https://doi.org/10.31925/farmacia.2020.3.17 **ORIGINAL ARTICLE**

ANTIBIOTIC RESISTANCE IN COMMUNITY-ACQUIRED PNEUMONIA. A ROMANIAN PERSPECTIVE

IONUȚ EMILIAN BLEJAN [1#], CAMELIA CRISTINA DIACONU [2#], ANDREEA LETIȚIA ARSENE [1], DENISA IOANA UDEANU [1#], MANUELA GHICA [1]*, DOINA DRĂGĂNESCU [1], GEORGE TRAIAN ALEXANDRU BURCEA DRAGOMIROIU [1], MIHAELA RĂDULESCU [3], HELENA C. MALTEZOU [4], ARISTIDES M. TSATSAKIS [5], MARIA PAPASAVVA [6], NIKOLAOS DRAKOULIS [6], DANIELA ELENA POPA [1]

[1] *"Carol Davila" University of Medicine and Pharmacy, Faculty of Pharmacy, Bucharest, Romania*
[2] *"Carol Davila" University of Medicine and Pharmacy, Clinical Emergency Hospital of Bucharest, Romania*
[3] *University of Economic Studies, Bucharest, Romania*
[4] *National Public Health Organization, 15123, Athens, Greece*
[5] *University of Crete, Medical School, Department of Toxicology and Forensic Sciences, 74100, Rethymno, Greece*
[6] *Research Group of Clinical Pharmacology and Pharmacogenomics, Faculty of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, 15771, Zografou, Greece*

**corresponding author: manuela.ghica@umfcd.ro*
[#] *Authors with equal contribution.*

Manuscript received: August 2019

Abstract

Community-acquired pneumonia (CAP) is one of the most common communicable diseases with a high mortality rate worldwide. Treatment is administered empirically based on clinical symptoms and the most commonly incriminated microorganisms in lower respiratory infections responsible for CAP. This study aimed to identify microorganisms responsible for CAP in patients hospitalized in an Emergency Hospital in Bucharest, Romania; to assess the impact of patients' comorbidities and age on the survival level and to establish the degree of antimicrobial resistance of the most important isolated species. A total of 170 patients diagnosed with CAP from December 2017 through December 2018 were studied. Statistical analyses were performed considering the following data: survival rate, comorbidities, initiated pharmacotherapy, antibiogram results in case of refractory treatments. The overall survival rate was 36% among patients. Cardiovascular disease was incriminated as the highest risk factor. Concerning refractory antibiotic treatment, the microbiological results revealed that the most common bacterial strains detected were *Klebsiella sp., Acinetobacter baumanii, S. aureus, E. coli* and *Pseudomonas,* with high multiple antibiotic resistance (MAR) index. The results point out a real concern for patients with refractory CAP due to high antimicrobial resistance to the administered antibiotics in Romania.

Rezumat

Pneumonia comunitară (PC) este una dintre cele mai frecvente boli transmisibile cu o rată mare de mortalitate la nivel mondial. Tratamentul este administrat empiric pe baza simptomelor clinice și a microorganismelor cel mai frecvent incriminate în infecțiile respiratorii inferioare responsabile de PC. Acest studiu a urmărit identificarea microorganismelor responsabile de PC la pacienții internați într-un spital de urgență din București, România; pentru a evalua impactul comorbidităților și vârstei pacienților asupra nivelului de supraviețuire și a stabili gradul de rezistență antimicrobiană a celor mai importante specii izolate. Au fost studiați 170 de pacienți diagnosticați cu PC din decembrie 2017 până în decembrie 2018. Analizele statistice au fost efectuate ținând cont de următoarele date: rata de supraviețuire, comorbiditățile, farmacoterapia inițiată, rezultatul antibiogramei în cazul tratamentelor refractare. Rata de supraviețuire globală a fost de 36% în rândul pacienților. Boala cardiovasculară a fost incriminată drept cel mai mare factor de risc. În ceea ce privește tratamentul cu antibiotice refractare, rezultatele microbiologice au relevat că cele mai frecvente tulpini bacteriene detectate au fost *Klebsiella sp., Acinetobacter baumanii, S. aureus, E. coli* și *Pseudomonas,* cu un indice MAR (*multiple antibiotic resistance*) ridicat. Rezultatele subliniază importanța particulară a pneumoniei refractare datorită rezistenței antimicrobiene la antibioticele administrate în România.

Keywords: community-acquired pneumonia; antibiotic resistance; multiple antibiotic resistance index

Introduction

Community-acquired pneumonia (CAP) is an acute infection of the lower respiratory tract with a high mortality rate worldwide. The diagnosis of community-acquired pneumonia can be established in patients without any contact with hospitals or other health care settings over a 3 months period before hospitalization [1, 2].

CAP is one of the most common causes of hospitalization for an infectious disease worldwide. A retrospective study from the Netherlands undertaken between 2008 and 2011 pointed out an incidence of 295 cases of CAP *per* 100,000 persons *per* year [3]. In USA, approximately 650 patients with CAP per 100,000 population are diagnosed yearly and 9% of these patients are hospitalized at least once more during the same year due to a new episode of CAP [4, 5].

The main risk factors for CAP are older age, viral respiratory infections, smoking, excessive alcohol consumption, chronic comorbidities (such as chronic obstructive pulmonary disease, asthma, bronchiectasis, congestive heart failure, diabetes mellitus, immunosuppressive diseases, stroke), or factors related to the lifestyle (living in shelters, institutionalized elderly patients, exposure to toxins) [6-8].

