CASE REPORT

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Acinetobacter baumannii Ventilator-Associated Pneumonia in critically ill patient with COVID-19 – Case Report and literature review

Zapalenie płuc u chorych wentylowanych mechanicznie wywołane przez *Acinetobacter baumannii* u krytycznie chorej pacjentki z COVID-19 – opis przypadku i przegląd literatury

Julia Siek[1,A-D] ✉, **Michał Borys**[2,E-F]

[1] *Student Scientific Club of 2nd Department of Anaesthesiology and Intensive Care, Medical University, Lublin, Poland*
[2] *2nd Department of Anaesthesiology and Intensive Care, Medical University, Lublin, Poland*
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Abstract

The onset of the COVID-19 pandemic originated from the city of Wuhan, the capital of Hubei province in central China. From there, the virus spread rapidly around the world. The World Health Organization (WHO) declared a pandemic on 11 March 2020. The COVID-19 pandemic has severely overburdened healthcare systems and led to huge economic losses. The rapid spread of the virus and the huge number of deaths meant that the need for sensitive, fast and accurate diagnostic technologies increased at this time. The main challenge facing the health service is the detection of asymptomatic cases, which are spreading rapidly in everyday interpersonal contacts. The virus is most commonly spread by droplets. The average incubation period is about 6.4 days. Characteristic symptoms among infected people include: fever, cough, shortness of breath, muscle pain or fatigue. SARS-CoV-2 infection can occur with varying intensity: asymptomatic, mild to moderate cases, severe cases, critical cases, and death. Patients with severe COVID-19 usually require endotracheal intubation and mechanical ventilation due to worsening respiratory failure. As a result of too long mechanical ventilation, bacterial infection often occurs, which can be fatal. The case report presents the causes of ventilator-associated pneumonia, and the risk of this complication in patients infected with COVID-19 based on a case report and literature review.

Key words

Acinetobacter baumannii, COVID-19, Ventilator-Associated Pneumonia

Streszczenie

Początku pandemii COVID-19 należy dopatrywać się w mieście Wuhan, stolicy prowincji Hubei w środkowych Chinach. Stamtąd wirus w zawrotnym tempie rozprzestrzenił się na cały świat. Światowa Organizacja Zdrowia (WHO) ogłosiła stan pandemii 11 marca 2020 roku. Pandemia COVID-19 w znacznym stopniu przeciążyła systemy opieki zdrowotnej i doprowadziła do ogromnych strat gospodarczych. Szybkie rozprzestrzenianie się wirusa i ogromna liczba zgonów spowodowały, że w tym czasie szczególnie wzrosło zapotrzebowanie na czułe, szybkie i dokładne technologie diagnostyczne. Głównym wyzwaniem stojącym przed służbą zdrowia jest wykrywanie przypadków bezobjawowych, które szybko szerzą się w codziennych kontaktach międzyludzkich. Wirus najczęściej przenosi się drogą kropelkową. Średni okres inkubacji to około 6,4 dnia. Do charakterystycznych objawów występujących wśród ludzi zakażonych zaliczamy: gorączkę, kaszel, duszność, bóle mięśni lub zmęczenie. Zakażenie SARS-CoV-2 może przebiegać z różnym natężeniem – występują przypadki bezobjawowe, przypadki łagodne do średnich, ciężkie przypadki, przypadki krytyczne oraz zakończone zgonem. Pacjenci z ciężkim COVID-19 przeważnie wymagają intubacji dotchawiczej i wentylacji mechanicznej z powodu nasilającej się niewydolności oddechowej. Często w wyniku zbyt długiej wentylacji mechanicznej dochodzi do zakażenia bakteryjnego, które może być fatalne w skutkach. Autorzy – na podstawie opisu przypadku i przeglądu literatury – przedstawiają przyczyny respiratorowego zapalenia płuc oraz ryzyko tego powikłania u pacjentów zakażonych COVID-19.

