | 1              | 1     |                         | 1       |                |                     |
| Serratia              | 37                        | 6     | 3              | 1     |                         | 2       | 1              |                     |
| CONS                  | 72                        | 1     | 2              | 12    |                         |         |                |                     |
| S. aureus             | 11                        | 3     |                |       |                         |         |                |                     |
| MRSA                  | 77                        | 1     | 11             | 13    |                         | 4       | 4              |                     |
| Streptococcus pneumonia | 1                      |       |                |       |                         |         |                |                     |
| Enterococcus          | 18                        | 2     |                | 1     |                         |         |                |                     |
| Streptococcus sp.     | 572                       | 91    | 59             | 33    |                         | 4       | 7              | 7                  |
| Total                 | 593                       | 100   | 100            | 100   |                         | 100     | 100            | 100                 |

NFB- Glucose-nonfermenting Gram-negative bacilli, CONS – Coagulase-negative staphylococci, MRSA - Methicillin-resistant Staphylococcus Aureus;
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%)  |
| Cefazolin                      | 105 (60.57%)     | 24 (24.24%)  | -                 | 23 (65.71%)  |
| Ceftriaxone                    | 117 (66.82%)     | 28 (28.28%)  | 6 (60%)           | 21 (60%)     |
| Cefotaxime                     | 75 (42.35%)      | 12 (12.12%)  | -                 | 10 (28.57%)  |
| Cefuroxime                     | 105 (60.57%)     | 48 (48.48%)  | 9 (90%)           | 22 (65.71%)  |
| Ceftazolin                     | 144 (82.28%)     | 34 (34.34%)  | 8 (80%)           | 28 (74.28%)  |
| Cefepine                       | 107 (61.14%)     | 23 (23.23%)  | 3 (30%)           | 20 (57.14%)  |
| Imipenem                       | 44 (25.14%)      | 5 (5.05%)    | -                 | 11 (31.42%)  |
| Ciprofloxacin                  | 80 (43.71%)      | 32 (32.32%)  | 7 (70%)           | 18 (51.42%)  |
| Meropenem                      | 89 (50.35%)      | 16 (16.16%)  | -                 | 13 (37.14%)  |
| Piperacillin/tazobactam        | 116 (66.28%)     | -            | -                 | 21 (60%)     |
| Ertrapenem                     | 74 (42.28%)      | 29 (55.77%)  | -                 | 10 (28.57%)  |

*— not tested

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

| Antimicrobial agent | MRSA (108) | CoNS (87) | Enterococcus (19) |
|---------------------|------------|-----------|-------------------|
| Ciprofloxacin       | 71 (65.74%)| 64 (35.36%)| 14 (73.68%)       |
| Chloramycin         | 83 (78.70%)| 69 (75.31%)| -                 |
| Clavulanicin        | 71 (65.74%)| 31 (35.53%)| -                 |
| Doxicinose          | 52 (59.77%)| 40 (45.97%)| -                 |
| Erythromycin        | 86 (79.62%)| 67 (75.81%)| -                 |
| Linezolid           | 2 (1.83%)  | 1 (1.15%)  | 1 (5.26%)         |
| Penicillin          | 103 (95.37%)| 82 (97.10%)| 13 (68.42%)       |
| Rifampicin          | 51 (47.22%)| 60 (65.96%)| -                 |
| Tetracycline        | 76 (70.37%)| 70 (80.46%)| 12 (63.15%)       |
| Teicoplanin         | 15 (12.03%)| 6 (5.89%)  | -                 |

*— not tested

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

| Antimicrobial agent       | Acinetobacter spp. (57) | Pseudomonas spp. (52) | Other NF-CoNS (96) |
|---------------------------|--------------------------|-----------------------|--------------------|
| Amoxicillin/clavulanic acid | 6 (10.52%)               | 19 (36.53%)           | 41 (42.70%)        |
| Cefazolin                 | 50 (86.86%)              | 39 (73.57%)           | 84 (31.7%)         |
| Ceftriaxone               | 31 (11.71%)              | 34 (63.38%)           | 6 (60%)            |
| Cefotaxime                | 49 (51.90%)              | 15 (30.33%)           | 63 (65.62%)        |
| Ceftazolin                | 9 (3.52%)                | 27 (51.92%)           | 87 (90.22%)        |
| Ceftazolin                | 43 (75.42%)              | 39 (75%)              | 79 (22.25%)        |
| Cefepime                  | 4 (7.01%)                | 25 (45.77%)           | 75 (78.12%)        |
| Imipenem                  | 42 (73.68%)              | 19 (36.53%)           | 53 (55.20%)        |
| Ciprofloxacin             | 44 (71.19%)              | 29 (55.77%)           | 43 (44.79%)        |
| Meropenem                 | 42 (73.68%)              | 31 (59.61%)           | 71 (80.30%)        |
| Piperacillin/tazobactam   | -                        | -                     | 83 (86.42%)        |
| Tetracycline              | -                        | -                     | 23 (22.39%)        |
K. pneumoniae 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 cefepime, 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 cefazidime 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, around 80% to clindamycin, tetracycline and erythromycin, 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 cefazidime and cefepime. 36.53% from the strains were resistant to imipenem and between 55-60% to ciprofloxacin, meropenem and ertapenem (table 6). The resistance to cefazidime and cefepime observed in our study was similar to that of a previous report on multidrug-resistant Pseudomonas aeruginosa, which also revealed that 90% 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 bacteria 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 (≥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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