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REVIEW ARTICLE

Acinetobacter baumannii pneumonia associated with mechanical ventilation due to COVID-19: epidemiology, clinical characteristics and therapy

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Summary

Less than 3% of people who get infected with COVID-19 need hospital treatment. However, up to one-third of the hospitalized patients with COVID-19 require invasive mechanical ventilation. Ventilator-associated pneumonia (VAP), caused by the multidrug-resistant *Acinetobacter baumannii* (*A. baumannii*), is an emerging infection in the intensive care units and can have fatal consequences for those patients who already have critical COVID-19. Countries of the Balkan peninsula have an exceptionally high prevalence of invasive carbapenem-resistant *Acinetobacter spp* in the hospital setting. Diagnosing this type of pneumonia is a challenging process. Furthermore, treatment complexities arise because of multidrug resistance. Novel therapeutic agents, such as sulbactam/durlobactam and zosurabalpin could be the new therapeutic opportunity for *A. baumannii*-induced VAP. Antimicrobial resistance of *A. baumannii* is not entirely understood, although several mechanisms have been identified. To adequately manage VAP it is important to isolate causative agents, have awareness of the resistance pattern, carefully dispense antibiotics, and identify risk factors. In this review, we discuss epidemiological characteristics, pathophysiological mechanisms, clinical presentation and diagnosis, as well as the current and novel treatments of *A. baumannii*-induced VAP.

Keywords: COVID-19, ventilator-associated pneumonia, *Acinetobacter baumannii*, multidrug resistance

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INTRODUCTION

Beside tremendous societal challenges of the coronavirus disease (COVID-19) pandemic (1-3), the underlying changes in the antimicrobial ecology since the onset of the pandemic seem to be a major threat, particularly in the hospital setting. COVID-19 has a heterogeneous clinical presentation, ranging from asymptomatic and mild forms to severe and critical clinical forms, which require treatment in the intensive care unit (ICU) (4). In relation with all patients with symptomatic COVID-19, severe illness develops in 13.4% to 19.1% of individuals, depending on the population sample (5, 6). However, approximately 2.3% - 9% of people who get infected with COVID-19 need hospital treatment, while respiratory failure requiring invasive mechanical ventilation (IMV) is reported among 2.3% - 33% of all hospitalized patients (7, 8). Despite the efforts to preserve lung function, cumulative mortality from COVID-19 among people on IMV ranges from 30% to 97% (9, 10). This can be partially attributed to systemic inflammation, multiorgan failure, and other complications associated with COVID-19, as well as to complications related to the IMV itself (9). Major complications of IMV include ventilator-induced lung injury (VILI) and ventilator-associated pneumonia (VAP) (9).

VAP accounts for the most common infection acquired in ICUs among patients with COVID-19, with an estimated cumulative incidence of 5% - 40% (11). Based on the time of the onset (within the first 4 days or after 4 days of hospitalization), two VAP entities were defined: an early onset ventilator-associated pneumonia (EVAP) and a late onset ventilator-associated pneumonia (LVAP) (10). The EVAP typically has milder clinical features and a more favorable prognosis, while LVAP is often attributed to multidrug-resistant microorganisms (10). Of multidrug-resistant (MDR) bacteria, *Acinetobacter baumannii* (*A. baumannii*) is often associated with the onset of VAP (12). In fact, carbapenem-resistant *A. baumannii* (CRAB) has been listed by the Centers for Disease Control and Prevention (CDC) as an urgent antimicrobial resistance threat in the United States just before the onset of the COVID-19 pandemic (13). Data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) for 2020 underscored an exceptionally high prevalence of invasive carbapenem-resistant *Acinetobacter spp.* (exceeding 80% of all *A. baumannii* isolates in hospitals) in the Balkan countries (13): Turkey (93.1%), Greece (94.6%), North Macedonia (97.4%), Bulgaria (82.9%), Romania (93.3%) Serbia (98.6%), Montenegro (100%), Bosnia and Herzegovina (97.9%) and Croatia (96.4%). This prevalence was about 2.5 times higher than those observed within the European economic area (38%), suggesting that the Balkan region may be an *Acinetobacter spp.* hotspot (14).

The purpose of this review is to summarize the existing scientific literature on epidemiological characteristics, clinical presentation, therapeutic challenges of *A. baumannii*- induced VAP during the COVID-19 pandemic.