Słowa kluczowe

respiratorowe zapalenie płuc, *Acinetobacter baumannii*, COVID-19

✉ Address for correspondence: Julia Siek, Student Scientific Club of 2nd Department of Anaesthesiology and Intensive Care, Medical University, Lublin, Poland
E-mail: siekjj@gmail.com

INTRODUCTION

Most patients with a severe course of COVID-19 require endotracheal intubation and mechanical ventilation due to respiratory insufficiency. Two-thirds of COVID-19 infected patients who required intensive care in the UK had mechanical ventilation within 24 hours of admission, as shown by the patient control in England, Wales and Northern Ireland [1]. The process of virus transmission is multifactorial, influenced by both environmental and behavioural factors (humidity, air quality, exposure time and proximity of contact) [2]. The SARS-CoV-2 virus that causes COVID-19 is transmitted through larger droplets and aerosols produced by breathing, talking, sneezing or coughing [2]. To a lesser extent, it can also spread through contaminated surfaces [2]. Due to the fact that only infectious virus particles are responsible for causing the infection, and not the RNA or protein residues themselves, the presence of the infectious SARS-CoV-2 virus is required for secondary transmission [2]. After the virus enters the cell and releases the genetic material, viral proteins necessary for further replication and translation are synthesized [2]. The formed mature viral particles are transferred in Golgi vesicles to the vicinity of the cell membrane and released outside in the process of exocytosis [2].

The SARS-CoV and MERS-CoV viruses responsible for previous epidemics, used intermediate hosts such as civets and camels [3]. Therefore, it is assumed that the SARS-CoV-2 virus, like its predecessors, has intermediate hosts [3]. Research indicates that they are RaTG13 and Pangolin-CoV extracted from dead Malayan pangolins, which had nucleotide compatibility with SARS-CoV-2 at the level of 91.02% [3]. Data on pangolins allow the conclusion that the existence of an intermediate host is likely [3]. Examination of frozen samples of the pangolins led to the identification of six complete genome sequences in the SARS-CoV-2 lineage [3]. Moreover, both bats and pangolins were sold alive or dead, legally or illegally, in wet markets in Wuhan, which may have been one of the causes of the outbreak of the Covid-19 pandemic [3]. Wet markets where the meat of dead and live animals are traded are an ideal environment for the transmission of bacteria and viruses from body fluids [3]. Moreover, poor hygiene practices may have been a key factor in the development of the Covid-19 pandemic [3]. However, there are some therapeutic options. Antiviral activity among natural substances has been demonstrated, among others, by sinapic acid, which is a natural compound of phenolic acid and is a derivative of cinnamic acid [4]. In addition, scientists tested four substances that are part of Withania somnifera [4], a medicinal plant widely used in the Indian medicinal system [4]. These four tested substances have an aromatic nucleus and it can bind to the hydrophobic domain of protein E and interfere with virus replication [4]. The last natural inhibitors of the SARS-CoV-2 protein are glycyrrhizic acid and β-boswellic acid [4]. Glycyrrhizic acid is effective against enveloped viruses, including SARS-CoV [4]. This acid is isolated from licorice [4]; however, research indicates that glycyrrhizic acid may interact with the SARS-CoV-2 S protein, inhibiting viral infection [4]. Both acids ultimately lead to the destruction of protein E [4]. In addition to natural substances, synthetic inhibitors of the SARS-CoV-2 protein have also been distinguished [4]. These include memantine, which inhibits virus replication, amantadine, which inhibits viroporin M2 of the influenza A virus, and hexamethyleneamiloride, which, in addition to inhibiting viroporin M2 of the influenza A virus, also inhibits viroporin of the SARS-CoV virus [4]. Retinoic acid, ursodeoxycholate and chenodeoxycholate can be added to the list of synthetic SARS-CoV-2 protein inhibitors [4].

It is noteworthy that patients with severe COVID-19 infection usually present the main risk factors for Ventilator-Associated Pneumonia (VAP) caused by Acinetobacter baumannii, which include hypertension, chronic obstructive pulmonary disease, chronic renal failure, length of stay in the Intensive Care Units (ICU), presence of organ failure and low blood oxygenation level [5]. The natural habitat of Acinetobacter baumannii is water and soil [6] and gained its notoriety due to its extensive resistance to antimicrobial agents [6]. This is a serious problem for doctors and patients, especially those staying in ICU [6]. This bacterium acquired resistance to antibiotics as a result of the acquisition of mobile genetic elements, such as transposons, plasmids and integrons [6]. As a result, multidrug resistance (MDR) strains have emerged [6]. The matter is further complicated by the increase in resistance to carbapenems, which are used as last-line antibiotic therapy to eliminate infections with multidrug-resistant Gram-negative bacteria [6]. Hospitalized patients are at increased risk because this virus penetrates through defects in the skin and respiratory tract [6]. It causes many infections of both skin and soft tissues, wound infections, bacteraemia, endocarditis, urinary tract infections, meningitis and pneumonia. The most common nosocomial infection occurring in mechanically ventilated patients in the ICU is pneumonia [6]. Patients with tracheal intubation and the aforementioned mechanical ventilation are at particular risk of an increased risk of bacterial pneumonia in ICU. Up to 80% of mechanically ventilated patients with COVID-19 may develop VAP [7]. Acinetobacter baumanii causes approximately 47% of cases of VAP in the ICU [5]. This bacterium is resistant to disinfection. It additionally creates a polysaccharide shell as well as biofilms, which contributes to its high pathogenicity [4–6]. This bacterium is transmitted through direct contact [6]. It is a widespread saprophyte found in nature and in hospital environments, where it survives on moist surfaces, such as respirators, but also on dry surfaces, such as human skin, which is an unusual feature for Gram-negative bacilli [6]. Lung infection most often occurs through microaspiration or contaminated intubation and endoscopy equipment [6]. In some people, they are also present among the bacteria that naturally colonize the mucous membranes of the throat, but in hospitalized patients they may multiply excessively [6].