The aetiology of CAP includes: typical microorganisms, atypical microorganisms, and respiratory viruses. The typical microorganisms involved are *Staphylococcus aureus*, aerobic Gram-negative bacteria, group A streptococci, or microaerophilic bacteria. Other microorganisms, such as *Legionella spp., Chlamydia pneumoniae, Mycoplasma pneumoniae, Chlamydia psittaci, Coxiella burnetti*, are those resistant to beta-lactams or those that cannot be cultured by traditional methods or cannot be visualized in Gram stain. Apart from influenza and rhinovirus, the viral agents involved in the pathophysiology of CAP may be parainfluenza viruses, adenoviruses, coronaviruses and respiratory syncytial viruses. The prevalence of these microorganisms depends on the geographical area, the season, the vaccination rates and the host comorbidities [9-13].

Despite the increasing use of microbiological tests and molecular diagnostic tests, in half of the cases of CAP, the pathological agent cannot be identified, meaning that treatment may be empirical [5, 14].

CAP complications occur especially in patients with various comorbidities, the most common being respiratory failure, bacteraemia with antibiotic resistant germs or fungus from *Aspergillum* or *Fusarium* genus, parapneumonic pleurisy and rarely, pulmonary abscess [15 - 18].

Selection of empiric antibiotherapy should be based on the proper antimicrobial resistance pattern knowledge in a particular geographical area, correlated with specific individual risk factors. Thus, the treatment targets the most probable microorganisms involved, such as: *Streptococcus pneumoniae, Haemophylus influenzae, Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella sp.*, etc. [1, 12, 19, 20].

In this context, the objectives of the present study are: i) to identify the microorganisms that produced CAP in patients hospitalized in an Emergency Hospital from Bucharest, Romania; ii) to establish the degree of antimicrobial resistance of the most important isolated species and iii) to assess the impact of patients' comorbidities and age on the survival level.

Materials and Methods

Subjects

The study was conducted between December 2017 and December 2018 and included a total of 170 patients consecutively hospitalized with CAP, during this time, at the Department of Internal Medicine within the Clinical Emergency Hospital, Bucharest, Romania.

The inclusion criteria considered the patients diagnosed with CAP without any contact with hospitals or other health care settings over a 3 months period before hospitalization [1, 2]. The exclusion criteria considered the patients which had been in contact with health care units or hospitals, three months prior diagnosis.

Each patient included in the study provided written informed consent. The study was conducted in accordance with the World Medical Association Declaration of Helsinki and was approved by the Institutional Ethics Committee of Clinical Emergency Hospital of Bucharest.

Sputum samples were collected and the microbiological analyses were performed by classical bacteriological diagnosis. The antimicrobial testing was performed by disc diffusion according to the guidelines of the Clinical and Laboratory Standards Institute [21].

Statistical analysis

Biostatistical analysis was implemented using the R statistical software (R version 3.5.3). For a relevant statistical analysis, antibiotic resistance was calculated as the ratio between the number of isolates identified as resistant over the total number of isolates tested for a particular antibiotic [15, 22].

Antibiotic resistance was also associated with multiple antibiotic resistance index (MAR) as a continuous type variable, computed for each isolate tested. MAR was calculated as a ratio between the number of antibiotics at which the isolate was resistant over the total number of tested antibiotics [15, 22].

The continuous variables were compared using Student's *t*-test for two groups. For more than two analysed groups we use one-way or two-ways analysis of variance (ANOVA) depending on the situation, followed by multiple comparisons, if the p-value indicated statistically significant differences ($a = 0.05$). Categorical variables had been analysed by Pearson-type tests.

Results and Discussion

Data were collected from 170 patients (male to female ratio 1:1) and the survival rate was 36% among patients. The first part of the research focused on individuals suffering from pneumonia and different comorbidities impact in relation to survival level. Nine comorbidities were identified among patients (Figure 1).

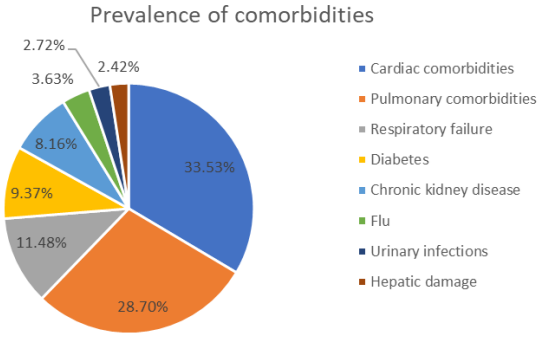


Figure 1.
The prevalence of comorbidities among the CAP diagnosed patients

Comorbidities with a particularly serious individual survival impact (Pearson's Chi-squared test with Yates' continuity correction) were cardiac ($P < 0.001$), pulmonary ($P < 0.001$), respiratory ($P < 0.01$) and diabetes ($P < 0.05$) (Figures 1 and 2). Flu and renal diseases did not influence the survival rate of the patients ($P > 0.05$).

The prevalence of comorbidities reveals that the most common, in descending order, are: cardiac comorbidities 33.53%, pulmonary comorbidities 28.7%, respiratory failure 11.5%, diabetes 9.37%, kidney disease 8.16%, the rest of them being rare, under 4% (Figure 1 and 2).