EPIDEMIOLOGAL CHARACTERISTICS

The presence of *A. baumannii* in hospital settings is reported worldwide. A combined incidence rate of *A. baumannii* among all hospital-acquired infections in Europe, Eastern Mediterranean region and Africa is estimated at 25.1 (95% CI 12.8-48.5) per 1,000 patients (15). A systematic review and meta-analysis of bacterial coinfection and secondary infection in patients with COVID-19 reported an *A. baumannii* prevalence of 3.5% and 14.3%, respectively (16, 17). A study conducted in hospitals in Belgrade (Serbia) reported that Gram-negative bacteria, including *Acinetobacter spp.*, *Pseudomonas aeruginosa*, and *Klebsiella/Enterobacter spp.* complex, were the most frequently isolated pathogens in patients with EVAP (39.7%, 13.8%, and 12.1%, respectively), thereby contributing to more than one-half of all early pneumonias (18). Similarly, in LVAP, *Acinetobacter spp.* and *Pseudomonas aeruginosa* were the most commonly isolated biological agents (18). Furthermore, in a study from the neighboring Croatia, during the COVID-19 pandemic, it was observed that the most common isolates in the ICU were those of *A. baumannii*, however, its frequency decreased in the post-pandemic period (19).

A study in Turkey reported almost a double increase in the prevalence of *A. baumannii* in the ICU during the COVID-19 pandemic compared to the pre-pandemic period, albeit the case-fatality ratio was similar (20). These pieces of evidence are compelling because the study included patients over a period of 27 months before and 27 months during the pandemic (20). One literature review indicated that *A. baumannii* in VAP during the COVID-19 pandemic was confirmed by deep bronchoalveolar lavage (BAL) in approximately 35%-45% of cases and endotracheal aspirate in about 40%-60% of cases (21, 22).

Community-acquired infections caused by *A. baumannii*, including pneumonia and bacteremia, are rare, even though they are associated with a relatively high mortality (23). Nevertheless, *A. baumannii* infections have become increasingly relevant as nosocomial infections, particularly in patients on IMV, because infected and colonized patients are major reservoirs of *A. baumannii* and spread with ease in hospital environment (24). More importantly, *A. baumannii* has the ability to survive on surfaces, especially plastic, in dry conditions, which allows for its ubiquitous presence in hospitals worldwide (25). The average duration of viability for sporadic *A. baumannii* strains is estimated at 27 days (range 21 to 32 days), whereas the average duration of viability for outbreak strains is 26 days (range from 21 to 33 days) (26). For this reason, the hygiene of stethoscopes, hands, and uniforms of healthcare professionals and medical stu-

dents is essential, not only during the COVID-19 pandemic, but at all times. Evidence shows that the incidence rate of MDR *A. baumannii* was 315.4 per 1000 ICU patient-days, with cumulative mortality rate being 52%-66% among those who are infected (27). A study by Novović et al. indicated that 64 isolates of *A. baumannii* were identified from COVID-19 patients admitted to the ICU in a local general hospital in Serbia, all of them requiring IMV and having poor COVID-19 outcomes (28).

Several hypotheses have been proposed to explain the increase in incidence of *A. baumannii*-induced VAP during the COVID-19 pandemic. Factors such as hospital overcrowding, a shortage of healthcare workers, and irrational use of antibiotics and immunosuppressants may be the underlying reasons (29). Thom et al. found that healthcare workers caring for patients known to be infected or colonized with *A. baumannii* carry this pathogen on their hands or gloves 30% of the time spent in hospital (30). In other studies *A. baumannii* was isolated from different sources and objects, including medical instruments, sinks, and toilet bowls, and protective equipment of healthcare professionals (31, 32). Interestingly, *A. baumannii* was identified in a swab from a plastic ventilator of the air conditioning unit 2.5 m above patient beds in an ICU of 40 m^2 in size, suggesting that it may be transmitted via airflow in addition to direct and indirect contact (19).

PATHOPHYSIOLOGICAL MECHANISMS

A major risk factor for the development of *A. baumannii* VAP is the presence of an endotracheal tube (33). In this way, infectious agents can enter the tracheobronchial system through the formation of a biofilm on the inner surface of the tube or via microaspiration around the balloon (33). As COVID-19 damages the cells of the respiratory tract, alters mucus production, and reduces cilial mobility, this cellular damage can modulate the upregulation of bacterial adhesion proteins (34). The disruption of tight junctions between cells results in lesions of the epithelial barrier, facilitating bacterial adhesion to the respiratory system cells and their paracellular migration (35). Furthermore, the altered immune function in COVID-19, coupled with changes in microbiota of the respiratory and gastrointestinal systems, further facilitates the susceptibility of COVID-19 infected patients to bacterial superinfections (36).

