# Carbapenem-Resistant Klebsiella Pneumoniae Associated with COVID-19


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*antibiotics*

MDPI

*Case Report*

# Carbapenem-Resistant *Klebsiella Pneumoniae* Associated with COVID-19

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**Abstract:** Infections with carbapenem-resistant *Enterobacteriaceae* are emerging as an important challenge in healthcare settings. Currently, carbapenem-resistant *Klebsiella pneumoniae* (CRKP) are the species of CRE most commonly encountered in hospitals. CRKP is resistant to almost all available antimicrobial agents, and infections with CRKP have been associated with high rates of morbidity and mortality, particularly among persons with prolonged hospitalization exposed to invasive devices. We report nine patients hospitalized in an intensive care unit (ICU) with severe coronavirus disease 2019 (COVID-19) who developed invasive infections due to carbapenemase-producing *Klebsiella pneumoniae* (CP-Kp), KPC and OXA-48, strains that have not been previously identified in our hospital. Despite ceftazidime/avibactam therapy, five patients died. Coinfections can contribute to a poor prognosis for patients with COVID-19, especially for high-risk populations such as elderly patients. Therefore, it is crucial to establish a rigorous program of antibiotic administration in intensive care units.

# Introduction

- Bacterial infections associated with viral infections are a major cause of morbidity and mortality.
- In previous influenza epidemics, secondary bacterial infections were found in 30% of cases, especially in intensive care units, and the germs most commonly associated with influenza infection were
  - Streptococcus pneumoniae,
  - Staphylococcus aureus
  - Streptococcus pyogenes

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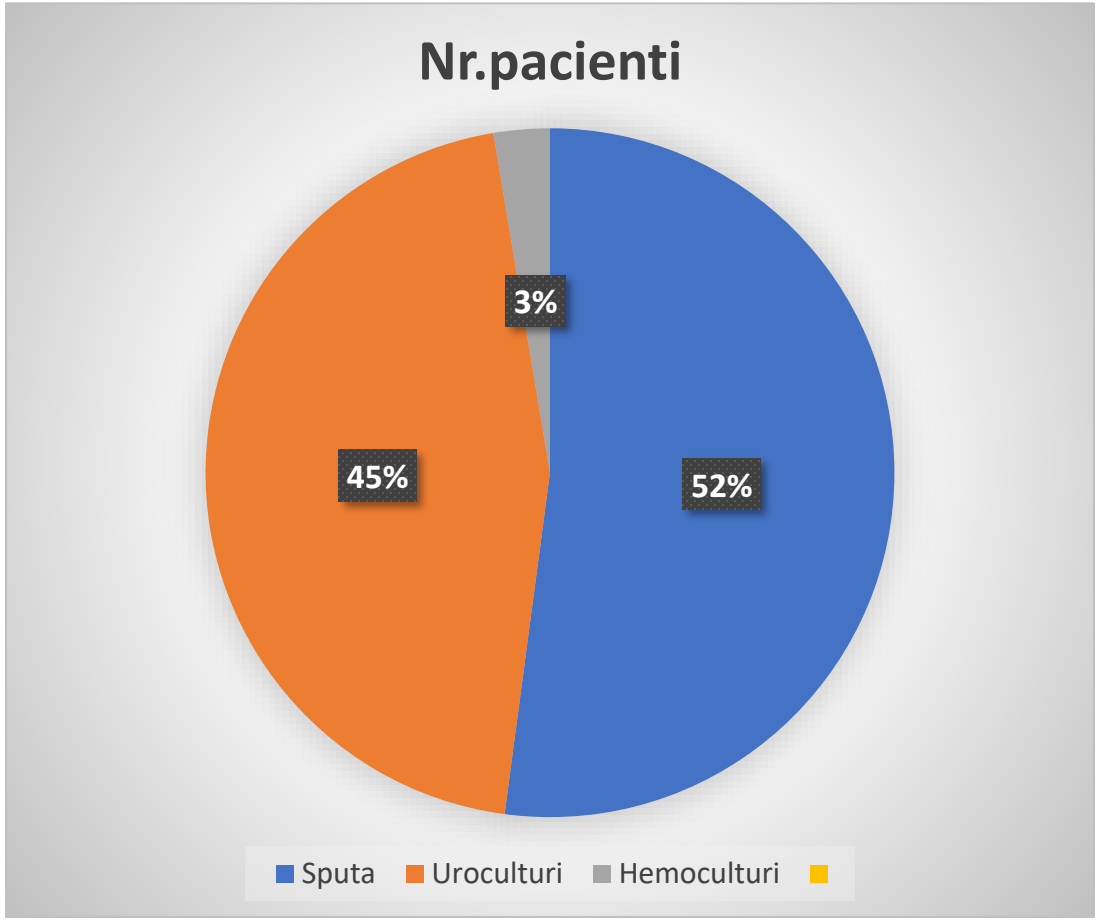
- A meta-analysis by Langford et al., published in 2020, showed that, in the case of 3338 patients hospitalized for COVID-19, a secondary bacterial infection was present in 6.9% of cases and was more common in critically ill patients (13.8%).