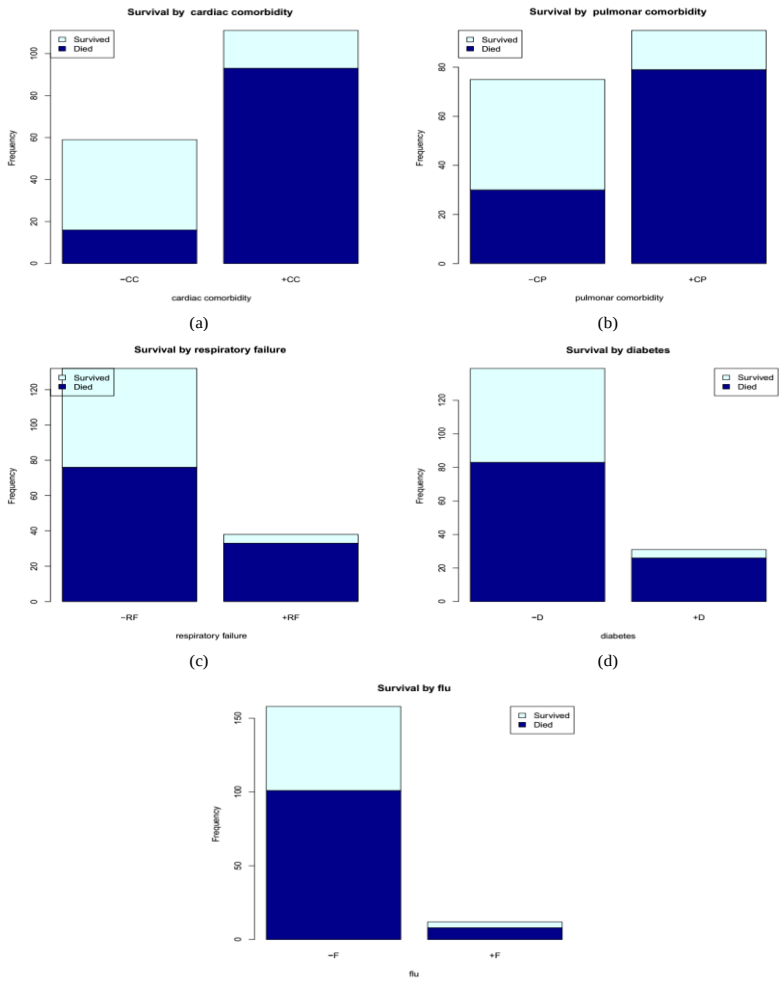


Figure 2.
Survival rate among patients with CAP according to the presence/absence of cardiac comorbidities (CC) (a), pulmonary comorbidities (CP) (b), respiratory failure (RF) (c), diabetes (D) (d) and flu (F) (e)

A significant impact was observed among survivors in relation to the age factor ($P = 0.012$). (Figure 3). The survival of individuals was investigated according to the number of comorbidities encountered in each study participant and a particularly significant impact was noticed ($P < 0.001$). The maximum number of comorbidities encountered was 6, in a patient who did not survive. (Figure 4).

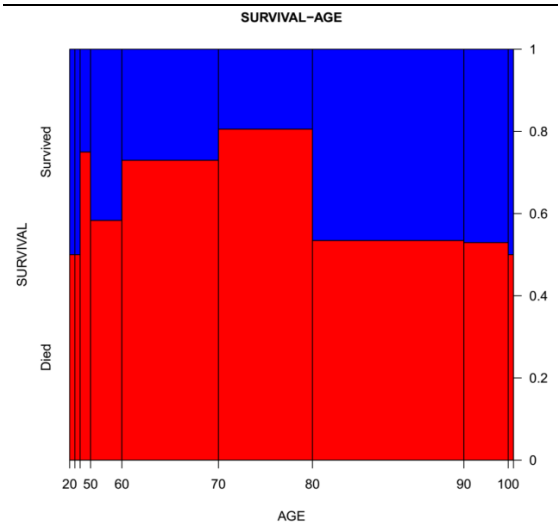


Figure 3.
The survival rate according to age in CAP patients

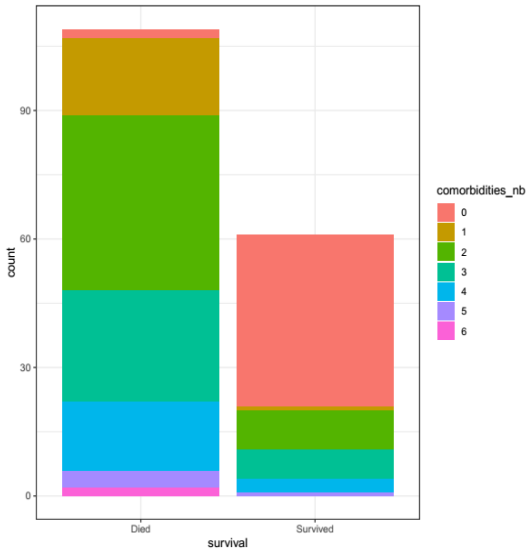


Figure 4.
The survival rate according to the comorbidities number in CAP patients

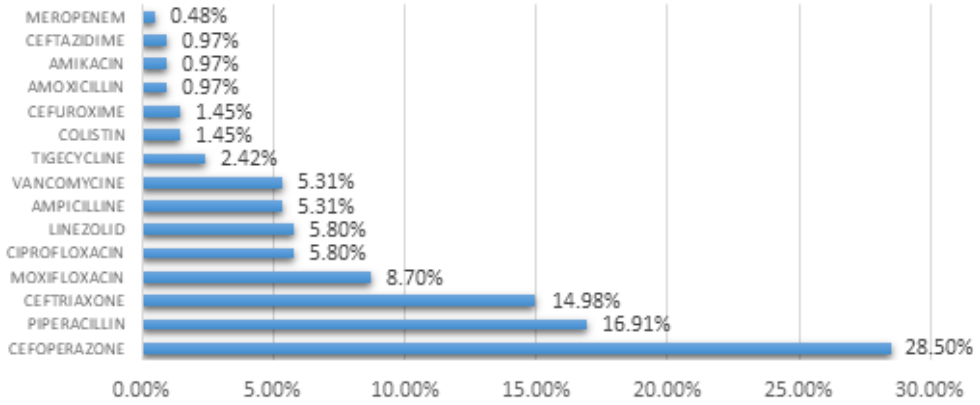


Figure 5.
The most prescribed antibiotics for the CAP patients included in this study according to the empirical based guidelines recommendations

Fifteen antibiotics were prescribed for the treatment, including the following antibiotic classes: cephalosporins, penicillins, fluoroquinolones or new generation antibiotics like linezolide and tigecycline.