It has been observed that *A. baumannii* has a wide range of virulence factors, such as versatile survival mechanisms which help to evade the immune response of the host, as well as the efficient interference capacity to bind, internalize, and induce apoptosis in host cells (37). Integral to these mechanisms are the outer membrane proteins (OMPs), such as the OmpA, which serve as the key facilitator in binding and internalization of *A. baumannii* in the host epithelial cells. Beside these interactions, OmpA initiates a cascade of apoptotic factors within the cells of the host which trigger cell death (38). The capsular exopolysaccharides of *A. baumannii* operate as a protective mechanism, shielding it from both environmental and host-related defense mechanisms (38). The degree of virulence of *A. baumannii* is linked to the structure of these exopolysaccharides, which acts as a dynamic resistance system (39).

CLINICAL PRESENTATION AND DIAGNOSIS

When a patient develops a new or progressive infiltrate on chest radiography, leukocytosis, and purulent tracheobronchial secretions VAP is suspected (40). A comparison of histological analysis and culture findings of lung samples obtained immediately after death suggested that the presence of a new and persistent (>48 h) infiltrate on chest radiography along with two or more of the following criteria: 1) fever >38.3°C, 2) leukocytosis >12 × 10^9/ml, and/or 3) purulent tracheobronchial secretions, had 69% chances of confirming the VAP diagnosis (sensitivity of 69% and specificity of 75%) (41). Sensitivity of these clinical criteria for VAP diagnosis is lower in patients with acute respiratory distress syndrome (ARDS) in critical COVID-19, making it challenging to detect new radiographic infiltrates (42). With regards to the ARDS, Bell et al. (43) reported a false-negative rate of 46% for clinical diagnosis of VAP. Consequently, suspected VAP in ARDS as a complication of COVID-19 could be high.

Systemic signs of pneumonia, such as fever, tachycardia, and leukocytosis, are non-specific and could result from COVID-19, VAP or any other condition in which the release of cytokines, such as interleukin-1, interleukin-6, tumor necrosis factor-alpha, and gamma interferon, is the primary immune response (44). In cases of purulent sputum, positive sputum cultures, fever, and leukocytosis without a new pulmonary infiltrate, a diagnosis of hospital-acquired tracheobronchitis should be considered, except when the ARDS-associated VAP is suspected (45).

While a normal chest X-ray is rarely associated with VAP, a study on surgical patients found that 26% of opacities were detected through computed tomography (CT), but not on portable chest X-ray (40). Furthermore, asymmetric lung infiltrates consistent with VAP can result from various non-infectious disorders, including atelectasis, chemical pneumonitis, asymmetric cardiogenic pulmonary edema, pulmonary embolism, cryptogenic organizing pneumonia, lung contusion, and drug-induced lung reactions (46). The overall radiographic specificity of lung opacities consistent with pneumonia is only 27% to 35% (40).

Accurate laboratory identification of causative agents is crucial, but remains controversial because of the challenges when differentiating between rapid bacterial col-

