

REVIEW



The COVID-19 pandemic: a target for surfactant therapy?

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ABSTRACT

Introduction: The dramatic impact of COVID-19 on humans worldwide has initiated an extraordinary search for effective treatment approaches. One of these is the administration of exogenous surfactant, which is being tested in ongoing clinical trials.

Areas covered: Exogenous surfactant is a life-saving treatment for premature infants with neonatal respiratory distress syndrome. This treatment has also been tested for acute respiratory distress syndrome (ARDS) with limited success possibly due to the complexity of that syndrome. The 60-year history of successes and failures associated with surfactant therapy distinguishes it from many other treatments currently being tested for COVID-19 and provides the opportunity to discuss the factors that may influence the success of this therapy.

Expert opinion: Clinical data provide a strong rationale for using exogenous surfactant in COVID-19 patients. Success of this therapy may be influenced by the mechanical ventilation strategy, the timing of treatment, the doses delivered, the method of delivery and the preparations utilized. In addition, future development of enhanced preparations may improve this treatment approach. Overall, results from ongoing trials may not only provide data to indicate if this therapy is effective for COVID-19 patients, but also lead to further scientific understanding and improved treatment strategies.

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic poses the most serious public health crisis since the Spanish Flu epidemic, and is currently the most serious social, economic, and political challenge throughout the world. In search for a cure or therapy, many granting agencies worldwide have rapidly made large, COVID-19-targeted, research investments, resulting in a wide range of preclinical studies and trials. For example, a simple PubMed search of 'COVID-19 treatment' yields more than 1,000 papers, all published since the end of 2019. These papers encompass studies on developing a preventative intervention (*i.e.*, vaccine development), studies targeting the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) specifically (*i.e.*, anti-viral therapy), therapies aimed at treating COVID-19 symptoms (*i.e.*, anti-inflammatory treatment) and/or enhancing supportive care (*i.e.*, mechanical ventilation). Strategies range from the design of novel COVID-19-specific drugs to repurposing drugs utilized in other conditions, with experimental strategies that involve clinical studies with various patient populations as well as pre-clinical animal studies. Although all these experimental approaches are reasonable in the context of the haste to develop effective COVID-19 therapies, the obtained data should be carefully interpreted taking into consideration the clinical-mechanistic understanding, the experimental design,

procedures, and limitations. Failure to do so may lead to overinterpretation of positive preclinical results and, conversely, unwarranted dismissal of promising interventions based on preliminary negative data.

The current review will explore the above considerations as they relate to the potential of exogenous surfactant therapy for COVID-19 patients. This approach represents a supportive therapy aimed at mitigating the progression of lung injury in patients with lung dysfunction due to COVID-19. As of the writing of this review there are five clinical trials of surfactant therapy for COVID-19 patients registered (Table 1) [1–5] and an initial report has been published on the utilization of this therapy in five individual patients [6]. We will provide an overview of surfactant function as well as both the success and failures of exogenous surfactant therapy in neonatal and adult respiratory distress syndrome. Subsequently, we will discuss five guiding postulates deemed important for the design and interpretation of clinical studies on exogenous surfactant therapy for COVID-19.

2. Pulmonary surfactant and surfactant therapy

A simplified overview of the history of pulmonary surfactant research is shown in Figure 1. Briefly, following its hypothetical description and the first experimental evidence for its

Article highlights

- Based on a strong rationale for exogenous surfactant therapy in COVID-19, there are currently five ongoing trials in this patient population.
- Past successes and failures of this therapy in various clinical conditions provides insight into the promise, as well as complexity, of using exogenous surfactant in COVID-19.
- It is important to design and interpret clinical trials for COVID-19 in context of our understanding of the experimental design, procedures, and limitations, including the timing, surfactant preparation, dose, and delivery technique.
- The success of exogenous surfactant therapy for COVID-19 and other pulmonary diseases can potentially be enhanced by utilizing it in combination with other drugs and therapies.

existence several decades later, a 60-year period ensued that encompassed many areas of science and medicine. Basic and pre-clinical research led to major discoveries in, among others, the composition, biophysical function, structure and metabolism of surfactant, as well as the development of exogenous surfactants that could be used for therapy. Paralleling this bench research were clinical studies on the role of surfactant

therapy in neonatal respiratory distress syndrome (NRDS) and adult respiratory distress syndrome (ARDS). Each of these topics are discussed further below.

