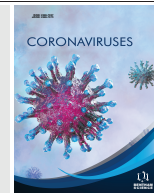


**BENTHAM
SCIENCE**

Synthetic Lung Surfactant Treatment for COVID-19 Pneumonia



Frans J. Walther^{1,*} and Alan J. Waring¹

¹Departments of Pediatrics and Internal Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, USA & The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, California, USA

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Abstract: COVID-19 has led to morbidity in millions of patients, ranging from mild flu-like symptoms to severe respiratory failure, necessitating oxygen supplementation and mechanical ventilation, and ultimately death. The SARS-CoV-2 virus reacts with angiotensin-converting enzyme 2 (ACE2) molecules that are especially found in alveolar epithelial type 2 cells in the lungs and thereby causes a loss in lung surfactant, a protein-lipid mixture that is crucial for both native immunity and reduction of surface tension in the lung alveoli. Lung surfactant insufficiency results in atelectasis and loss of functional lung tissue amid an inflammatory storm and may be countered by treating COVID-19 pneumonia patients with exogenous lung surfactant, preferably by aerosol delivery of a novel dry powder synthetic lung surfactant. More research on timing, dosing, and delivery of synthetic lung surfactant in patients with COVID-19 pneumonia is of crucial importance to implement this approach in clinical practice.

Keywords: lung surfactant, alveolar type 2 cells, respiratory failure, SARS-CoV-2, COVID-19, pneumonia.

1. INTRODUCTION

Progress is often made when disaster strikes and out of the box improvisation is sometimes the only way to cope with a life-threatening situation. The current Coronavirus pandemic has led to morbidity in millions of patients, ranging from mild flu-like symptoms to severe Acute Respiratory Distress Syndrome (ARDS), necessitating oxygen supplementation and mechanical ventilation, and ultimately death. The availability of intensive care beds and protective equipment and supplies in the community has quickly become a daily hot issue. Staying at home, keeping social distancing, and wearing facemasks has severely affected our daily lives and the economy, but it is necessary to interrupt the transmission of the SARS-CoV-2 virus (COVID-19) in the community until protective vaccines and antiviral drugs become available.

COVID-19 produces an acute viral infection in humans with an incubation time between two and 14 days, and a mean around five days [1]. Common clinical symptoms are fever, cough, fatigue, muscle pain, and dyspnea. In severe cases, rapid onset of respiratory failure occurs around day nine from the onset of clinical symptoms [2]. Specific diagnostics include viral detection with real-time polymerase chain reaction (RT-PCR) and imaging of lung pathology with a chest CT scan that typically shows bilateral and peripheral ground-glass opacities and consolidation [3].

SARS-CoV-2 is a positive-sense single-stranded RNA virus. It has a spherical shape, and the spike (S) protein lo-

cated on the surface of its envelope forms pronounced projections, which, in electron micrographs, create an image reminiscent of a solar corona [4]. Most probably, the S protein, located on the surface of the virus, reacts with Angiotensin-Converting Enzyme 2 (ACE2) molecules in the lungs [5], thereby sharing the same cell entry receptor with the SARS-CoV virus. The SARS-CoV-2 virus is genetically closely related to the SARS-CoV virus that led, in 2002-2003, to a novel coronavirus outbreak with a high fatality rate (11%), but this SARS epidemic was contained by implementing strict public health measures. On the contrary, SARS-CoV-2 is less deadly and transmits far more easily than SARs-CoV, thereby leading to the current pandemic [6].

ACE2 is expressed in humans in the epithelia of the lungs, small intestines, heart, liver, and kidneys [7]. In the lungs, ACE2 is especially found in alveolar epithelial type 2 cells. The ACE2 concentration is higher in men than among women and increases with age, which may explain the incidence pattern of COVID-19 pneumonia. Binding of ACE2 to SARS-CoV-2 virus may increase its expression, resulting in damage to the alveoli. The affinity of SARS-CoV-2 for ACE2 is 1-2 times higher than that of SARS-CoV. The expression of ACE2 varies in individuals of different races and leads to differences in susceptibility to clinical illness and in the severity of the disease course [8-12]. Following infection, SARS-CoV-2 replicates in the cells of the respiratory and intestinal epithelium, leading to cytopathic changes and associated clinical symptoms. In SARS-CoV-2-infected macaques, virus was detected in alveolar type I and II cells and in ciliated epithelial cells along the respiratory tract [13]. The attack on alveolar type 2 cells by

*Address correspondence to this author at the Department of Pediatrics, The Lundquist Institute, 1124 W Carson Street, Torrance, California, USA; Tel: (310) 974-9592; E-mail: fjwalther@ucla.edu

SARS-CoV-2 results in a loss of active surfactant and native immunity.