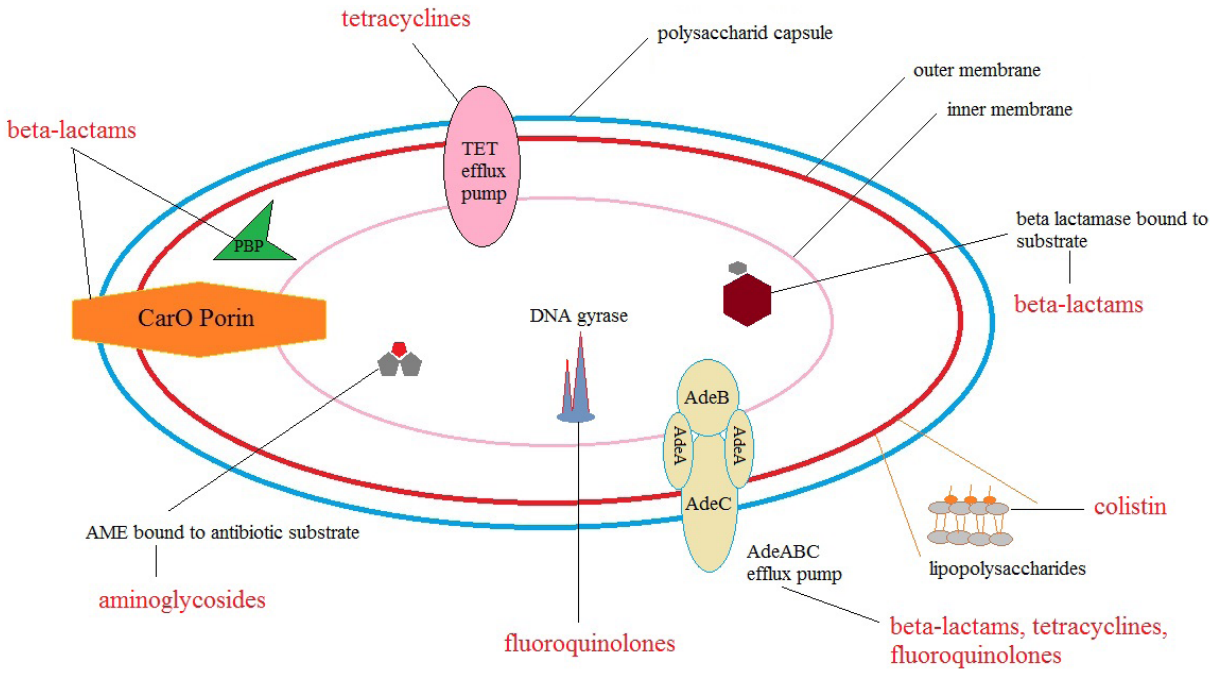

Figure 1. Resistance mechanisms of *A. baumannii* (PBP-penicillin binding protein, AME-aminoglycoside modifying enzymes)

onization in ventilated patients, coinfection, and VAP (47). Literature data support the sampling of respiratory secretions, tissues, blood, and pleural fluid to confirm VAP. In less than 10% of VAP cases, the infection spreads into the bloodstream or pleural space (46). Therefore, the experts recommend obtaining two sets of blood cultures and performing thoracentesis for non-loculated pleural effusions (≥10 mm in diameter) on chest X-rays with lateral decubitus as part of a suspected VAP (48). For loculated effusions, ultrasound-guided aspiration may be necessary (40). However, it is important to note that the sensitivity of blood cultures for VAP diagnosis is lower than 25% (49). Even when positive, infectious agents may originate from extrapulmonary sites of the infection in up to 64% of cases, despite the presence of VAP (49).

Gram staining and non-quantitative or semi-quantitative cultures of tracheal secretions have advantages, including reproducibility and minimal technical requirements, without the need for a specialized equipment (50). The semi-quantitative scoring of Gram stain was established based on the number of bacteria per high-power (×1,000) oil immersion field, utilizing the following criteria: 0 = absence of bacteria per field; 1+ = fewer than one bacterium per field; 2+ = 1–5 bacteria per field; 3+ = 6–30 bacteria per field; and 4+ = more than 30 bacteria per field (51). However, these studies contribute minimally to the sensitivity and specificity of the clinical diagnosis of VAP, as the upper respiratory tract quickly becomes colonized by lung pathogens within hours of intubation, even in the absence of pneumonia (52). In a study involving 48 patients with respiratory failure, the concordance between non-quantitative tracheal cultures and lung tissue cultures obtained through an open lung biopsy was only 40% (53). In that study, in patients with histologically confirmed pneumonia, endotracheal aspirates (ETA) exhibited sensitivity of 82%, but specificity of only 27%. Prior antibiotics use can result in a false-negative rate of 10 to 40% as well (54).

To potentially improve the specificity of VAP diagnosis and prevent the unnecessary use of antibiotics, some studies explored the role of quantitative cultures of respiratory secretions (40). These include non-bronchoscopic methods, such as quantitative cultures of endotracheal aspirates (QEA) and blind sampling of secretions from distal airways through the endobronchial catheter (40).

CHALLENGES OF MUTLI-DRUG RESISTANCE

Mechanisms of antibiotic resistance of *A. baumannii* can be categorized into three groups: (1) reduction of membrane permeability or increase in efflux of the antibiotic; (2) genetic mutation or post-translational modification; (3) hydrolysis or modification (55). Visual representation of the key resistance mechanisms of A. baumannii is provided in Figure 1. Based on these mechanisms, it can be concluded that *A. baumannii* has a remarkable ability to acquire antimicrobial resistance. It has been previously identified that *A. baumannii* is resistant to penicillins, macrolides, trimethoprim, and fosfomycin (56). Resistance to cephalosporins, carbapenems, aminoglycosides, and fluoroquinolones has also been documented in *A. baumannii* strains (57). Infections caused by the CRAB result in a prolonged hospital stay, poor outcomes, and increase in healthcare costs compared to the infections caused by carbapenem-susceptible strains (58).