2.1. Pulmonary surfactant

The foundation for exogenous surfactant therapy lies in the discovery and an appreciation of the functional significance of the endogenous form of this material. The existence of a surface active material that facilitated lung expansion was hypothesized in the 1920s by von Neergaard [7], but it was not until the 1950s that experimental evidence demonstrated that lungs contained a substance that facilitated breathing with minimal effort [8–10]. It is now well established that pulmonary surfactant lines the alveolar surface where it reduces the surface tension to near zero values upon expiration [11]. Furthermore, as one of the first materials encountered by inhaled pathogens and substances that reach the alveoli, surfactant also plays an essential role in the host defense mechanisms of the lung [12]. Endogenous surfactant consists of ~80% phospholipid (PL), 7–10% neutral lipids (mainly cholesterol) and ~10% surfactant-associated proteins

Table 1. Ongoing clinical trials of surfactant therapy to treat COVID-19 patients.

Surfactant preparation	Delivery method	Dose	Timing	Targeted enrollment	Sponsor	Ref.
Bovacant (Alveofact)	Inhalation delivery with nebulized preparations	1080 mg to 3240 mg at 45 mg/mL for 3 doses per day	Within 24 hours of ventilation	24 adults	University Hospital Southampton NHS Foundation Trust, UK	[1]
Bovine Lipid Extract Surfactant (BLES)	Intratracheal instillation	50 mg/kg at 27 mg/mL up to 3 doses per day	ASAP and within 48 hours of ventilation	20 adults	Lawson Health Research Institute, Canada	[2]
Poractant alfa (Curosurf)	Fiberoptic bronchoscopy-directed endobronchial administration	48 mg/kg at 16 mg/mL, distributed 5 lobar bronchi	Within 72 hours of ventilation	20 adults	Hospital of Mantes-la-Jolie, France	[3]
Synthetic KL4 (Lucinactant)	Intratracheal instillation	80 mg/kg	Endotracheal intubation and ventilation	30 adults	Windtree Therapeutics, USA	[4]
Poractant alfa (Curosurf)	Intratracheal instillation	30 mg/kg at 80 mg/mL for 3 doses per day	Within 48 hours of ventilation	85 adults	Chiesi Farmaceutici S.p.A.	[5]

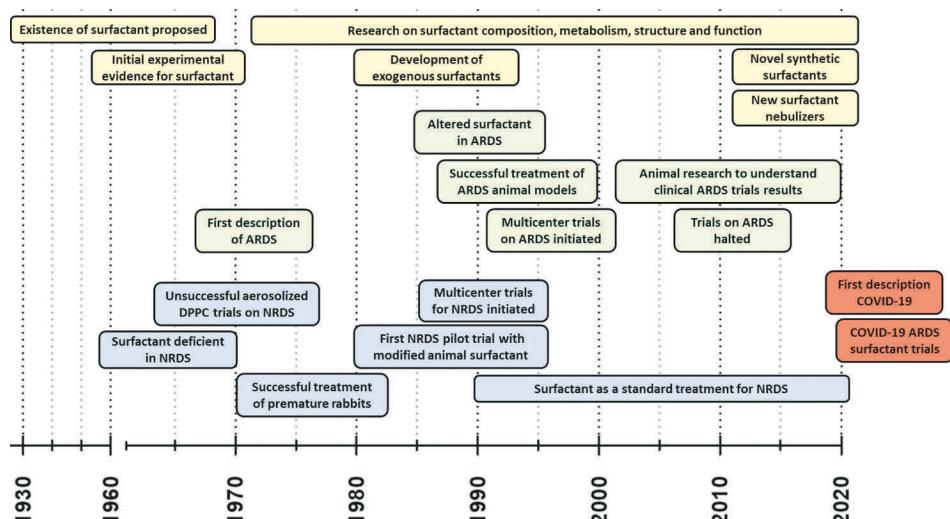


Figure 1. A Century of surfactant research: Biophysical and physiological studies led ultimately to successful treatment of NRDS. ARDS trials were less successful possibly because they encompassed many complex diseases. Advances in exogenous surfactant development and delivery, combined with the known initiating event leading to COVID-19 ARDS, may make this condition amenable to surfactant treatment. Yellow boxes = basic research, green boxes = ARDS-related events, blue boxes = NRDS related events, orange boxes = COVID-19.



