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Venovenous extracorporeal membrane oxygenation (VV ECMO) in community-acquired pneumonia caused by Klebsiella pneumoniae. What went wrong?

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ABSTRACT

Despite the progress that has been made in the field of medicine, severe hypoxic respiratory failure due to pneumonia has significant mortality. The etiology of pneumonia can be very different but possible complications include sepsis and acute respiratory distress syndrome (ARDS), resulting in patient's increased risk of death. Severe respiratory failure in the course of ARDS, which does not respond to conventional therapy, is an indication for the implementation of venovenous extracorporeal membrane oxygenation support (VV ECMO). However, even with the use of targeted antibiotic therapy and advanced methods of extracorporeal life support, successful outcomes are not achieved. The location of the site of infection and the administration of targeted antibiotic therapy seem obvious to the patient's prognosis. Antimicrobial therapy can only succeed if a few basic conditions are met. First of

all, the right antibiotic should be used, given in the effective dose and as soon as possible after the onset of septic symptoms. In addition, the possibility of penetration of the active substance to the place affected by the inflammatory process also determines the probability of success of the therapy. This article presents a case report of Klebsiella pneumonia in a 38-year-old man and briefly discusses the challenges of modern medicine. In this case, the treatment was not successful, despite the known ethology, use of the targeted antibiotic therapy and advanced methods of extracorporeal life support. Further researches are needed to help improve treatment outcomes in this group, critically ill patients.

Key words: pneumonia, sepsis, acute respiratory distress syndrome, extracorporeal membrane oxygenation

1. INTRODUCTION

Pneumonia has been known for hundreds of years. Already in the fifth century BC it was described by Hippocrates. However, the greatest progress in understanding of lung diseases, including pneumonia, was associated with Rene Theophile Hyacinthe Laënnec – who, in 1816, invented the stethoscope. He also described the pathological symptoms present in the physical examination of patients with pneumonia [1, 2].

The most common pathogens for community-acquired pneumonia (CAP) in Poland are *Streptococcus pneumoniae* (30-42%), *Klebsiella pneumoniae* (20%), *Mycoplasma pneumoniae* (10-15%), *Chlamydophila pneumoniae* (3-40%) and *Haemophilus influenzae* (8-10%) [3]. *Klebsiella pneumoniae* is a pathogen that may be responsible for both community-acquired pneumonia and hospital-acquired pneumonia (HAP) [4]. This Gram-negative bacterium is sensitive to tigecycline, colistin and the aminoglycosides [5]. Unfortunately, the build-up of resistance among bacteria caused that strains producing enzymes with a expended spectrum of activity (extended-spectrum beta-lactamases; ESBL) appeared among the Klebsiella strain, which are only sensitive to carbapenems. In the absence of control over the use of antibiotics and their abuse, multidrug-resistant strains also appeared. This is particularly important for the treatment of infections in a hospital setting where carbapenem-resistant *Klebsiella pneumoniae* (CRKP) strains, which due to the production of carbapenemases, are very challenging to treat. In addition to pneumonia, they can cause bacteremias, pyogenic liver abscesses, urinary tract infections, endophthalmitis, and meningitis [6]. Infections of this kind can occur in every region of the world [7].

The patient being treated in the intensive care unit (ICU) is exposed to infection with the hospital flora and may develop HAP or ventilator-associated pneumonia (VAP) [8]. VAP is probably when occurs not earlier than 48 hours after the insertion of the endotracheal tube and is accompanied by changes in sputum/BAL, as well as positive quantitative/semiquantitative culture for pathogens. It is still one of the most common nosocomial infections in the intensive care units [9] and occurs in 9–27 % of patients with mechanical ventilation [10]. The most frequent pathogens that cause VAP are *Pseudomonas* spp. (24.4 %), *Staphylococcus aureus* (20.4 %, of which >50 % MRSA), Enterobacteriaceae (14.1 % – includes *Klebsiella* spp., *E. coli*, *Proteus* spp., *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp.), *Streptococcus* spp. (12.1 %), *Hemophilus* spp. (9.8 %), *Acinetobacter* spp. (7.9 %) [10].