Expectedly, *A. baumannii* is resistant to a wide spectrum of antibiotics, such as penicillins, macrolides, tri-

methoprim, and fosfomycin (59-61). Moreover, this bacterium displays an extraordinary capacity to develop antimicrobial resistance to cephalosporins, carbapenems, aminoglycosides, and fluoroquinolones, as evidenced by previous data (59). The remaining challenge focuses around the increasing resistance to carbapenems, the last line of defense against infectious agents caused by multidrug-resistant Gram-negative bacteria. Although tigecycline represents one of the last resort therapies for MDR *A. baumannii*, resistance to this antibiotic has been reported already (62). A study from Serbia emphasized that the primary mechanism behind tigecycline resistance in *A. baumannii* isolated in the Balkan hospitals was the overexpression of antibiotics efflux pump (63).

Resistance to carbapenem in *Acinetobacter spp.* is often linked to the acquired production of carbapenemases, with class D beta-lactamases, or oxacillinases (OKSAs), having a major role in this process (64). At the present moment, distinct groups of OKSA-type carbapenemases found in *A. baumannii* include OKSA-23-like, OKSA-24/40-like, OKSA-58-like, OKSA-143-like, OKSA-235-like groups, alongside an intrinsic chromosomal group similar to OKSA-51 (64-66). In addition, acquired resistance to aminoglycosides and fluoroquinolones has been observed in *A. baumannii* strains that produce carbapenemases (67).

In a recent study from Serbia, mutations in the PmrB protein were identified as the main factor in colistin resistance (68). The finding that chromosomal mutations were the culprit for colistin resistance (ColR) in Serbia may have implications for other global high-risk clonal lineages (68). This challenges a previous belief that resistant strains disseminated and subsequently proliferated locally (68). Research by Strateva et al. suggested that a rise of OXA-72 increases the risk of horizontal transfer of antibiotic resistance genes (ARGs) in nosocomial *A. baumannii* isolates and other Gram-negative bacteria through plasmids and transposable mobile genetic elements in Bulgaria (69). The increasing resistance of ColR *A. baumannii* clones suggests that there is an urgent need for a comprehensive global surveillance system of AMR (69).

THERAPEUTIC APPROACHES

General principles in treatment of VAP caused by *A. baumannii* while having COVID-19 include an isolation of a causative agent, identification of sensitivity and resistance patterns, rational antibiotic dispensing, and justification for de-escalation or discontinuation of antibiotics usage (70). Irrational antibiotics usage is especially relevant in the Serbian hospital setting as increased use of many antibiotics has been recorded over the COVID-19 pandemic (71, 72). A study of trends in antibiotics use pre- and during the COVID-19 pandemic in Serbia documented a significant increase in the use of antibiotics labelled as "Watch" and "Reserve" drugs (72). Moreover, more than one-half of children treated for COVID-19 in the first pandemic wave in Serbia received antimicrobial agents without clear indication of bacterial superinfection (71).

The treatment of CRAB depends on the antibiogram and severity of clinical presentation, but generally involves colistin administration, either alone or in a combination with other antibiotics (75). Treatment of carbapenem-sensitive strains is carried out as a monotherapy using imipenem or meropenem (75). Most commonly used antibiotics in combination with colistin for CRAB are ampicillin/sulbactam, fosfomycin, tigecycline, and meropenem (75). A combination of colistin with meropenem has shown to be either equally as effective or less effective compared to colistin alone and it is not being used if the minimum inhibitory concentrations of *A. baumannii* are high (75). Combinations of colistin with other antibiotics (ampicillin/sulbactam, fosfomycin, tigecycline) have also been more effective than colistin alone (72). Given that intravenous administration of colistin does not provide sufficient drug concentrations in lung tissue, inhalation of colistin may be a better option for VAP caused by CRAB, in addition to the previously described intravenous antibiotics administration (76).