(SP) by weight [13]. The major PL components are phosphatidylcholine (PC) ~80%, approximately half of which is disaturated, and ~15% acidic PLs, phosphatidylglycerol plus phosphatidylinositol [14]. The low molecular weight hydrophobic proteins, SP-B and SP-C, are essential for surfactant PL biophysical properties [15,16]. The other two surfactant proteins, SP-A and SP-D, are large calcium-dependent, oligomeric collectins, which have important roles in the innate host defense system [17]. Additionally, SP-A can act in conjunction with the lipids and hydrophobic proteins to enhance the biophysical properties of surfactant [18].

2.2. Surfactant therapy for Neonatal Respiratory Distress Syndrome (NRDS)

Soon after its discovery, the clinical relevance of pulmonary surfactant became apparent from the observation that premature infants suffering from Hyaline Membrane Disease, now known as NRDS, were deficient in this substance [10]. This finding led to the concept that supplementing the premature, surfactant deficient lung with an exogenous form of this material would be beneficial. Indeed, after several decades of research, successful exogenous surfactant treatment was reported in the late 1970s to early 1980s [19,20]. Subsequent clinical trials demonstrated a marked decrease in mortality due to prematurity and exogenous surfactant therapy is currently utilized throughout the world for the treatment of NRDS [21].

Underlying this success story are the enormous hurdles that were overcome, and the important insights that were obtained along the way. For example, an early setback was a large negative clinical trial in which the main component of surfactant, DPPC, was aerosolized into the lungs of premature infants suffering from NRDS [22]. In hindsight, this was the first illustration that not all exogenous surfactants have equal efficacy [23]. It became clear that animal-derived surfactants were most effective [13,24]. These bovine or porcine-derived preparations contain all the surfactant phospholipids as well as the hydrophobic proteins, SP-B and SP-C, which allow the lipids to rapidly form a functional surface film [13,15]. The hydrophilic proteins SP-A and SP-D are not essential for the biophysical properties and these highly immunogenic proteins are removed from the animal-derived preparations during processing. Initial synthetic surfactants, although helpful, were clearly not as effective as these animal derived preparations, mostly due to the difficulty generating artificial forms of SP-B and SP-C [13,25]. However, progress in the abilities to synthesize molecules with SP-B and/or SP-C like properties have improved the future potential of synthetic preparations [24,26].

Other important findings that helped advance the development of this therapy were aspects related to optimal dosing, timing, and the method of administration. Currently, the most common delivery method is as an intratracheal bolus administration of a surfactant suspension at a dose of approximately 100 mg/kg bodyweight, approximately matching the surfactant pool in term infants [27,28]. Aerosol delivery is also being explored, as it allows administration without intubation, however, this is at the cost of rapidly delivering a high dose

[29,30]. As prematurity is the primary cause of NRDS, surfactant can be administered at, or soon after, the baby's first breath. In this setting, surfactant prevents the development of lung damage rather than treating it.

2.3. Surfactant therapy for Acute Respiratory Distress Syndrome (ARDS)

The unqualified success of treating premature infants with surfactant led to animal experiments and clinical trials attempting to extend this therapy to other diseases, most notably ARDS [31]. This syndrome denotes acute respiratory failure with differing levels of hypoxia and diffuse lung infiltrates and is one of the conditions associated with the most severely affected COVID-19 patients [32]. Prior to COVID-19, the incidence was estimated at 50 cases per 100,000/year (~75,000/year in the USA) with mortality of approximately 35% [33,34]. Causes for ARDS include direct lung insults (bacterial or viral induced pneumonia, aspirations, near drowning, thoracic contusions, irradiation, inhalation of toxic materials, etc.) and indirect systemic causes (sepsis, hypovolemic shock, burn trauma, pancreatitis, general trauma including bone fractures, etc.) [35–38]. There is no effective pharmacological therapy for ARDS, and treatment is mostly supportive including mechanical ventilation with increased oxygen levels [39]. Regardless of the initiating insult leading to ARDS, an extensive body of literature has documented that both alterations to surfactant and inactivation of this material occurs in ARDS and these contribute to lung dysfunction [35–38]. Furthermore, data mostly from animal studies indicate that the essential supportive therapy for ARDS, mechanical ventilation, can further disturb the surfactant system [40]. Together, these considerations led to the suggestion that exogenous surfactant would be beneficial in this condition.

