Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to Editors

Ventilator-associated pneumonia (VAP) caused by carbapenem-resistant *Acinetobacter baumannii* in patients with COVID-19: Two problems, one solution?

Dear editor,

In late 2019, a cluster of pneumonia cases reported from Wuhan City (Hubei Province, China) were associated with a novel betacoronavirus, first called the 2019 novel coronavirus (2019-nCov) [1]. Posteriorly, the sequence of 2019-nCov genome reveled 89% similarity and 80% identity with SARS-CoV, the causative agent of the 2002–2003 pandemic of severe and acute respiratory syndrome (SARS). Since then, the International Committee on Taxonomy of Viruses renamed the 2019-nCov as SARS-CoV-2, and the World Health Organization (WHO) defined that this pathogen causes the coronavirus disease of 2019 (COVID-19) [2–4].

The outbreak of COVID-19 started in Wuhan quickly spread worldwide, and in March 11th, 2020 the WHO declared a pandemic state. By June 20th, 2020, SARS-CoV-2 had infected 14,668,298 people and caused 609,511 deaths in almost all countries around the world [5]. The symptoms of COVID-19 can range from mild, self-limiting respiratory tract illness to severe progressive pneumonia, which can evolve to multiorgan failure and death [1]. Patients with severe COVID-19 usually need endotracheal intubation and mechanical ventilation due to airway failure. For instance, two-thirds of patients with COVID-19 who required critical care in the UK needed mechanical ventilation within 24 h of admission, following by immediately transfer to intensive care units (ICUs) [6,7].

Importantly, patients with tracheal intubation and mechanical ventilation are at increased risk to acquire bacterial ICU-pneumonia [8]. Thus, Deng et al. [9] analyzed electronic medical records of 25 patients with COVID-19 in Renmin Hospital at Wuhan University and showed that bacterial pneumonia might be associated with the death of patients with the novel coronavirus. Likewise, Wang et al. [10] showed that the levels of procalcitonin, a bacterial infection marker, are almost four times higher in patients who died from COVID-19 than in those who recovered from the disease. Also, a study with 11 patients showed that cases of COVID-19 associated with bacterial pneumonia were considerably more severe [11]. These findings indicate that ventilator-associated pneumonia (VAP) could worsen the clinical condition of COVID-19 patients, requiring special attention by health professionals.

Gram-negative bacilli have been detected in sputum and tracheal aspirates cultures of mechanically ventilated patients with severe COVID-19 [11,12]. Lescure and collaborators (2020) identified *Acinetobacter baumannii* as the causative agent of VAP in a patient infected by SARS-CoV-2 [12]. *A. baumannii* is an aerobic Gram-negative opportunistic, glucose non-fermentative, and non-motile coccobacillus commonly found in various environments, such as soil and water. This bacterium can adhere to medical devices (including the system used for mechanical ventilation) and survive up to 33 days in dry surfaces [13–15]. Furthermore, the acquisition of multiple drug resistance, especially to carbapenems, has made this pathogen a major public health concern [16].

A. baumannii is responsible for approximately 47% of VAP cases in ICUs [17]. It is commonly resistant to disinfection, and the production of a polysaccharide capsule and formation of biofilms contribute to the high pathogenicity of this bacterium [13–15]. More importantly, patients with severe COVID-19 usually present the main risk factors observed to VAP caused by *A. baumannii* (*i.e.*, hypertension, chronic obstructive pulmonary disease, chronic renal failure, length of ICU stay, presence of organ failure, and low blood oxygenation level) [18–20]. Thus, rigid application of infection control precautions should be taken to prevent infections by *A. baumannii* in patients with COVID-19 on mechanical ventilation.

Carbapenem antibiotics are considered the last therapeutic option to treat VAP caused by multidrug-resistant *A. baumannii* [21]. However, since 1991, when the first carbapenem-resistant *A. baumannii* (CRAB) was reported, a considerable increase in the number of these resistant strains has been documented worldwide [22,23]. In 2015 in Greece, 94.5% of *A. baumannii* isolates were resistant to imipenem, while in North American hospitals (2008), 58% of the strains were identified as CRAB [23]. Colistin, also known as polymyxin E, is considered one of the last therapeutic options to treat CRAB infections. However, it is highly nephron- and neurotoxic [24], so that its intravenous use in critically ill patients with COVID-19 and co-infection with CRAB must be closely monitored. On the other hand, nebulized colistin increases the concentration of this drug in the infection site, decreasing kidney and nerve damage due to its limited systemic distribution [25]. Thus, we hypothesize that the use of nebulized colistin is a reasonable choice for most critically ill patients with COVID-19 co-infected with carbapenem-resistant Gram-negative pathogens.

Interestingly, the use of nebulized colistin may also improve the outcomes of pulmonary infections by SARS-CoV-2. Haukenes and Bjerkestrand (1973) showed that polymyxin B, a drug from the same pharmacological class as colistin, reduced the cytopathogenic effect of the enveloped viruses Mumps and Herpes simplex [26]. We hypothesize that this antibiotic might protect the cells against the deleterious effects of the enveloped virus by negatively interacting with the lipidic component of the viral envelope. Since SARS-CoV-2 is an enveloped virus [4], it might be susceptible to this effect of polymyxins. However, to date, no evidence of their biological activity has been found. A theoretical study suggested that colistin may interact with proteins involved in the replication cycle of the novel coronavirus. This polymyxin can form hydrogen bonds with the amino acid residues Thr24, Thr25, and Thr26, which are crucial to the enzymatic activity of the main protease (M^{pro}) of SARS-CoV-2 (also known as 3C-like protease) [27]. M^{pro}, a key enzyme for coronavirus replication, is responsible for processing the viral polypeptide into structural and functional proteins [4].

The screening and treatment of bacterial co-infection, especially VAP, is essential to ensure a better clinical outcome in patients with

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severe COVID-19. The isolation of *A. baumannii* from patients with COVID-19 highlighted the importance of preventing co-infections caused by this pathogen, which depending on the regional endemicity may be associated with resistance to carbapenems. In these cases, we hypothesize that patients would benefit from the use of nebulized colistin due to its low systemic toxicity. Additionally, we encourage studies to characterize possible therapeutic benefits of the inhaled use of colistin in severe cases of COVID-19 and to determine the potential antiviral of this polymyxin *in vitro* against SARS-CoV-2. However, the use of this drug should be performed only when strictly necessary since colistin is an antibiotic considered the ultimate resort, and resistance to this class usually results in intractable infections.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110139.

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