Alveolar type 2 cells produce and secrete lung surfactant, a mixture of phospholipids and proteins that reduces surface tension at the air-liquid interface in the alveoli. Mammalian lung surfactant consists of approximately 80% phospholipids, 10% neutral lipids, and 10% proteins. Among the four surfactant proteins, surfactant proteins A and D (SP-A and SP-D) play an important role in the native immunity of the lung, whereas surfactant proteins B and C (SP-B and SP-C) are surface-active and reduce surface tension in the alveoli. The absence of SP-B in the lung is lethal in both humans and mammals [14]. The discovery of surfactant deficiency, as a cause of neonatal Respiratory Distress Syndrome (RDS) in preterm infants [15], has been a starting point for the successful treatment of immature preterm infants with intratracheal instillation of exogenous lung surfactant [16]. First generation clinical surfactant preparations were derived from bovine and porcine lungs and consist of surfactant lipids and the surfactant proteins B and C (SP-B and SP-C) [17]. These animal-derived lung surfactants have led to a sharp reduction in morbidity and mortality among preterm infants [16]. More recently, the availability of highly functional SP-B and SP-C analogs has led to the development of advanced synthetic lung surfactants for the treatment of preterm infants with RDS [17].

Direct or indirect injury of alveolar epithelial type 2 cells in Acute Respiratory Distress Syndrome (ARDS) is also associated with lung surfactant deficiency and/or insufficiency by surfactant inactivation. Various studies in animal models and pediatric and adult intensive care patients with ARDS due to bacterial pneumonia and sepsis have shown positive effects of treatment with bovine or porcine lung surfactant [18-20]. Although limited availability and high costs of these animal-derived clinical surfactants have hampered their clinical application in ARDS, the development of synthetic lung surfactants with high surface activity has opened a new treatment modality in ARDS and pneumonia [21].

The clinical symptoms of severe respiratory distress due to COVID-19 infection are not unlike ARDS, as seen in severe community and aspiration pneumonia. Autopsies in COVID-19 cases have shown diffuse alveolar damage and lymphocytic inflammatory infiltrates in the lungs, consistent with viral-induced early ARDS [22, 23]. Desperation due to the severity and high mortality of respiratory failure in COVID-19 patients has led to compassionate use of clinical surfactant in intensive care departments and social media anecdotes of improvements in their clinical status. However, despite comparable symptomatology and pathology, ARDS, due to bacterial pneumonia and COVID-19 viral pneumonia, may not react similarly to a therapeutic intervention like exogenous surfactant administration. This leads to a multitude of questions. Which surfactant preparation may be best and what about timing, mode of administration, and dosing?

So, where to go from here if we want to support COVID-19 pneumonia patients with exogenous surfactant therapy? Surfactant therapy for SARS-CoV-2 viral pneumonia may be given at two time-points during the course of the disease, i.e. (a) during the dyspneic phase to avoid the need for mechanical ventilation or (b) during or soon after intubation for res-

piratory failure and the start of mechanical ventilation. The first approach might be most effective as it could halt the devastating effect of SARS-CoV-2 on the lung by countering surfactant deficiency and inactivation and the cytokine storm. Various synthetic lung surfactant preparations are available in the research community for this purpose [17]. Among these preparations, a synthetic dry powder lung surfactant developed for aerosol delivery [24] would be most interesting as it can not only be used (or repeated) in stages of early respiratory failure in a non-hospital setting, but also during or after tracheal intubation in the intensive care. Intratracheal delivery of a liquid surfactant preparation, such as the animal-derived surfactant preparations currently used clinically in preterm infants with RDS, requires intubation and will increase the fluid load in airways, which are already battling with lung edema. Dosing is another issue as we only have surfactant dosing schedules for infants and young children (usually 100-200 mg/kg), that provide a huge overload over the 4 mg/kg of endogenous lung surfactant present in healthy adult lungs [25]. Repeated lung doses, equivalent to the surfactant pool size, may theoretically provide enough surfactant to alleviate the burden of surfactant insufficiency in COVID-19 pneumonia.

As shown above, COVID-19 pneumonia patients may benefit considerably from exogenous surfactant treatment. The use of a synthetic dry powder lung surfactant, designed for aerosol delivery, offers the opportunity to start treatment during the early stages of a COVID-19 infection. Surfactant dosing is a pivotal issue for further research as dosing schedules for adults cannot be extrapolated from existing data obtained in newborn infants. There is a crucial need for further research into timing, dosing, and delivery of synthetic lung surfactant treatment in COVID-19 pneumonia patients.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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