Unfortunately, it is not easy to cure a patient infected with Acinetobacter baumannii. This is due to the numerous resistance mechanisms that this bacterium has. The modest list of antibiotics used in the treatment of Acinetobacter baumannii infection includes ampicillin-sulbactam, polymyxins, minocycline, tigecycline and cefiderocol [8]. Sulbactam is an irreversible, competitive beta-lactamase inhibitor which, when administered in high doses, has the ability to saturate penicillin-binding proteins (PBP) 1 and 3 [8]. Other beta-lactamase inhibitors do not have this unique method of action, therefore sulbactam has an additional advantage in treatment [8]. The combination of ampicillin and sulbactam is administered in a 2:1 ratio. Polymyxins show reliable *in vitro* activity against isolates of

Carbapenem-resistant Acinetobacter baumannii (CRAB), the literature here focuses primarily on polymyxin E (colistin) [8]. Minocycline has a bactericidal effect against Acinetobacter baumannii, and its synergistic effect with colistin, rifampicin and carbapenems is also known [8]. Tigecycline is a derivative of minocycline and should not be used in monotherapy if other more effective antibiotics are available [8]. It has activity against CRAB, although resistance has also been reported [8]. Unfortunately, clinical experience is very limited due to conflicting reports [8]. Cefiderocol has been reported to be effective against most CRAB isolates [8]. Additionally, cefiderocol was developed for the treatment of MDR Gram-negative infections and approved for the treatment of complicated urinary tract infections [8].

CASE REPORT

On 28 October, day six after cesarean section, the 36-year-old patient was admitted to the ICU of the Independent Public Clinical Hospital No. 1 (SPSK 1) in Lublin, eastern Poland, from the ICU of the Independent Public Healthcare Centre (SPZOZ) in Łuków in the Lublin province. From 31 October, the general condition and ventilation parameters deteriorated rapidly, and dyspnea appeared. It was necessary to support the breathing with high-flow nasal oxygen therapy. On the same day, antigen tests were also performed for SARS-CoV-2 infection, which turned out to be positive. On 3 November, saturation decreased with symptoms of severe respiratory failure, the trachea was intubated, and invasive ventilation was implemented for analgosedation and skeletal muscle relaxation. After consultation with the ECMO (Extracorporeal Membrane Oxygenation) centre, the patient was qualified for extracorporeal membrane oxygenation (VV ECMO) therapy. The patient was cannulated and VV ECMO therapy started in the hospital in Łuków, after which she was transferred to the ICU SPSK 1 in Lublin. After admission, Duolevel ultraprotective ventilation was started in analgosedation and relaxation. Basically, muffled bubble murmur was audible. Fluid therapy was performed under the control of PICCO (Pulse Contoru Cardiac Output) haemodynamic monitoring. Laboratory tests were ordered and cultures taken.

The next day, the patient remained in a very severe condition, sedated with a continuous infusion of Propofol and Fentanyl, and the administration of muscle relaxants continued. In the review of the lung ultrasonography, consolidations were found on the right parasubular side, while on the left side there was less intensity of the C line than on the right side. No abnormalities were found in the echo review. The circulatory system was efficient and was constantly under the control of haemodynamic monitoring using the PICCO method. On the third day of hospitalization, the patient's condition deteriorated rapidly in the evening hours. It was noticed that the patient was experiencing increasing arterial hypotension accompanied by a decrease in peripheral vascular resistance and skin changes in the thoracic and trunk areas. A continuous infusion of norepinephrine was started, and a bolus of crystalloids was given. The decision was also made to start empiric antibiotic therapy (Meropenem, Linezolid), access to the central vessel was also replaced, and anti-allergic treatment used