Acinetobacter baumannii is an opportunistic pathogen, which is associated mainly with infections in cachectic, non-immunocompetent and critically ill patients [11]. Furthermore, according to the Infectious Diseases Society of America, this pathogen is one of the six most significant multidrug-resistant microorganisms in hospitals worldwide [12].

Pneumonia, regardless of a nosocomial or community-acquired etiology, can progress to acute respiratory distress syndrome (ARDS) [6]. When ARDS persists for a long enough

period and does not respond to conventional treatment and therapies, it may be an indication for the use of extracorporeal membrane oxygenation (ECMO) – one modality of Extracorporeal Life Support [13].

Another common complication of pneumonia is sepsis [14], which can cause organ dysfunction or even imminent danger to life. Antibiotic therapy is a causative treatment of infection, but even the identification of the etiological factor and the use of targeted antibiotic therapy does not guarantee a cure for serious infections.

This article reveals that despite the use of antibiotics according to antibiograms obtained in microbiological tests and using them in high doses, in some cases, treatment of pulmonary infection is ineffective.

2. CASE REPORT

A 38-year-old construction worker without previous medical history, after three days of outpatient treatment, was admitted to hospital with a diagnosis of right-sided lobar pneumonia. Empirical antibiotic therapy was included using ceftazidime and ciprofloxacin. After identifying the presence of *Klebsiella pneumoniae* in the respiratory tract, targeted antibiotic therapy was included. The chest CT revealed extensive areas of alveolar and interstitial infiltrates with the type of pulmonary tissue consolidation. Because of the presence of pleural fluid, the drain was inserted into the right pleural cavity. At the same time, due to the development of acute renal failure, renal replacement therapy was necessary. In view of the picture of deepening shock with multi-organ failure. After using all the possibilities of conventional therapy, on the seventh day of treatment, the patient was transferred to the ECMO Center for further treatment with the use of venovenous extracorporeal membrane oxygenation (VV ECMO).

On admission to the intensive care unit, the patient was in a critical condition – in septic shock and symptoms of multiorgan failure. According to APACHE II, one of several intensive care unit scoring systems, the patient scored 31 points which predicts death risk to be 87%.

On admission, arterial-blood gas test revealed respiratory acidosis: pH 7.09, P_aCO_2 80.6 mm Hg and oxygenation index PaO_2/FiO_2 1.0.

Immediate treatment was implemented using ECMO support. The patient required a noradrenaline infusion to stabilize the circulatory system and multimodal sedation, with the periodic use of muscle relaxants. In the first day, bronchoscopy was performed with the collection of material for microbiological examination. From the obtained bronchoalveolar lavage (mini-BAL) two pathogens were grown: *Klebsiella pneumoniae* and *Acinetobacter baumannii*. Targeted therapy was instituted: meropenem against *Klebsiella* and colistin against *Acinetobacter*.

A CT scan of the head revealed an area with an ischemic stroke image in the left hemisphere, in the occipital lobe. In turn, the chest CT showed the areas of the ground glass opacities in the left lung – mostly consolidated in the lower and perilous lobe. The right lung was largely airless with the bronchogram (mainly alveolar lesions). No findings in the CT of the abdominal cavity.

In the following days, intensive treatment was continued, including targeted antibiotic therapy, bronchoscopy, respiratory therapy, enteral nutrition, parenteral nutrition, alignment of water and electrolyte balance as well as acid-base balance. On the 18th day, for the stabilization of the circulatory system, an adrenaline infusion was added. The control chest CT and chest X-ray showed a progression of changes in the pulmonary parenchyma (Figures 1, 2). Despite the targeted antibiotic therapy, in the following cultures from the respiratory tract, the same bacteria were constantly isolated (*K. pneumoniae* and *A. baumannii*). The

extracorporeal life support, as well as other intensive care therapies, did not manage to keep the patient alive. The death occurred on the 33rd day of treatment.