The most commonly used were cefoperazone 28.50%, piperacillin 16.91%, ceftriaxone 14.98%, An important variety within the therapeutic schemes was encountered, with a statistically significant difference (Chi test one sample, $P < 0.001$) between the prescribed drugs (Figure 5).

Thirteen bacterial strains were detected in 29 patients. The most prevalent strains identified were: *Klebsiella* (23.25%), *Acinetobacter baumannii* (18.6%), *S. aureus* (13.95%), *E. coli* (11.62%) and *Pseudomonas* (11.62%), while *Enterobacter*, *Serratia*, *Providencia*, *Proteus*, *Morganella*, *Moraxella*, *Enterococcus*, *Citrobacter* were identified in a relatively, small percentage, < 5% (Figure 6).

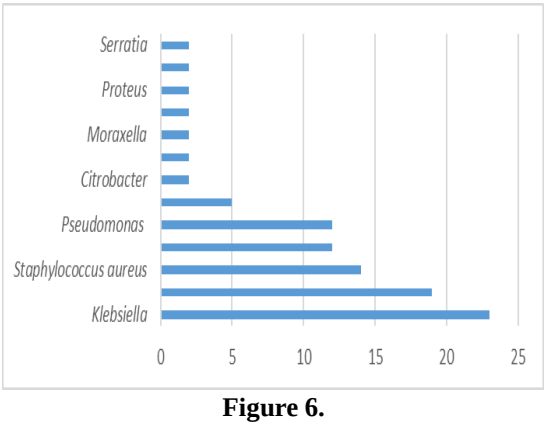


Figure 6.
The prevalence of the bacterial strains in the antibiogram in CAP patients

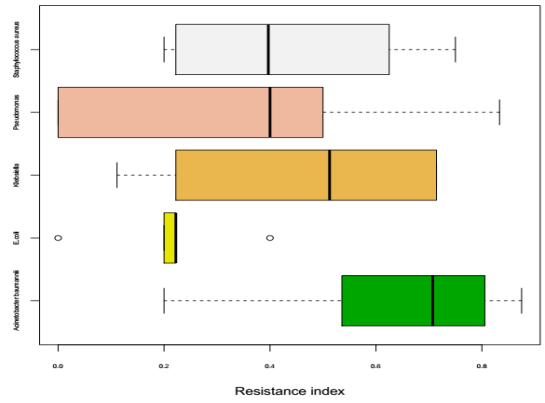


Figure 7.
The resistance index of the most prevalent bacterial strains in CAP patients

One-way ANOVA with Welch correction was used for the comparison of MAR index of the most prevalent bacterial strains (P = 0.013) followed by Tukey's multiple comparisons. A significant difference (P = 0.042) was detected between the least resistant strain of *E. coli* (median MAR = 0.222) and the most resistant *Acinetobacter baumannii* (median MAR = 0.707) (Figure 7).

Klebsiella strains showed absolute resistance to ampicillin (100%), high resistance to amoxicillin (88%), ciprofloxacin (60%) and sensitivity (100%) to amikacin, meropenem, tigecycline (Figure 8)

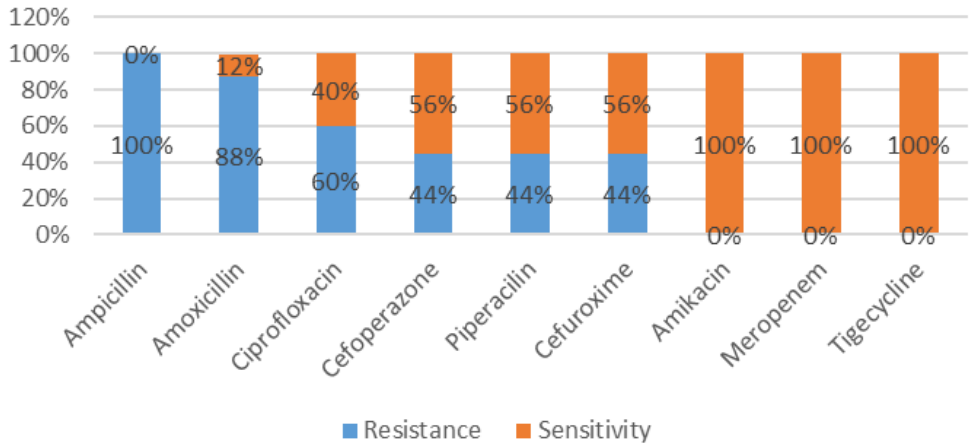


Figure 8.
Resistance/sensitivity antibiotic profile determined for *Klebsiella sp*.

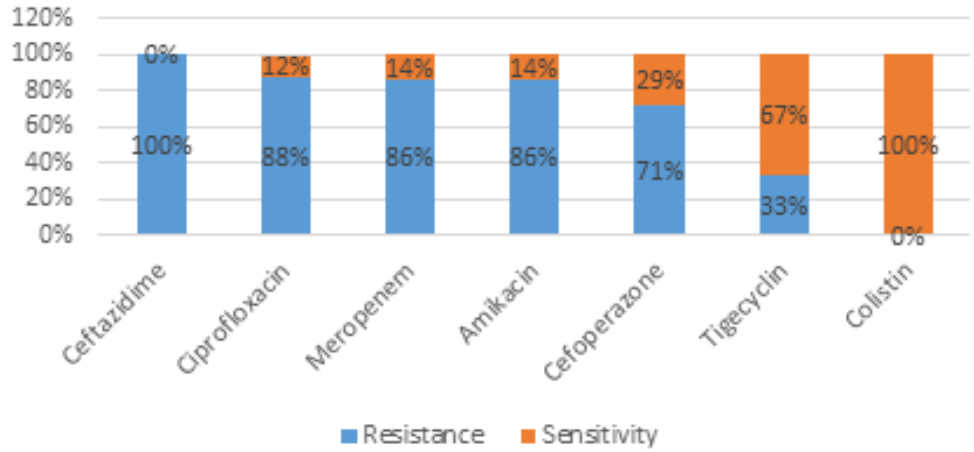


Figure 9.
Resistance/sensitivity antibiotic profile determined for *Acinetobacter baumannii*