- The most common bacteria were
  - Mycoplasma pneumoniae
  - Gram-negative germs
    - ESBL-positive Klebsiella pneumoniae,
    - ESBL-positive Pseudomonas aeruginosa,
    - carbapenem-resistant Klebsiella pneumoniae
    - highly resistant Acinetobacter baumannii

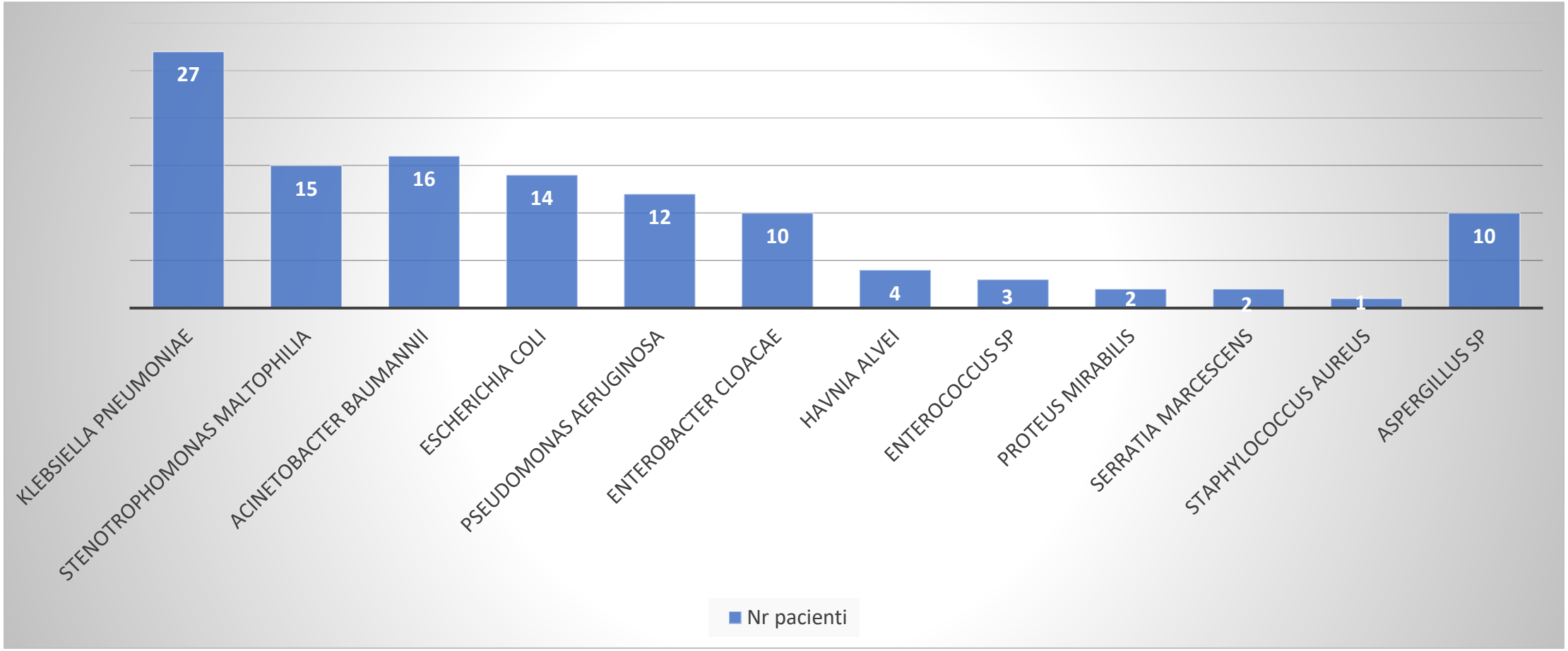
Langford, B.J.; So, M.; Raybardhan, S.; Leung, V.; Westwood, D.; MacFadden, D.R.; Soucy, J.-P.R.; Daneman, N. Bacterial co-infection and secondary infection in patients with COVID-19: A living rapid review and meta-analysis. Clin. Microbiol. Infect. **2020**, 26, 1622–1629. [