NEW THERAPEUTIC POSSIBILITIES

Sulbactam/durlobactam (KSACDURO®) represents a co-formulated antibacterial compound to manage infections arising from the *A. baumannii-calcoaceticus* complex (ABC) (77, 78). Concurrent administration of durlobactam, a potent serine β-lactamase inhibitor exhibiting broad-spectrum activity, in conjunction with sulbactam, a well-established class A β-lactamase inhibitor effective against *A. baumannii*, prevents enzymatic degradation of sulbactam by β-lactamases produced by ABC (78). Sulbactam/durlobactam was also approved in the United States in 2023 for adult patients who had hospital-acquired bacterial pneumonia and VAP caused by ABC (77).

Zosurabalpin represents a novel category of macrocyclic peptide antibiotics (MPA) highly efficient against *Acinetobacter spp.*, specifically targeting CRAB-calcoaceticus strains (79). The outer membrane of Gram-negative bacteria is composed of an asymmetrical double layer with phospholipids in the inner layer and lipopolysaccharide (LPS) in the outer layer (79). The synthesis of LPS is finalized within the cell at the inner membrane. To facilitate the formation of the outer membrane, components of the LPS transporter in the inner membrane assemble into a subcomplex that extracts LPS from the double layer (79).

Progress in the field of reverse vaccinology, proteomics, and genomics has certainly improved vaccine development. Despite the success of experimental vaccines against *A. baumannii* on animals, their application in humans is still limited. This is, in part, attributed to a rela-

tively small number of vaccine antigen targets identified thus far, which does not allow for satisfactory vaccine effectiveness (80). Difficulties with purification and limited safety profile warrant more research in this field (80).

CONCLUSION

Epidemiological data suggest that the incidence of *A. baumannii* in ICUs during the pandemic has been on the rise. It is potentially linked to hospital overcrowding and antibiotic misuse. The complexity of clinical presentation and differential diagnosis requires a more accurate identification methods to differentiate VAP from other conditions. Effective managing *A. baumannii* VAP while having COVID-19 involves several principles: identification of the bacterium in biological specimen, understanding local resistance patterns, implementing a rational antibiotic regimen, and justifying antibiotic de-escalation or cessation. It is critical to eliminate risk factors such as endotracheal and nasogastric tubes, tracheostomy, reintubation, enteral nutrition, corticosteroid use, stomach pH modifiers, supine positioning, prior antibiotics, poor infection control, and contaminated equipment. The rise of multidrug resistance poses a significant challenge, with limited options for an effective treatment. Novel therapeutic possibilities, such as sulbactam/durlobactam and zosurabalpin, offer promising results, but research in vaccine development could potentially become a long-term solution for *A. baumannii* VAP prevention.

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PNEUMONIJA PROUZROKOVANA ACINETOBACTER BAUMANII TOKOM MEHANIČKE VENTILACIJE USLED INFEKCIJE KOVIDOM 19: EPIDEMIOLOŠKE I KLINIČKE KARAKTERISTIKE I TERAPIJA

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Sažetak

Manje od 3% ljudi koji su zaraženi infekcijom kovid 19 imaju potrebu za bolničkim lečenjem. Međutim, jednoj trećini hospitalizovanih pacijenata sa kovidom 19 je neophodna invazivna mehanička ventilacija. Pneumonija povezana sa korišćenjem respiratora (PPKR) čiji je prouzrokovač multirezistentni *Acinetobacter baumannii* (*A. baumannii*) je nova infekcija u jedinicama intenzivne nege i može imati fatalne posledice kod osoba sa teškom formom infekcije izazvane kovidom 19. Zemlje Balkanskog poluostrva imaju izuzetno visoku prevalenciju karbapenem rezistentnih *Acinetobacter spp* u bolnicama. Dijagnoza ove pneumonije je prilično komplikovana. Štaviše, složenost lečenja nastaje usled rezistencije *A. baumannii* na više antibiotika. Novi lekovi, kao što su sulbaktam/durlobaktam i zosurabalpin pokazali su dobru efektivnost u borbi protiv PPKR izazvane *A. baumannii*. Antimikrobna rezistencija *A. baumannii* nije u potpunosti rasvetljena, iako je definisano nekoliko mehanizama. Za adekvatno lečenje PPKR važno je izolovati uzročnika, imati na umu mehanizme rezistencije, pažljivo dozirati antibiotike i identifikovati faktore rizika. U ovom preglednom radu biće razmotrene epidemiološke karakteristike, patofiziološki mehanizmi, klinička slika i dijagnostika, kao i aktuelne i nove terapijske mogućnosti PPKR izazvane *A. baumannii*.

Ključne reči: kovid 19, pneumonija povezana sa ventilacijom, Acinetobacter baumannii, multirezistencija na lekove

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