The autopsy revealed necrosis, intravascular blood clots, atelectasis and infarction foci within the lungs, as well as numerous subpleural and central abscesses, which can be seen in the images (Figures 3, 4).

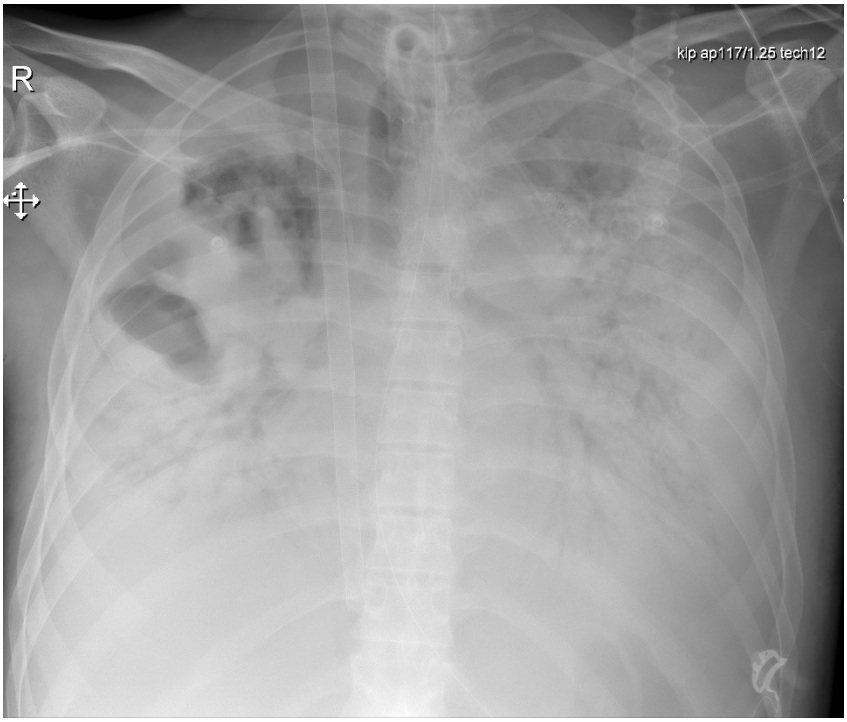

Figure 1. Chest X-ray revealing extensive infiltrates in the pulmonary tissue, areas of pneumothorax – due to which the patient had a drain to the right pleural cavity – and bicaval dual lumen cannula for ECMO.