# Spitalul de Boli Infectioase Constanta martie – octombrie 2020

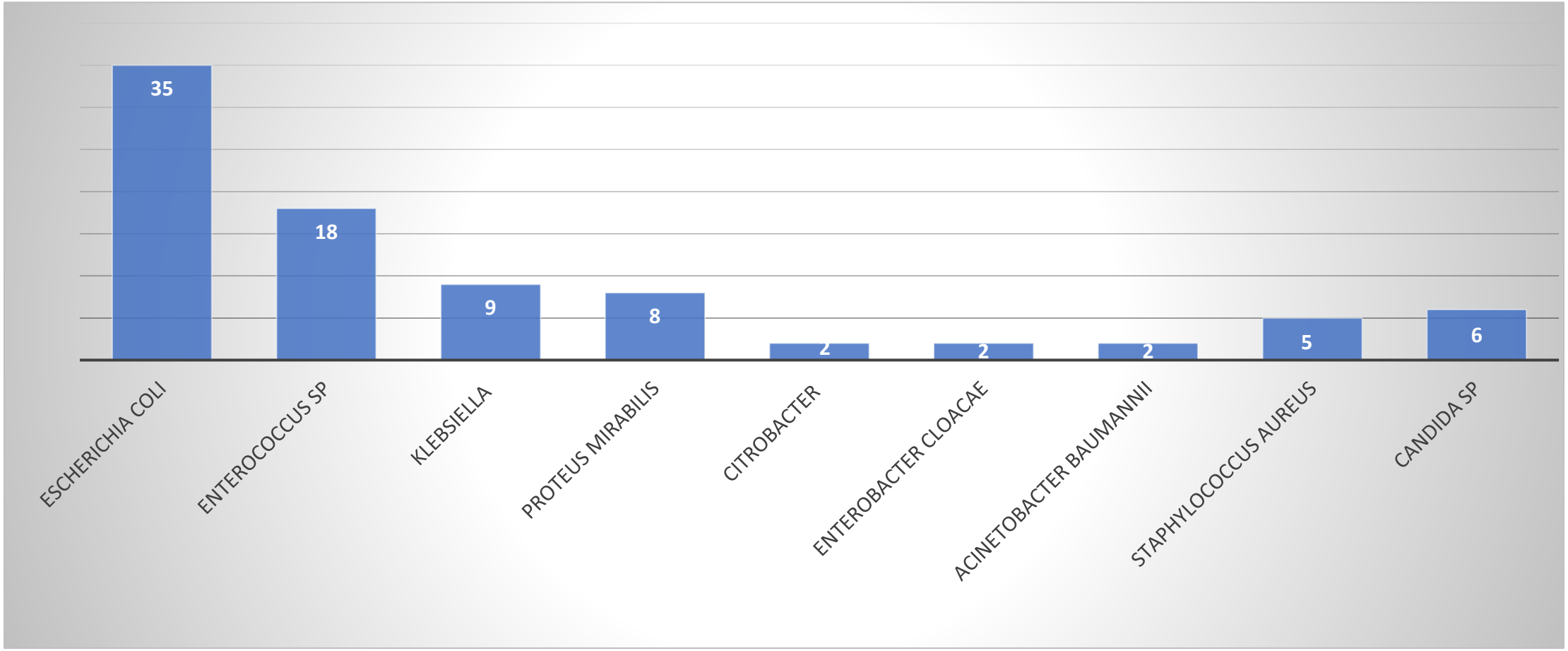
- 1573 pacienti spitalizati
- 190 pacienti cu infectii bacteriene/fungice (12%)
  - 99 ex sputa
  - 86 uroculturi
  - 5 hemoculturi



# Etiologie – ex sputa



# Etiologie – Uroculturi




Candida albicans – 1 pt, Candida krusei -2 pts Candida glabrata – 3 pts

- Infection with **carbapenem-resistant Enterobacteriaceae (CRE)** or carbapenemase-producing Enterobacteriaceae is emerging as an important challenge in health-care settings.
  - *Escherichia coli*,
  - *Enterobacter aerogenes*,
  - *Enterobacter cloacae* complex,
  - *Klebsiella pneumoniae*
  - *Klebsiella oxytoca*.