Antimicrobial susceptibility tested for *Acinetobacter baumannii* demonstrated absolute resistance to ceftazidime (100%), high resistance to ciprofloxacin (88%), meropenem (86%), amikacin (86%), cefoperazone (71%) and low levels of resistance to tigecycline (33%) and colistin (0%) according to Figure 9

Staphylococcus aureus strains were 100% resistant to ampicillin, 67% amoxicillin and 60% piperacillin. No resistance (0%) was detected for vancomycin, tigecycline and linezolid (Figure 10).

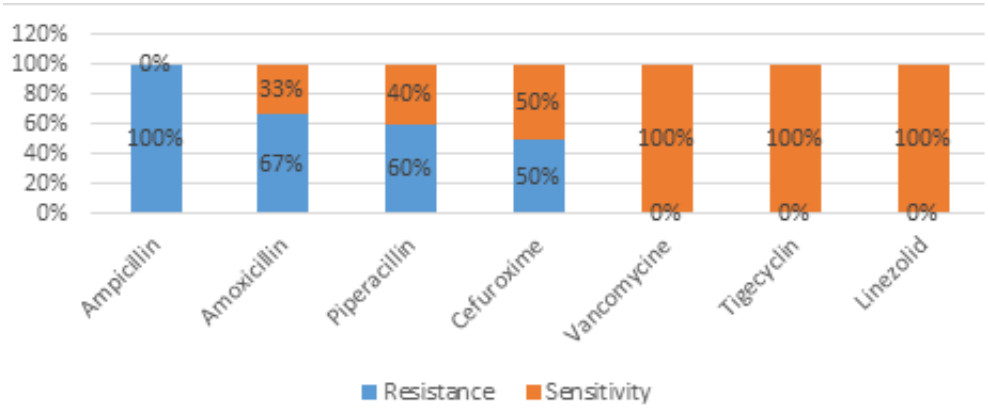


Figure 10.
Resistance/sensitivity antibiotic profile determined for *Staphylococcus aureus*

E. coli sensitivity profile (Figure 11) revealed a high level of resistance to Ampicillin and Amoxicillin (80%) and antimicrobial activity for Amikacin, Cefoperazone, Meropenem, Piperacillin and Tigecycline.

In the case of *Pseudomonas* strains, the analyses (Figure 12) revealed high-level resistance to ciprofloxacin and ceftazidime (75%), a decreased resistance to meropenem (20%) and sensitivity to piperacillin and colistin.

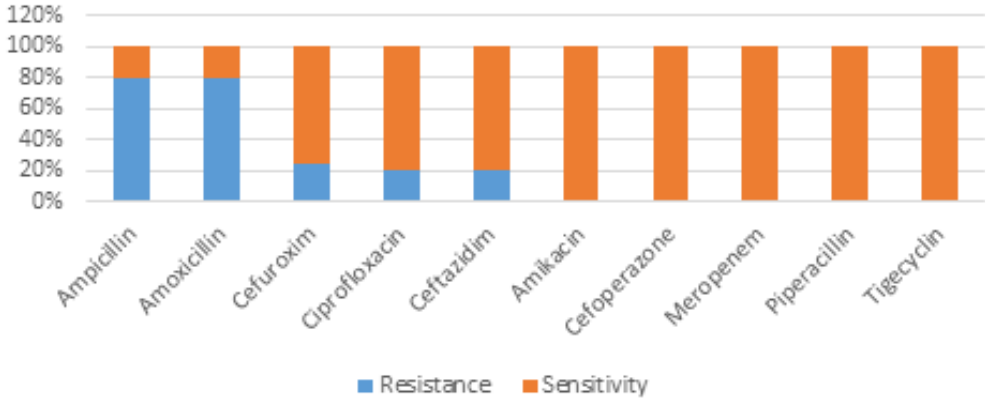


Figure 11.
Resistance/sensitivity antibiotic profile determined for *Escherichia coli*