Initial investigations into the efficacy of exogenous surfactant in animal models of ARDS and early phase 1 clinical trials demonstrated potential for this therapy [35]. Unfortunately, subsequent large-scale multi-center trials were not successful [41–45], and a meta-analysis of the data suggested that although surfactant may improve blood oxygenation, it did not improve survival [38,46]. While these failures largely curtailed clinical interest in this approach over the last 15 years, the emergence of COVID-19 associated ARDS has initiated a reconsideration of this clinical approach [47]. As will be discussed further below, examining the animal and other mechanistic studies that help explain the negative results in clinical trials for ARDS in general, will provide important insights into the utilization of this therapy for COVID-19 specifically.

3. Surfactant therapy for COVID-19

3.1. Postulate 1: There is a strong rationale for surfactant therapy in COVID-19

Prior to delving into factors influencing outcomes of clinical trials for COVID-19 patients, it is important to assess the rationale for this therapeutic approach by weighing the arguments for and against trying this therapy in the COVID-19 patient population. It should be noted that COVID-19 is

characterized by a variety of responses in infected people ranging from individuals who are asymptomatic to patients that develop severe respiratory failure requiring prolonged mechanical ventilation. Mortality within this latter group is extremely high [48] and would, for the purpose of this discussion, comprise the main target group for exogenous surfactant therapy.

The first consideration used to potentially oppose this treatment approach is that the severely affected COVID-19 patients develop ARDS and, as mentioned earlier, surfactant trials for this syndrome have largely been negative [46,49]. This assessment implies that COVID-19 and the associated circumstances and protocols are similar to those tested in the ARDS trials, an aspect further discussed below. The second concern is that there is currently no direct evidence that surfactant is dysfunctional in the lungs of COVID-19 patients. This is mainly because bronchoalveolar lavage sampling of COVID-19 patients is associated with high risks considering the infectious nature of SARS-CoV-2. The third concern also relates to the risk of spreading the infection, namely the potential of viral exposure of health-care workers involved in surfactant administration [50]. Extensive protocols are required to assure the safety of the people involved in administering the therapy. A final, generic, concern, that applies to all therapies is that of potential negative side effects associated with the treatment. For exogenous surfactant, this concern is relatively minor since the extensive experiences with exogenous surfactant administration in both neonates and ARDS patients have provided a strong indication that the treatment is safe and well tolerated.

Counteracting the arguments above are several considerations supporting the use of exogenous surfactant in COVID-19 patients. Although, as noted above, direct evidence is still lacking, indirect evidence suggests that surfactant dysfunction is a significant contributing factor to the lung dysfunction associated with COVID-19. One line of evidence for this is that SARS-CoV-2 infects the surfactant producing type II alveolar cells [50–52]. Also, a recent study of the lung transcriptome in COVID-19 demonstrated a downregulation of the surfactant proteins due to the viral infection [53]. Further, surfactant impairment has been observed in all animal studies and in patients with ARDS, regardless of the underlying insult leading to the lung dysfunction [35,54–56]. More importantly, experimental and clinical studies on exogenous surfactant in ARDS suggest benefits for this therapy if: 1) surfactant is administered early during the development of respiratory failure, close to, if not in conjunction with, the onset of mechanical ventilation, 2) is used in patients with direct lung injury, and 3) utilizes a highly functional exogenous surfactant preparation [35]. These factors all favor the potential of this treatment strategy in COVID-19 population.

Based on the above considerations, several groups have initiated trials to test the hypothesis that exogenous surfactant is of benefit in patients with COVID-19 [1–5]. Table 1 provides a brief overview of the currently registered trials. Each of the trials is relatively small, ranging from 20 to 85 patients to be enrolled with a primary focus on treatment initiated early after the onset of mechanical ventilation. The relative low

enrollment in these trials indicates that they may not be sufficiently powered to determine significant effects on mortality and/or ventilator-free days; the primary outcomes will be the feasibility, safety, and physiological benefit. Differences among the trials include the method of delivery and the use of different surfactant preparation, with both synthetic and animal-derived surfactants being tested.