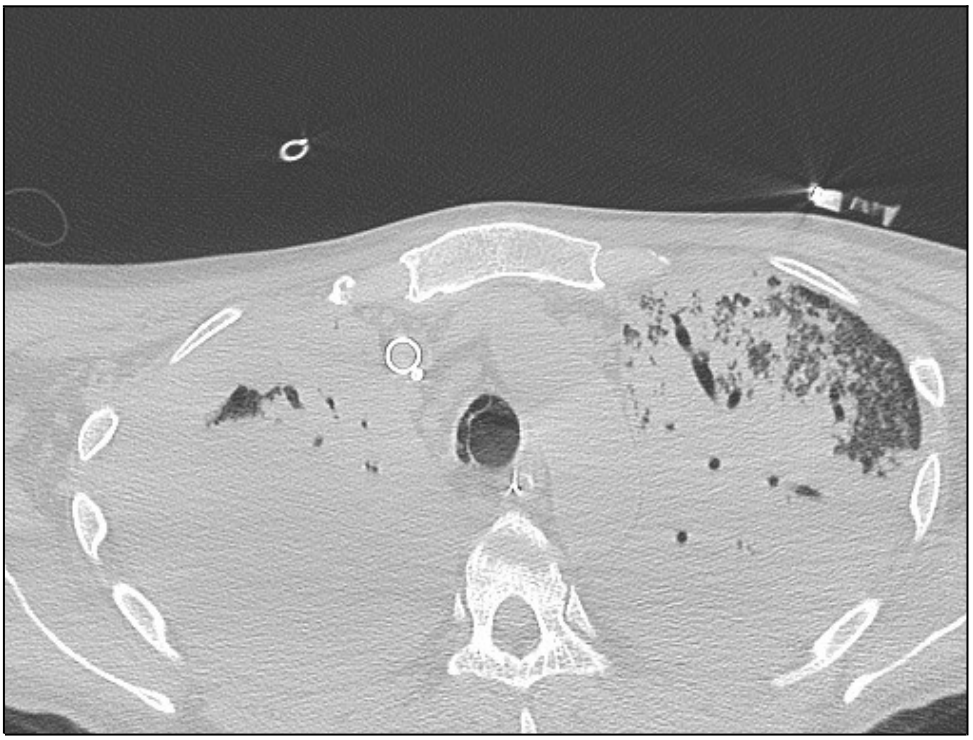

Figure 2. Chest CT showing airless pulmonary tissue with the bronchogram. CT – computed tomography.

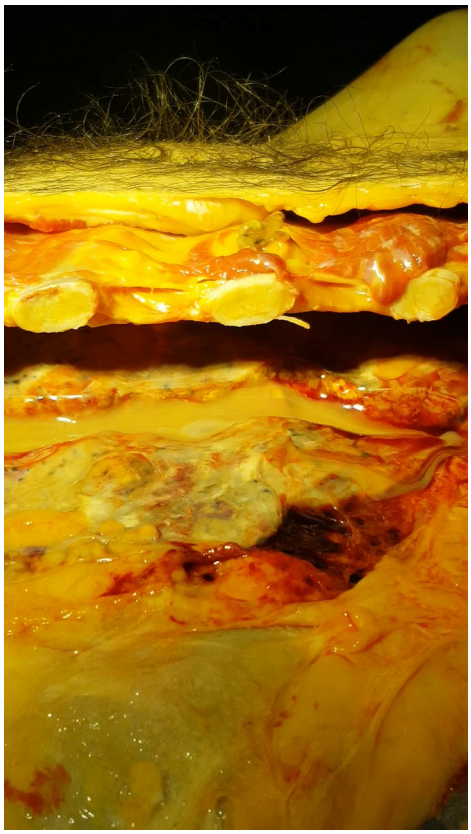

Figure 3. The picture of the right lung taken during autopsy.