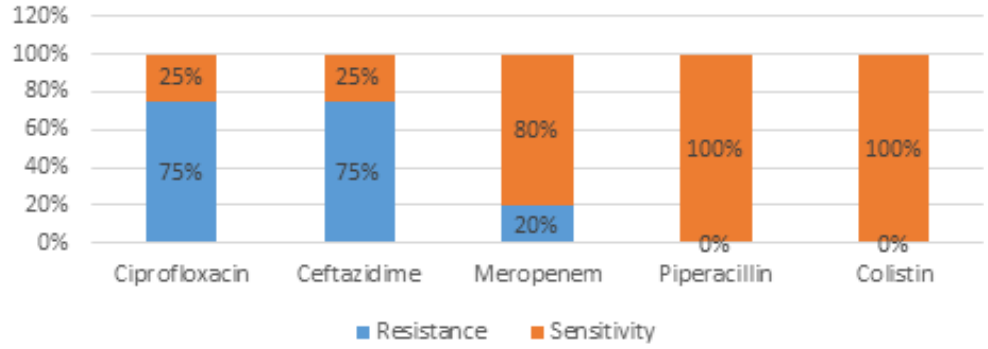
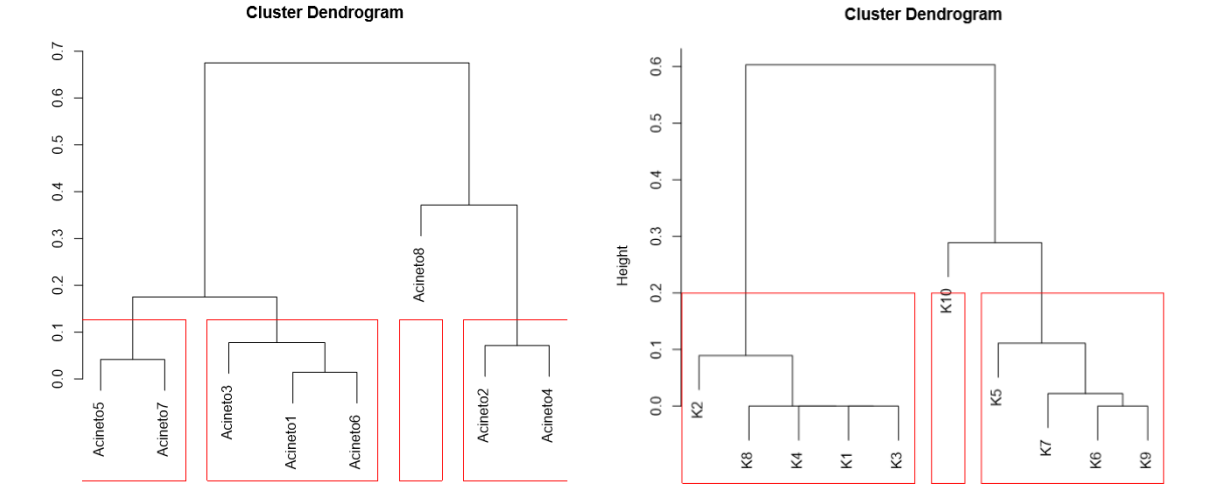


Figure 12.
Resistance/sensitivity antibiotic profile determined for *Pseudomonas* sp.

The clustering analysis showed 4 clusters for *Acinetobacter baumannii*; two in the sensitive area, probably with slightly decreased resistance and 2 in the high resistance area. (Figure 13a). *Klebsiella* analysis highlighted 3 clusters, one in the sensitive area and 2 in the high resistance area. (Figure 13b).



(a) (b)

Figure 13.
Cluster analysis of resistance for *Acinetobacter baumannii* (a) and *Klebsiella pneumoniae* (b)

Community acquired pneumonia is an infectious disease with a high mortality rate worldwide. Patient survival is affected by several factors like age and associated comorbidities. The aetiology of CAP includes most often bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, or viral pathogens, such as influenza or rhinovirus. In a large proportion of cases, the pathologic agent remains unidentified, despite a complete microbiological workup [23, 24]. During the last years, changes in the prevalence of different etiological agents of CAP were observed. Due to the widespread use of pneumococcal vaccination, a decline of CAP prevalence with *S. pneumoniae* has been observed [10, 25]. The prevalence of CAP with *S. pneumoniae* is higher in Europe than in the USA (30% *versus* 10 - 15%), where the vaccination rates are also higher [25]. Nowadays, respiratory viruses are highly evoked as causes of CAP, based on the present available molecular diagnostic methods [14].

Due to the difficulties in the identification of the involved pathogenic microorganisms, guidelines recommend empirical antibiotic treatments, targeting the most probable bacterial strains [5, 26].

The patients' survival rates in the current study were decreased mainly in the case of those aging between 60 - 80 years old. Comorbidities encountered among patients and cardiovascular diseases were incriminated as the highest risk factor for CAP patients' outcome.

Microbiological analyses were required in case of refractory antibiotic treatments. The results revealed that the most common bacterial strains detected were *Klebsiella sp.*, *Acinetobacter baumanii*, *S. aureus*, *E. coli* and *Pseudomonas.* These types of pathogens are more commonly encountered in nosocomial infections and quite rare in CAP, according to the most recent clinical studies published. [1, 5, 27].

Among all European countries, Greece also faces one of the highest rates of carbapenem-resistant in Gram-negative bacteria [28]. In particular, from January 2011 through June 2012 a total of 7477 cases of carbapenem-resistant infections were notified in the frame of an Action Plan to combat infections due to carbapenem-resistant, Gram-negative pathogens, which translates to a mean incidence of 0.48 *per* 1,000 patient-days, and an associated crude 28-day mortality of 34.4% was recorded [28]. In response to these alarming indexes, the second phase of the Action Plan was implemented in all hospitals across the country, consisting of enhanced standard infection control practices, isolation of carriers and infected patients from non-carriers, and strict implementation of contact precautions [28]. Another concern about the bacteria resistance pattern resides in the geographical factors in the actual context of migration and different health systems intersections [29].

The antibiogram of the bacterial strains responsible for the treatment resistant CAP cases exhibit a concerning resistance profile to the more commonly recommended and prescribed antibiotics like Amoxicillin, Ampicillin and Ciprofloxacin [1, 25, 27, 30].

The results of the present study showed that the most prescribed antibiotics were cephalosporines, penicillines and fluoroquinolenes but resistant strains were identified for some representatives of these classes.

The bacteria from the ESKAPE group (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp.*) were identified in CAP patients. This group of bacterial strains are not specific for this disease [7, 31, 32]. The highest antibiotic resistance according to MAR (multiple antibiotic resistant index) was detected for *Acinetobacter baumanii*, *Klebsiella* sp. and *S. aureus*, which are part of the ESKAPE

group, namely the bacterial strains with known resistance to the present antibiotic treatment schemes. Several strains showed resistance to Meropenem and Amikacin, which were considered a solution to the refractory treated patients, raising real future concerns for the CAP diagnosed patients.