While the results from these trials are eagerly awaited, the initial clinical experience with surfactant administration in COVID-19 patients has already been published [6]. Busani and colleagues reported on the treatment of 5 critically ill, mechanically ventilated, COVID-19 patients with a dose of 30 mg/kg of lean body weight of poractant alfa (Curosurf®, Chiesi Farmaceutici S.p.A., Parma, Italy) [6]. The results showed an improvement in oxygenation after 1 h in 4 of the 5 patients and all 5 patients demonstrated improved oxygenation and compliance at the 6-h time-point [6]. In this population four of the five treated were still alive at the end of the 30-day study protocol. Although an uncontrolled study must be interpreted carefully, these results do demonstrate technical feasibility and provide a promising initial observation.

3.2. Postulate 2: The individual aspects of exogenous surfactant therapy are complex

Experience with the development of successful exogenous surfactant therapy in NRDS, as well as, to date, unsuccessful treatments in ARDS have enhanced our understanding of the factors influencing the efficacy of this material. This includes the different exogenous surfactant preparations available, the dose and dosing schedule, the delivery method and the timing for the initiation of surfactant administration (Figure 2). Understanding, and optimizing, each of these aspects appears essential.

3.2.1. Surfactant preparation

The minimally required property of any exogenous surfactant preparation is to be able to form a DPPC containing surface film that is capable of reducing surface tension during lateral compression (*i.e.* expiration) [13]. These functions, adsorption and surface tension reduction, are readily testable *in vitro* using a variety of techniques and all currently available clinical surfactants will exhibit appropriate biophysical functionality in such a setting [13,57]. However, in the context of efficacy in a complex disease, other aspects need to be considered. For example, the viscosity of the material may influence delivery upon instillation as a bolus. More importantly, the resistance to adverse environmental factors, which may be encountered when administered to an injured lung, would be desirable. These can include the ability to counteract inhibition by serum proteins that have leaked into the lung, and to phospholipase and protease activities present within the inflamed alveolar environment [58].

Based on available data from NRDS and studies on surfactant inhibition by serum proteins, modified-animal surfactants containing both hydrophobic proteins may be optimal. These preparations, such as Infasurf, BLES, and Curosurf have also proven safe and effective. Synthetic surfactants have the

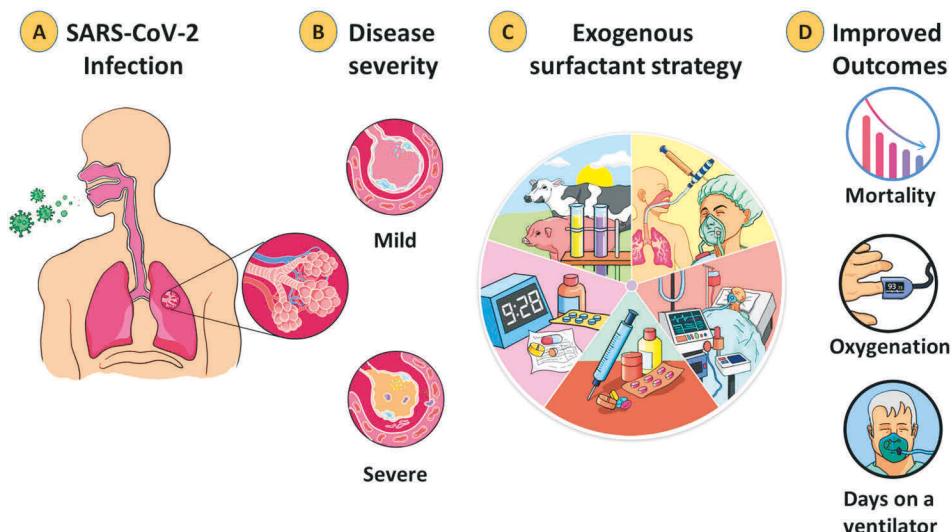


Figure 2. Considerations for surfactant treatment in COVID-19: **A)** People of all ages can be infected with SARS-CoV-2 leading to **B)** different severities, or a progression in severity, in affected people possibly requiring hospitalization and mechanical ventilation, which will influence **C)** the specific strategy of exogenous treatment such as dosage, timing of intervention, source of surfactant, method of application, intubation and ventilation procedures and combination with other therapies, ultimately leading to **D)** improved outcomes such as lower mortality, better blood oxygenation and lung compliance and fewer days in the ICU on a mechanical ventilator.