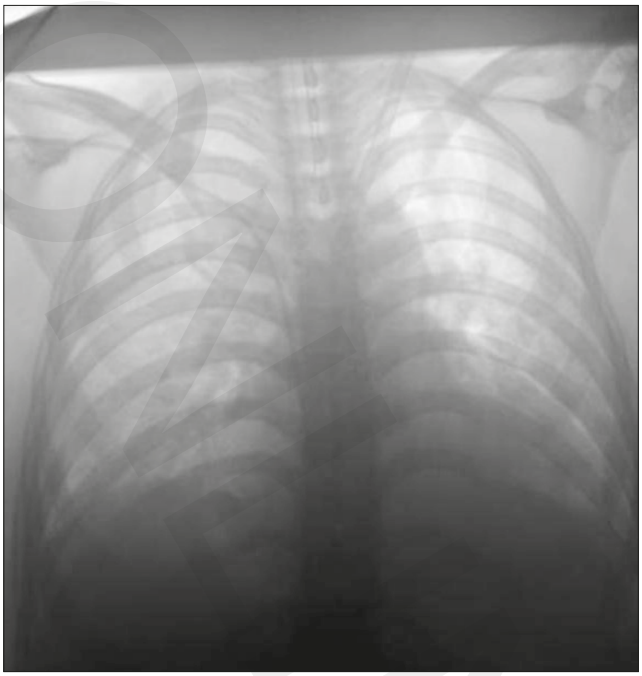

Figure 1. Lung changes observed during x-ray examination performed on the day of admission of the patient to hospital

(Adrenaline, Clemastin, Hydrocortison). On the fifth day of stay, the circulatory system was inefficient and required the supply of catecholamines under haemodynamic control. Due to high leukocytosis, a gynaecological consultation was ordered the next day, which showed the presence of peripheral oedema and minimal swelling of the labia majora and minor. There were slight bleeding and muco-bloody staining in the vagina. Culture was taken from the cervical canal area for microbiological examination.

Table 1. Culture results

URINE	LACK
NASOPHARYNX	LACK
ANUS	LACK (PHYSIOLOGICAL FLORA OF GESTINAL DUCT)
SWAB FROM CERVIX	ESCHERICHIA COLI, ACINETOBACTER BAUMANNII
BLOOD	ENTEROBACTER CLOACAE
MINI BAL	CANDIDA ALBICANS
WOUND	ACINETOBACTER BAUMANNII
BAL	ACINETOBACTER BAUMANNII
INSERTION	LACK

MINI BAL – mini *bronchoalveolar lavage, BAL- bronchoalveolar lavage*

The outer mouth of the cervix was open to the fingertip – no possibility of inserting the finger any deeper due to the resistance encountered when attempted. Cervical canal cultures were also collected. Transabdominal (TA) examination showed a properly contracting uterine body with no visible signs of obstetric stasis. The projection of the right appendages showed no visible changes, while a limited reservoir of fluid was observed in the projection of the left appendages. On the eighth day, VV ECMO (veno-venous extracorporeal membrane oxygenation) therapy was completed. The circulatory system was still inadequate,

requiring continuous administration of catecholamines under the control of haemodynamic monitoring. Heart rate was steady at around 100 beats per minute. A trace amount of faeces from the genital tract was observed. Two packs of platelet cell concentrate were transfused.

Table 2. Comparison of the morphology results on admission and after 7 days of hospitalization

	On admission	After 7 days hospitalization
WBC	15.09 K/uL	16.07 K/uL
RBC	3.82 M/uL	3.64 M/uL
HGB	10.9 g/dl	10.4 g/dl
HCT	33.2%	34.4%
MCV	86.9 fl	94.5 fl
MCH	28.5 pg	28.6 pg
MCHC	32.8 g/dl	30.2 g/dl
PLT	173 K/uL	7 K/uL

WBC – *white blood cells; RBC* – red blood cells; HGB – haemoglobin' HCT – haematocrit, MCV-mean corpuscular volume, MCH-mean haemoglobin content, MCHC-mean haemoglobin concentration; PLT – thrombocytes

On the eleventh day, the patient was diagnosed with a high fever, above 39°C, despite the administration of broad-spectrum antibiotics. The circulatory system was still ineffective and required the administration of very high doses of noradrenaline under the control of haemodynamic monitoring. The heart rate was approximately 110 beats per minute. Swelling of the hands and lower legs was observed. Culture was taken from the genital tract and from the postoperative wound. On the twelfth day, the patient›s condition remained unchanged. A CT (computed tomography) scan of the chest and abdominal cavity with contrast was performed.