Conclusions

The present study pointed out a high mortality rate among patients diagnosed with community acquired pneumonia in Bucharest, Romania. The low survival rate depended on the age, associated comorbidities and the microorganisms responsible for the respiratory infection. In case of the refractory CAP, the microbiological analyses were performed and the results revealed the presence of some strains, specific for the nosocomial infections (*Acinetobacter baumanii*, *Klebsiella* sp., *Escherichia coli*, *S. aureus* and *Pseudomonas sp.*) with high resistance to the most commonly prescribed antibiotics.

To understand the pathogenic and clinical features of CAP, especially in the case of difficult to eradicate germs with high bacterial resistance, long-term clinical, genetic and epidemiological studies are required. It is imperative to establish a nation-wide surveillance system for resistant and multi-drug resistant pathogens in healthcare facilities and the community, in order to guide interventions. Patterns of antibiotic prescription in ambulatory services and hospitals should also be studied. The results of this study may be useful in drawing up "bacterial resistance maps".

Acknowledgement

This work was financially supported by “Carol Davila” University of Medicine and Pharmacy through Contract no. 23PFE/17.10.2018 funded by the Ministry of Research and Innovation within PNCDI III, Program 1 – Development of the National RD system, Subprogram 1.2 – Institutional Performance – RDI excellence funding projects.

Conflict of interest

The authors declare no conflict of interest.

References

1. Prina E, Ranzani OT, Torres A, Community-acquired pneumonia. *The Lancet*, 2015; 386(9998): 1097-1108.
2. Quan TP, Fawcett NJ, Wrightson JM, Finney J, Wyllie D, Jeffery K, Jones N, Shine B, Clarke L, Crook D, Walker AS, Peto TE, Infections in Oxfordshire Research Database (IORD), Increasing burden of community-acquired pneumonia leading to hospitalisation, 1998-2014. *Thorax*, 2016; 71(6): 535-542.
3. Rozenbaum MH, Mangen MJ, Huijts SM, van der Werf TS, Postma MJ, Incidence, direct costs and duration of hospitalization of patients hospitalized with community acquired pneumonia: A nationwide retrospective claims database analysis. *Vaccine*, 2015; 33(28): 3193-9.
4. Ramirez JA, Wiemken TL, Peyrani P, Arnold FW, Kelley R, Mattingly WA, Nakamatsu R, Pena S, Guinn BE, Furmanek SP, Persaud AK, Raghuram A, Fernandez F, Beavin L, Bosson R, Fernandez-Botran R, Cavallazzi R, Bordon J, Valdivieso C, Schulte J, Carrico RM, University of Louisville Pneumonia Study Group, Adults hospitalized with pneumonia in the United States: Incidence, epidemiology, and mortality. *Clin Infect Dis.*, 2017; 65(11): 1806-1812.
5. Restrepo MI, Aliberti S, ERS guideline compliant antibiotics among hospitalized patients with Community-acquired pneumonia on the ward service. *Eur Resp J.*, 2018; 52(Suppl 6): PA2036.
6. Almirall J, Serra-Prat M, Bolíbar I, Balasso V, Risk factors for community-acquired pneumonia in adults: A systematic review of observational studies. *Respiration*, 2017; 94(3): 299-311.
7. Self WH, Wunderink RG, Williams DJ, Zhu Y, Anderson EJ, Balk RA, Fakhran SS, Chappell JD, Casimir G, Courtney DM, Trabue C, Waterer GW, Bramley A, Magill S, Jain S, Edwards KM, Grijalva CG, *Staphylococcus aureus* Community-acquired pneumonia: Prevalence, clinical characteristics, and outcomes. *Clin Infect Dis.*; 2016; 63(3): 300-309.
8. Simonetti AF, Garcia-Vidal C, Viasus D, García-Somoza D, Dorca J, Gudiol F, Carratalà J, Declining mortality among hospitalized patients with community-acquired pneumonia. *Clin Microbiol Infect.*, 2016; 22(6): 567.e1-567.e7.
9. Tavassoli M, Afshari A, Drăgănescu D, Arsene AL, Burykina TI, Rezaee R, Antimicrobial resistance of *Yersinia enterocolitica* in different foods. A review. *Farmacia*, 2018; 66(3): 399-407.
10. Cilloniz C, Martin-Loeches I, Garcia-Vidal C, San Jose A, Torres A, Microbial etiology of pneumonia: Epidemiology, diagnosis and resistance patterns. *Int J Mol Sci.*, 2016; 17(12): 1-18.
11. Cillóniz C, Torres A, Niederman M, van der Eerden M, Chalmers J, Welte T, Blasi F, Community-acquired pneumonia related to intracellular pathogens. *Intens Care Medicine*, 2016; 42(9): 1374-1386.
12. Dumke R, Schnee C, Pletz MW, Rupp J, Jacobs E, Sachse K, Rohde G, Capnetz Study Group, *Mycoplasma pneumoniae* and *Chlamydia* spp. infection in community-acquired pneumonia, Germany, 2011-2012. *Emerg Infect Diseas.*, 2015; 21: 426-434.
13. Voicu M, Cristescu C, Zbârcea CE, Voicu A, Buda V, Suciu L, Suciu M, Proks M, Bild V, Comparative study of antimicrobials use and the antibiotic resistance of Gram negative strains. *Farmacia*, 2017; 65(2): 225-229.
14. Gadsby NJ, Russell CD, McHugh MP, Mark H, Conway Morris A, Laurenson IF, Hill AT, Templeton KE, Comprehensive molecular testing for respiratory pathogens in community-acquired pneumonia. Version 2. *Clin Infect Dis.*, 2016; 62(7): 817-823.
15. Arghir OC, Alves Pereira PM, Rașcu A, Dantes E, Borgazi E, Iliescu DM, Oțelea MR, Cambrea SC, The impact of migrant tuberculosis on the chimioresistance pattern of antituberculosis drugs in a low burden tuberculosis European country. *Farmacia*, 2018; 66(3): 537-540.