theoretical advantage that they could be synthesized to be resistant to proteases. For example, peptoid protein mimics of SP-B and SP-C will be resistant to degradation thereby potentially delivering a prolonged activity [59]. Nevertheless, to date, most successful therapies have been achieved with animal-based surfactants and further development of optimal synthetic surfactants is still required. Finally, it should be noted that all exogenous surfactants to date are devoid of the hydrophilic proteins SP-A and SP-D, despite these proteins exhibiting potential beneficial effects in the setting of lung injury [60,61]. As animal-derived versions of these large glycoproteins would be immunogenic, inclusion of these proteins would only be feasible with synthesized human forms of these proteins.

3.2.2. Dose and dosing schedule

Possibly the most problematic aspect of a surfactant treatment strategy to establish is the appropriate dose, since both concentration and volume are important, and the optimal dosing schedule. This is particularly relevant for bolus instillation protocols; for aerosolization dosing is technique-dependent. Successful use of a dose of approximately 100 mg PL per kg bodyweight, delivered as 4 mL/kg at 25 mg/mL, was established for neonates [62]. This dose (*i.e.*, 100 mg/kg) approximates the surfactant pool size of term neonates [27,28]. Minor adjustments for different preparations can readily be made. In general, in the NRDS scenario the treatment aims to restore the deficient material after which the infant will start producing endogenous material, in part facilitated by reutilization of surfactant constituents through recycling mechanisms. The clinical trials on exogenous surfactant for ARDS were initially based on the dose given in NRDS, with redosing hours or days apart [35], but further optimization of the appropriate dose and dosing schedules will clearly be required for the use of this therapy for ARDS due to COVID-19.

The amount of surfactant in a healthy adult lung is estimated at 10 mg/kg (*i.e.*, approximately one-tenth of the surfactant pool size of term neonates) [28], but doses of 100 mg/kg and higher are justified by the need to get adequate distribution and to overcome edema and serum protein inhibition of surfactant. The volume required to deliver the appropriate dose of surfactant needs to be balanced between the ability to distribute the material throughout the lung, which improves with larger instillation volumes, while avoiding challenging an already edematous lung with additional fluid. Interestingly, a recent study has suggested that the volumes employed for surfactant treatment with ARDS should be increased relative to those employed for NRDS [63]. The basis for this suggestion is that the airway surface area in the adult lung is over 100-fold larger than in the neonates and larger volumes would mitigate the effect of material lost in coating the airways. This theoretical consideration will have to be thoroughly examined in animal studies before clinical application can be considered.

The optimal timing of redosing patients with surfactant, and the number of required doses, remain largely unknown and appear somewhat arbitrary in most previous ARDS trials. Animal studies generally investigated single doses within short timeframes and, as such, offer little insight. Since the restoration of a functional surfactant system is reflected *via* increases in oxygenation and compliance, these outcomes provide useful guides for redosing. Overall, however, the dosing schedule of exogenous surfactant administration remains primarily directed by trial and error and needs to be optimized in future clinical trials.

3.2.3. Delivery method

A third consideration in designing a successful clinical trial for the surfactant therapy in COVID-19 patients is the method of surfactant delivery. The two general options for COVID-19 trials are bolus instillation and aerosolization. A third method

suggested for ARDS is using a diluted surfactant suspension to lavage the lung thereby removing inhibitory and inflammatory material from the injured lung while leaving behind some of the exogenous surfactant [64]. While theoretically appealing this invasive method does not appear appropriate for the COVID-19 population from the perspective of healthcare worker safety.

The most common method utilized in studies on ARDS has been the bolus instillation, a technique also adopted by four out of the five trials listed in Table 1 [2–5]. This technique involves instilling the surfactant suspension directly into the trachea of the patient. Although there are some methodological differences among studies, for example related to patient positioning and the number of aliquots delivered, these will be ignored for this general discussion. The major advantage of bolus delivery is that a large amount of surfactant can be delivered rapidly. The distribution of the material, in this method, is mainly determined by gravity as well as the use of a ventilatory sigh subsequent to the administration. A potential disadvantage is that the technique also requires pausing of ventilation and paralysis of the patient during the process of delivery. In addition, the procedure has not been thoroughly standardized or automated and thus can be impacted by the skills and experience of the clinician-investigator.