- Ambler clasification - three major classes of enzymes are involved in carbapenem resistance:
  - class A carbapenemases (K. pneumoniae carbapenemase, KPC)
  - class B metallo-β-lactamases (MBL),
  - class D β-lactamases (OXA-48-like carbapenemases)

- Klebsiella pneumoniae spp. are asymptomatic colonizers of the human gastrointestinal tract and common opportunistic human pathogens
  - Klebsiella pneumoniae carbapenemases OXA-48, encoded by blaOXA-48
  - Klebsiella pneumoniae carbapenemases KPC, encoded by blaKPC

Munoz-Price, L.S.; Poirel, L.; Bonomo, R.A.; Schwaber, M.J.; Daikos, G.L.; Cormican, M.; Cornaglia, G.; Garau, J.; Gniadkowski, M.; Hayden, M.K.; et al. Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. Lancet Infect. Dis. **2013**, 13, 785–796.

- Risk factors for acquisition and infection

  - Multiple comorbidities (malignancy, congestive heart failure, chronic lung disease,chronic kidney disease and diabetes);
  - long-term antimicrobial treatment;
  - critical illness;
  - various invasive devices (mechanical ventilation, urinary catheter, central vascular access, dialysis and endoscopy);
  - transfusion events
  - exposure to other colonized patients

# Materials and Methods

- Nine critically ill patients admitted to the ICU wards in our hospital for SARS-CoV-2 infection were enrolled in the present study.

- The identification of the Klebsiella strains, testing of the antimicrobial susceptibility and characterization of the CRKP isolates was performed with the automatic systems MALDI-TOF MS 1000, VITEK 2-Compact 15 and diffusimetric, using ROSCO confirmatory discs.

- The antimicrobial susceptibility was interpreted in accordance with the European Committee for Antimicrobial Sensitivity Testing (EUCAST) 2021.

# Results

- Out of 25 positive biological products for multidrug-resistant germs, CRKP were detected in nine patients only in the ICU (36%).
  - 11.1% Klebsiella Pneumoniae strains from COVID-19 patients were positive for the blaOXA-48 gene (from sputum);
  - 44.4% were positive for the blaKPC gene (two from sputum, one from urine and one from blood)
  - 55.5% were positive for the both genes blaKPC and blaOXA-48 from
  - sputum

| Pts | Sex | Age Years | Comorbidities | Clinical Forms COVID-19 | ETI | Immunosuppressive Treatment | Biologic Product | CRKP | Evolution |
|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 74 | heart failure, hypertension, atrial fibrillation, chronic kidney disease, anemia | critical | yes | 1, 2, 3, 4 | sputum | KPC, OXA-48 | death |
| 2 | F | 47 | hypertension breast cancer, hypothyroidism | severe | no | 1, 3, 4 | sputum | KPC, OXA-48 | good |
| 3 | F | 67 | myasthenia gravis, hypothyroidism | critical | no | 1, 2, 3, 4 | sputum | KPC, OXA-48 | death |
| 4 | M | 63 | hypertension, hypothyroidism obesity dyslipidemia | severe | no | 1, 3, 4 | urine | KPC | good |
| 5 | M | 75 | hypertension diabetes | severe | no | 1, 3, 4 | sputum | KPC, OXA-48 | death |
| 6 | F | 70 | hypertension, asthma heart failure, peripheral venous insufficiency | critical | no | 1, 2, 3, 4 | blood | KPC | death |
| 7 | M | 61 | hypertension | severe | no | 1, 2, 4 | sputum | KPC | good |
| 8 | F | 55 | hypertension, asthma, obesity | critical | no | 1, 2, 3, 4 | sputum | KPC | good |
| 9 | M | 73 | hypertension gastric ulcer chronic pancreatitis | severe | no | 1, 2, 4 | sputum | OXA-48 | death |

Legend: pts = patients, F = female, M = male and TI = endotracheal intubation. 1 = Dexamethasone, 2 = Tocilizumab, 3 = Anakinra and 4 = Hyperimmune plasma.