16. Tanase A, Colita A, Ianosi G, Neagoe D, Branisteanu DE, Calina D, Docea AO, Tsatsakis A, Ianosi SL, Rare case of disseminated fusariosis in a young patient with graft vs. host disease following an allogeneic transplant. *Exp Ther Med.*, 2016; 12(4): 2078-2082.
17. Ungureanu A, Zlatian O, Mitroi G, Drocaş A, Ţîrcă T, Călina D, Dehelean C, Docea AO, Izotov BN, Rakitskii VN, Cioboată R, Spandidos DA, Tsatsakis AM, Găman A, *Staphylococcus aureus* colonisation in patients from a primary regional hospital. *Mol Med Rep.*, 2017;16(6): 8771-8780.
18. Zlatian O, Balasoiu AT, Balasoiu M, Cristea O, Docea AO, Mitrut R, Spandidos DA, Tsatsakis AM, Bancescu G, Calina D, Antimicrobial resistance in bacterial pathogens among hospitalised patients with severe invasive infections. *Exp Ther Med.*, 2018; 16(6): 4499-4510.
19. Allan R, Martin SW, Al-Haddad M, Community-acquired pneumonia. *Anaest Intens Care Medicine*, 2016; 17: 510-513.
20. Faverio P, Aliberti S, Bellelli G, Suigo G, Lonni S, Pesci A, Restrepo MI, The management of community-acquired pneumonia in the elderly. *Eur J Intern Med.*, 2014; 25(4): 312-319.
21. Kassim A, Omuse G, Premji Z, Revathi G. Comparison of Clinical Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing guidelines for the interpretation of antibiotic susceptibility at a University Teaching Hospital in Nairobi, Kenya: A cross-sectional study. *Ann Clin Microbiol Antimicrob.*, 2016; 15: 1-7.
22. Călina D, Docea AO, Rosu L, Zlatian O, Rosu AF, Anghelina F, Rogoveanu O, Arsene AL, Nicolae AC, Drăgoi CM, Tsiaoussis J, Tsatsakis AM, Spandidos DA, Drakoulis N, Gofita E, Antimicrobial resistance development following surgical site infections. *Mol Med Rep.*, 2017; 15(2): 681-688.
23. Kara S, Akçay MŞ, Ekici Ünsal Z, Bozkurt Yılmaz HE, Habeşoğlu MA, Comparative analysis of the patients with community-acquired pneumonia (CAP) and health care-associated pneumonia (HCAP) requiring hospitalization. *Tuberk Toraks.*, 2019: 67(2): 108-115.
24. Yamana H, Matsui H, Tagami T, Hirashima J, Fushimi K, Yasunaga H, De-escalation *versus* continuation of empirical antimicrobial therapy in community-acquired pneumonia. *J Infect.*, 2016; 73(4): 314-325.
25. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, Reed C, Grijalva CG, Anderson EJ, Courtney DM, Chappell JD, Qi C, Hart EM, Carroll F, Trabue C, Donnelly HK, Williams DJ, Zhu Y, Arnold SR, Ampofo K, Waterer GW, Levine M, Lindstrom S, Winchell JM, Katz JM, Erdman D, Schneider E, Hicks LA, McCullers JA, Pavia AT, Edwards KM, CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among US adults. *N Engl J Med.*, 2015; 373(5): 415-427.
26. Uranga A, España PP, Bilbao A, Quintana JM, Arriaga I, Intxausti M, Lobo JL, Tomás L, Camino J, Nuñez J, Capelastegui A, Duration of antibiotic treatment in community-acquired pneumonia: a multicenter randomized clinical trial. *JAMA Internal Medicine*, 2016; 176(9): 1257-1265.
27. File TM, Community-acquired pneumonia. *The Lancet*, 2003; 362(9400): 1991-2001.
28. Maltezou HC, Kontopidou F, Dedoukou X, Katerelos P, Gourgoulis GM, Tsonou P, Maragos A, Gargalianos P, Gikas A, Gogos C, Koumis I, Lelekis M, Maltezos E, Margariti G, Nikolaidis P, Pefanis A, Petrikkos G, Syrogiannopoulos G, Tsakris A, Vatopoulos A, Saroglou G, Kremastinou J, Daikos GL, Working Group for the National Action Plan to Combat Infections due to Carbapenem-Resistant, Gram-Negative Pathogens in Acute-Care Hospitals in Greece. Action Plan to combat infections due to carbapenem-resistant, Gram-negative pathogens in acute-care hospitals in Greece. *J Global Antimicrob Resist*., 2014; 2(1): 11-16.
29. Maltezou HC, Theodoridou M, Daikos GL, Antimicrobial resistance and the current refugee crisis. *J Global Antimicrob Resist.*, 2017; 10: 75-79
30. Handy LK, Bryan M, Gerber JS, Zaoutis T, Feemster KA, Variability in antibiotic prescribing for community-acquired pneumonia. *Pediatrics*, 2017; 139(4): 1-10.
31. Founou RC, Founou LL, Essack SY, Clinical and economic impact of antibiotic resistance in developing countries: A systematic review and meta-analysis. *PLoS ONE*, 2017; 12(12): 1-18.
32. Lee JS, Giesler DL, Gellad WF, Fine MJ, Antibiotic therapy for adults hospitalized with community-acquired pneumonia: a systematic review. *JAMA*, 2016; 315(6): 593-602.