The alternative delivery method, utilized in one of the COVID-19 trials [1], is aerosolization. Methodological differences exist with the concept of surfactant aerosolization including different devices (particle size, output) and experimental set-ups within the ventilation circuit [30]. The most appealing advantages of aerosol delivery are that it can be incorporated into the patient's ventilation circuit which minimizes user dependency, it allows for continuous surfactant delivery over a prolonged period of time, and it is likely safer from the perspective of health-care personnel involved in the procedure. Another advantage of aerosolized surfactant is its potential to be distributed homogeneously throughout the lung as demonstrated in animal studies [65,66]. However, at a macroscopic level, the distribution of the material with this technique is dependent on airflow and only those regions of the lung that are aerated will receive aerosol [67]. A further disadvantage of aerosol delivery is the fact that only a small percentage of the generated aerosol will reach the alveolar surface, with the remainder being deposited in the ventilation circuit or exhaled. The procedure also requires careful monitoring as to not plug filters placed in the exhalation arm of the circuit.

3.2.4. Timing of administration

It is known that the injured lung, even the partially injured lung, is highly susceptible to markedly enhanced injury [68]. During the early pilot studies implementing surfactant use in premature neonates, it was noted that surfactant treatment was least effective in those infants with low oxygenation values. It was recognized that delayed treatment most likely resulted in epithelial damage, serum permeability and, almost certainly, inhibition of the administered exogenous surfactant. These findings led to the current paradigm of administration soon after intubation whenever oxygenation is significantly

impaired. Animal studies of ARDS have also demonstrated that exogenous surfactant is more effective in mitigating injury compared to treating a severe lung injury [69]. For example, exogenous surfactant treatment of donor lungs *prior to* storage and transplantation mitigated lung injury during the subsequent reperfusion after surgery [70,71]. Thus, a logical conclusion, related to exogenous surfactant for ARDS patients, is that early treatment is optimal. Unfortunately, the multifactorial nature of this syndrome, as well as the variability and/or delays in disease diagnosis associated with reaching trial inclusion criteria, has limited the institution of early treatment in ARDS trials to date. Consequently, the high prevalence of COVID-19 and identification of infected individuals *prior to* admission to the ICU may provide a unique scenario in which treatment can be initiated early during the development of severe lung dysfunction.

However, a particularly critical component of the disease development is this institution of mechanical ventilation with the COVID-19 patients. This supportive therapy, although essential to maintain adequate blood oxygenation, can also propagate lung injury [72]. Animal studies indicate that one of the mechanisms by which this occurs is through the alterations of surfactant due to mechanical ventilation [40]. Additional studies have also demonstrated that maintaining a functional surfactant system mitigates the damaging effects of mechanical ventilation. As an example, it was recently demonstrated that aerosolized surfactant could mitigate the mechanical ventilation-induced decrease in oxygenation in rats [73]. Although the responses to mechanical ventilation in patients with ARDS may be more complex than in these animal studies, in the context of COVID-19, the initiation of mechanical ventilation likely represents an appropriate, minimally invasive, opportunity for the initiation of surfactant-based interventions. Consistent with this suggestion, the majority of trials listed in Table 1 aim to administer surfactant relatively soon after the onset of mechanical ventilation.

3.3. Postulate 3: Everything is interconnected

Whereas the above discussion focused on individual factors impacting exogenous surfactant efficacy, it is important to realize that all of these factors influence each other. A prime example of this aspect was shown in a study utilizing an adult sheep model of surfactant deficiency to examine different treatment strategies [74]. It was observed that instillation of one surfactant preparation, BLES, resulted in higher oxygenation values than another preparation, Survanta. However when these preparations were administered *via* aerosolization the trend was reversed with Survanta yielding higher oxygenation values as compared to BLES [74]. Thus, rather than separately optimizing each individual factor that can influence surfactant's efficacy, it is important, or at least ideal, to design a suitable strategy to collectively optimize all interrelated factors for a specific pathophysiology.