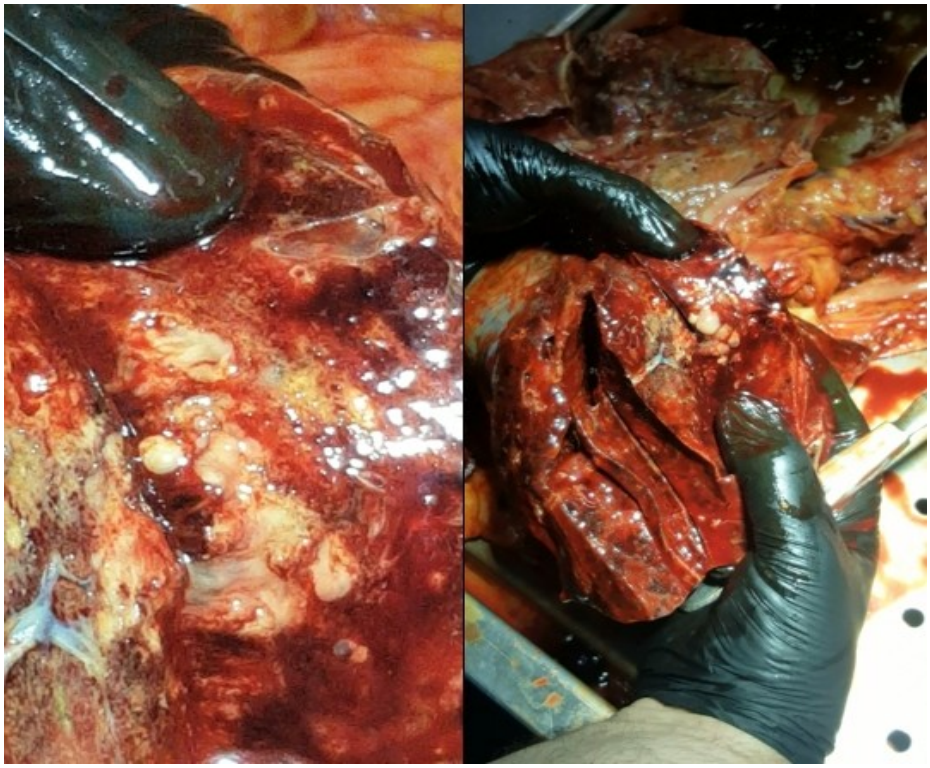

Figure 4. The picture of the left lung, where multiple abscesses were found.

3. DISCUSSION

One of the challenges for modern medicine is increasing resistance to antimicrobial agents. Based on reports from The European Centre for Disease Prevention and Control (ECDC), it can be concluded that the percentage of carbapenem-resistant strains of *Acinetobacter* spp. shows an upward trend. Generally, resistance is higher in the area of Eastern and Southern Europe. In 2015, Poland joined the group of countries in which the percentage of resistant strains exceeds 50%. Percentage of invasive isolates with resistance to carbapenems is shown in Figure 5 [15] and Figure 6 [16].

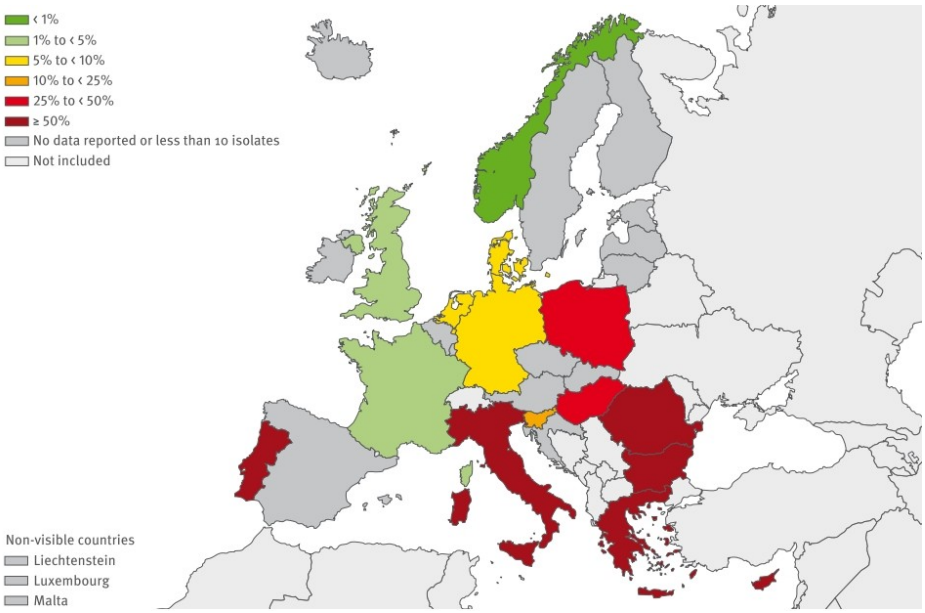

Figure 5. *Acinetobacter* spp. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/ EEA countries, 2012 [15].