Table 3. Comparison of results of the abdominal CT examination performed on 13 November and 25 November 2021

	13/11/2021 (12th day of hospitalization)	November 25, 2021 (24th day of hospitalization)
LUNGS	The presence of extensive, speckled areas of shading resembling milk glass. Within the lower lobes, there were extensive areas of shade consolidation inflammation. A small amount of free fluid was visible in the pleural cavities.	The parenchymal densities in the supra-diaphragmatic parts of both lungs were slightly lower than in the previous study. A small amount of fluid in the pleural cavities.
LIVER	Enlarged with reduced density – features of fatty liver.	Magnified, homogeneous, no focal changes.
GALLBLADDER	Enlarged, no calcified deposits visible on CT.	Extensive without calcified deposits visible on CT.
PANCREAS	Enlarged, in terms of the head, body and tail. In the head area, it underwent a slightly heterogeneous, weaker contrast enhancement. Surrounded by a liquid mantle.	Moderately dilated, with blurred outlines, no focal changes-image as in the case of oedema changes, fluid and infiltrative changes in the surrounding adipose tissue.
KIDNEYS	Within the cortical layer of the left kidney, there was visible a hypodense area that did not undergo contrast enhancement.	Correct size, showed weaker contrast enhancement. The cup-pelvic systems of both kidneys not dilated.
ABDOMINAL CAVITY	The presence of free fluid in the abdominal cavity and the minor pelvis – ascites.	More free fluid than before in the peritoneal cavity.

The chest CT scan was characteristic of COVID-19 viral pneumonia, while the abdominal CT scan showed acute pancreatitis. On the 15th day of hospitalization, a fibroscopic tracheostomy was performed with a bronchial tree toilet. Numerous milky streaks of thick mucus were observed in the fibroscopic examination. BAL (bronchoalveolar lavage) culture was taken. On the 23rd day, due to the positive antigen test which confirmed the presence of COVID-19 infection, the patient was again X-rayed.

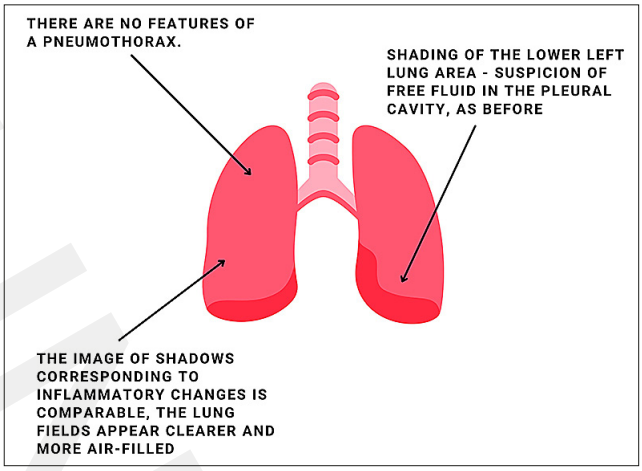

Figure 2. Lung changes observed during X-ray performed on the 23rd day of hospitalization

On the 24th day of hospitalization, a CT scan with contrast between the abdominal cavity and the pelvis was performed (Tab. 3). The picture was characteristic of acute pancreatitis, a slight progression was noted compared to the previous study. On the 28th day, the patient›s condition was still severe. A very large amount of mucopurulent discharge was still being sucked out of the respiratory tract. The circulatory system remained efficient with a tachycardia tendency of up to 120 beats per minute. Peristalsis was alive, no retention was observed, and diarrhea was present. The patient was not feverish. On that day, the patient was transferred to the ICU SPZOZ in Łuków for further treatment.

DISCUSSION

The presented clinical case showed a very severe form of VAP in a patient infected with the COVID-19 virus. However, cases of bacterial infection in COVID-19 patients are quite common [9]. This type of infection can be difficult to diagnose as a number of non-communicable diseases can mimic the image of radiographic infiltrates, systemic inflammation, and the impairment of oxygenation that are characteristic of VAP [10–13]. To reduce misdiagnosis and facilitate appropriate antimicrobial therapy in VAP, guidelines promote culture-based approaches [14]. Molecular tests for detecting multiple pathogens (both viruses and bacteria) are increasingly available, and may eliminate unnecessary antimicrobial therapy in the near future while improving the detection of difficult-to-breed organisms [14]. Studies have shown that patients infected with the COVID-19 virus are definitely more likely to develop VAP than patients without COVID-19 [14]. In addition, the incidence of VAP may vary depending on the bacteriological test used [15–19]. Most