| Pts | Length of Stay in Hospital (Days) | Days of ICU Intake after Hospital Admission | Length of Stay in ICU (Days) | Day after Admission in Hospital CRKP Was Diagnosed | Antimicrobial Therapy before CRKP Confirmation |
|---|---|---|---|---|---|
| 1 | 25 | 7 | 18 | 9 | meropenem |
| 2 | 14 | 5 | 4 | 6 | levofloxacin |
| 3 | 30 | the patient was hospitalized only in ICU | 30 | 18 | meropenem + linezolid |
| 4 | 17 | 5 | 7 | 13 | ceftriaxone + doxycycline |
| 5 | 18 | the patient was hospitalized only in ICU | 18 | 8 | meropenem |
| 6 | 48 | 2 | 46 | 25 | meropenem + colistin |
| 7 | 10 | 3 | 4 | 11 | meropenem |
| 8 | 29 | 7 | 10 | 23 | meropenem |
| 9 | 18 | 7 | 11 | 12 | ceftriaxone + doxycycline |

Legend: pts = patients, CRKP—carbapenem-resistant *Klebsiella pneumoniae*. ICU—intensive care unit.

- After isolation of the blaKPC gene and the blaOXA-48 gene, ceftazidime/avibactam was administered
- five patients died; the unfavorable evolution towards death was correlated especially with
  - late diagnosis
  - ages over 70 years (median age—71.8 years),
  - the administration of tocilizumab
  - the presence of CRKP in the sputum and blood

| Antibiotics | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| Ampicillin | R | R | R | R | R | R | R | R | R |
| Amoxicillin–Clavulanic acid | R | R | R | R | R | R | R | R | R |
| Piperacillin–tazobactam | R | R | R | R | R | R | R | R | R |
| Cefotaxime | R | R | R | R | R | R | R | R | R |
| Ceftazidime | R | R | R | R | R | R | R | R | R |
| Cefepime | R | R | R | R | R | R | R | R | R |
| Ertapenem | R | R | R | R | R | R | R | R | R |
| Imipenem | R | R | R | R | R | R | R | R | R |
| Meropenem | R | R | R | R | R | R | R | R | R |
| Amikacin | R | R | R | R | S | S | S | R | S |
| Gentamicin | R | R | R | R | R | S | S | R | R |
| Ciprofloxacin | R | R | R | R | R | R | R | R | R |
| Fosfomycin | R | R | R | R | R | S | R | R | R |
| Sulfamethoxazole–Trimethoprim | S | R | R | S | R | R | R | S | R |
| Ceftazidime/avibactam | S | S | S | S | S | S | S | S | S |

R = resistant and S = sensitive.

# Discutions

The European Centre for Disease Control (ECDC) reported that, in Europe, 7.5% of Klebsiella pneumoniae isolated from blood cultures were resistant to carbapenems

In Romania

- Lixandru et al. (2015) analyzed, for the first time, the situation of CRKP infections and concluded that the carbapenemase most frequently detected is OXA-48, representing 79% of the CRKP strains.
- 2018 by Baicus et al. discovered that OXA-48 was the most frequently identified genotype in 73.77% of cases (45 isolates); only 1.63% (one isolate) presented blaOXA-48 and blaKPC,

# Discutions

With severe COVID-19 cases, the percentage of carbapenem resistant Klebsiella pneumoniae (CR-Kp) infections increased, leading to a higher mortality rate (30–70%).

The spread of multidrug-resistant (MDR) bacteria, especially Klebsiella MDR during the COVID-19 era, was facilitated by the increased consumption of antibiotics during this period.

International studies indicate that approximately 70% of hospitalized patients with COVID-19 receive antibiotics, most often with broad spectrums, despite a lack of evidence of bacterial coinfections

# Conclusions

In the ICU, the prevalence of KPC-Kp infections has increased significantly in the COVID-19 period compared to the non-COVID period (3.8%).

Coinfections can contribute to a poor prognosis for patients with COVID-19, especially for high-risk populations such as elderly patients.

Immunosuppressive treatments can lead to the unfavorable evolution of patients coinfected with COVID-19 and multidrugresistant Klebsiella.

- The results obtained show that we need to focus more on the CP-Kp infections among COVID-19 patients owing to their extreme fragility, probably linked to
  - immunosuppressive therapy, and
  - prolonged ICU hospitalization.

- Therefore, it is crucial to establish a rigorous program of antibiotic administration in intensive care units, as well as compliance with the universal precautions that lead to limiting the spread of germs.