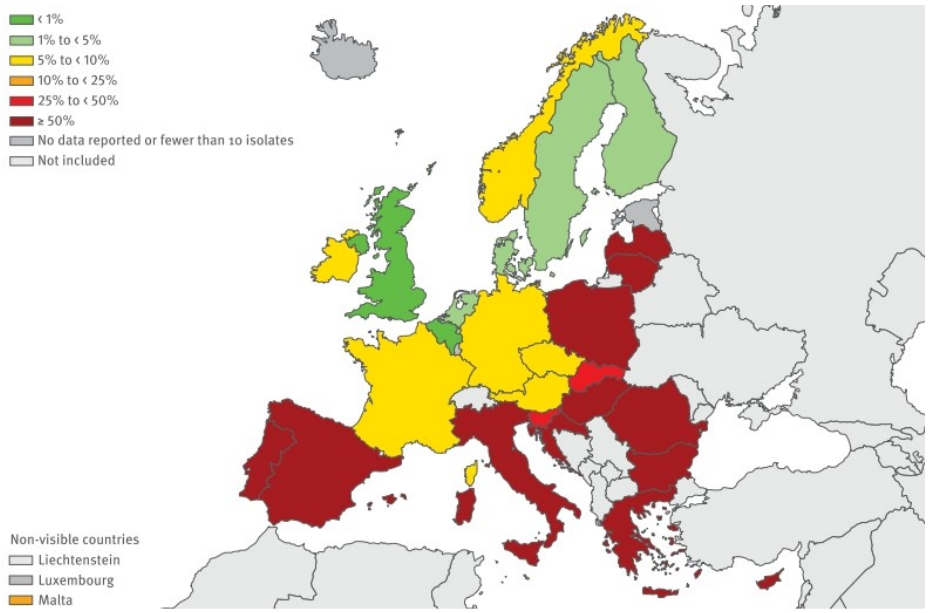

Figure 6. *Acinetobacter* spp. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2015 [16]

In this case, the treatment that resulted from the antibiogram was used, so other factors have had to contribute to the failure of therapy.

Another challenge for antimicrobial therapy is the problem of antibiotic penetration and obtaining the required concentration in the site of infections. Antibiotic doses are usually established among healthy volunteers or patients with mild or moderate infection. While the group of septic patients differs significantly from those previously mentioned due to changes in volume distribution (VD), in hemodynamics, changes in renal and hepatic excretion, or due to fluid overload. For this reason, there is no sign of equality between pharmacokinetics in healthy patients and pharmacokinetics in septic patients. In a study published by Joukhadar et al. [17], after administration of a single intravenous dose of 4.0 g piperacillin, the achieved concentrations of antibiotic in plasma and other fluid spaces were compared in six patients in septic shock and in six age- and gender-matched healthy volunteers. It turned out that the penetration of drugs into the interstitial fluid of muscular and fat tissues is clearly lower in septic patients.

To achieve the success of antibacterial therapy it is essential to identify the pathogen with its minimum inhibitory concentration (MIC). Then there is necessary to select the appropriate antibiotic and determine the site of infection. The last element is a patient whose body will still be able to respond to the treatment. And only when we use the appropriate antibiotic acting on the concrete pathogen, whose main focus of infection is known, and we treat the patient, in whose body the drug can adequately penetrate the fluid spaces, can the therapy of infection be successful [18].

ECMO is a device that does not cure, but gives time to conduct effective therapy, which is antibiotic therapy in the case of infections. In the absence of the effectiveness of antibiotic therapy and the inability to effectively fight the infection by the patient's immune system - therapy, as in the previously described case, is not effective. ECMO is a very invasive technique, hence the indications for the inclusion of therapy cannot be heroic [13]. Antibiotics as a causal treatment of infections should be used according to the principles of rational

antibiotic therapy, that is, at the right dose and as early as possible, but also as briefly as possible.

Despite the targeted antibiotic therapy, no progress was achieved, and the patient died.

4. CONCLUSIONS

In the case of a critically ill patient, despite the use of appropriate antibiotic therapy and advanced methods of extracorporeal life support, there is a high risk of treatment failure.

Several conditions must be met to achieve the therapeutic success of the infection. One of them certainly is antibiotic penetration. Penetration of antibacterial agents from plasma into interstitial fluid within the tissues that are involved in the disease process may turn out insufficient and preclude the success of the therapy.

Real-time drug monitoring can be an important factor increasing the probability of antibiotic therapy success.

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