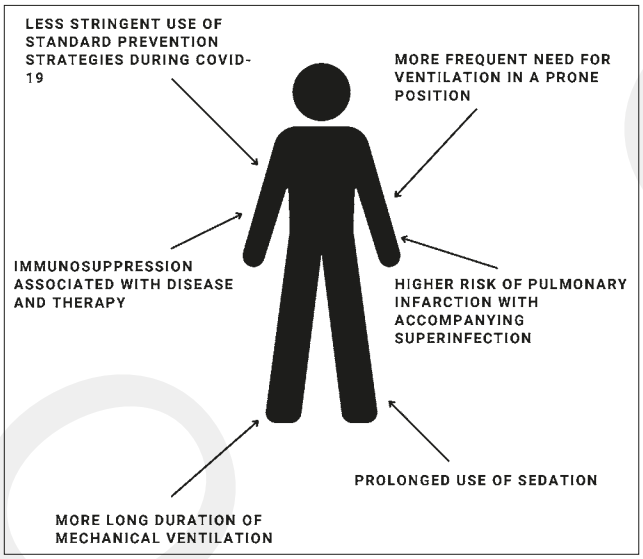

Figure 3. Factors influencing increased risk of VAP in SARS-CoV-2 infections compared to other ARDS

VAP is diagnosed on the basis of bacteriological analysis of tracheal aspirates (42.6%) [7].

In the presented patient, the cause of VAP was probably Acinetobacter baumannii, a bacterium that is a fairly common cause of VAP. Research shows that the incidence of VAP between 1 January 2015–31 December 2015, was approximately 6.9% (237/3424) and 35.9% (85/237) of cases were caused by Acinetobacter baumannii [20].

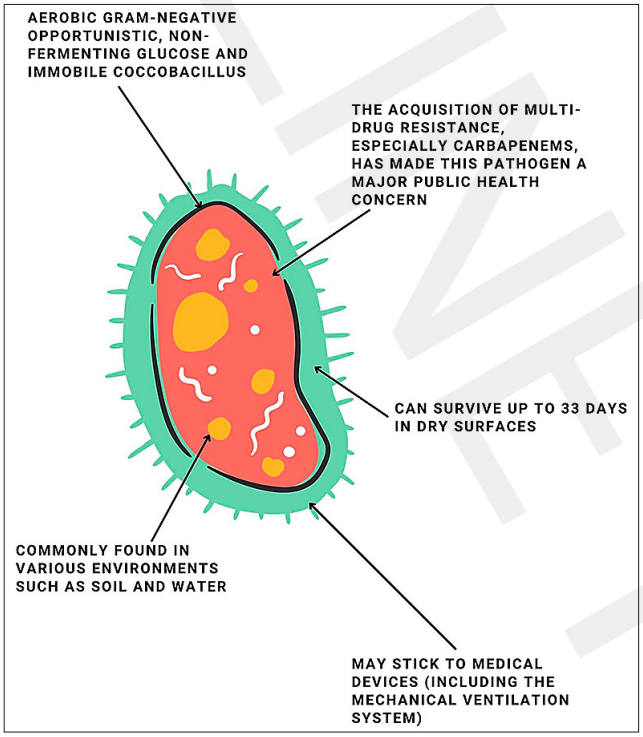

Figure 4. Characteristics of Acinetobacter baumannii

MDR-induced (*multidrug-resistant)* respiratory pneumonia Acinetobacter baumannii remains the main cause of high mortality in critically ill patients [21]. Acinetobacter baumannii is responsible for approximately 8% -14% of VAP in the United States and Europe, and 19% -50% of cases in Asia, Latin America, and some Middle Eastern countries [21]. Although Acinetobacter baumannii-related VAP appears to be prone only to immunosuppressed individuals, community-induced community-acquired pneumonia (CAP) is a cause for concern [22–23]. Accumulating scientific evidence on the role of Acinetobacter baumannii in respiratory infections must be taken into account for better surveillance and control [21].

SUMMARY

COVID-19 is responsible for making people more susceptible to VAP. Providing appropriate sterile conditions for sampling from the respiratory tract, together with minimizing contamination from the proximal tract, combined with sensitive diagnostic tests to reduce false-negative results, will certainly help in the appropriate selection of antibiotics. Rapid diagnosis and proper pharmacological management will reduce the number of fatal VAP cases in the future.

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