Most of the clinical trials performed to date for ARDS have utilized a specific surfactant treatment strategy in a heterogeneous patient population defined by reaching the entry criteria for ARDS. This included people with



a variety of insults leading to ARDS, as well as considerable discrepancies in the timing of administration. Within at least a couple of these trials, retrospective analysis showed that improvements were observed in patients with direct lung injury as compared to indirect initiating events such as sepsis [75,76]. Given that COVID-19 is a direct lung insult, *i.e.*, lung infection by SARS-CoV-2 being the initiating event, and that normally there will be an awareness of the infection at the time of ICU admission or at least at the onset of mechanical ventilation, it will be possible to provide a more consistent surfactant treatment strategy with a more homogeneous patient population. This would be further facilitated by the large number of current cases. Nevertheless, it should be noted that the impaired gas exchange observed in COVID-19 patients has been described as falling between two extreme phenotypes [77–79]. The L phenotype is characterized by having relatively high compliance in which low oxygenation values may be due to perfusion-related pathophysiology. In contrast, the H phenotype has impaired compliance leading to the observed hypoxemia. These concepts, which are somewhat oversimplified here, are the topic of intense discussion within the COVID-19 literature related to lung mechanics in these patients. Nevertheless, for the purpose of this discussion, the impact of pathophysiological differences at the time of initiating surfactant treatment strategies should be carefully considered. Two scenarios are described below.

The first scenario appears to be the approach taken by the trials listed in **Table 1**, which is the initiation of treatment soon after the onset of mechanical ventilation. This approach takes advantage of the unique situation within the COVID-19 pandemic, the ability to treat early in the development of ARDS symptoms. At this early time point, it is likely that different delivery techniques can be successfully employed. As these patients will likely still have adequate lung compliance, aerosol delivery is feasible since it would provide a noninvasive method to administer the surfactant with the aim to maintain functional surfactant levels. This will involve a device whereby the aerosolizer is incorporated, and potentially synchronized, with the ventilator. Although a discussion regarding the different types of aerosolizers is beyond the scope of this review, the device should ideally have a high output, deliver aerosols that maintain surfactant activity and are small enough to assure alveolar distribution, and should not interfere with ventilator parameters. This latter aspect can occur through aerosolizer-associated airflow, deposition of surfactant within the ventilatory circuit or *via* plugging of expiratory filters by the exhaled particles.

Intratracheal instillation is also feasible at this time-point which will ensure that a high dose of surfactant is delivered quickly. In this technique, patient positioning may help with proper distribution of the material. Experience with the instillation technique is important in order to not create stable bubbles which can block airways. As the goal is to maintain a functional surfactant system, dose and dosing schedule for this approach are difficult to determine based on available information; a daily administration, at doses similar to those given to neonates, may represent a reasonable starting point.

For both techniques, all available exogenous surfactants with proper biophysical properties will be suitable. Although mortality is obviously an important outcome for any COVID-19 trial, focus of this 'early treatment strategy' would be on mitigating lung injury during ventilation. As such, outcomes such as oxygenation and other physiological parameters, as well as ventilator free days, will be important. In addition, since ventilation can impact systemic inflammation, analysis of cytokines, chemokines and lipid mediators within the serum of the patients may be helpful in assessing the effects of the treatment beyond clinical outcomes.

The second potential scenario for surfactant administration is to provide this treatment at a later stage when the patient displays critical lung injury consistent with severe ARDS. In this situation, decreased compliance may be indicative of surfactant dysfunction, and therapy will aim to restore this pathophysiological condition. This strategy was employed by the reported study by Busani *et al.* in which patients with severe lung injury were treated [6]. Considerations for treatment at this time-point within the progression of the disease are different than those described above. As the lungs of these patients will have reduced compliance, aerosolization is no longer a logical treatment option as it would lead to deposition of the surfactant in the compliant areas of the lung rather than the collapsed injured regions. Instillation of a high dose of surfactant is therefore required. The surfactant preparation should have good biophysical properties not only by itself but also in the edematous conditions that may be encountered in these injured lungs. Since the main outcomes may be oxygenation and lung compliance, dosing schedules could be based on the deterioration of those parameters. The results reported by the Italian group are encouraging as it not only shows that this therapy is safe, but also indicates that investigation into exogenous surfactant as a rescue or compassionate therapy is still worthwhile.

3.4. Postulate 4: Surfactant therapy can be enhanced or combined with other therapies

While the outcomes of the ongoing clinical trials are eagerly awaited, ongoing research is trying to improve this therapy. This encompasses improvements in the effectiveness of the individual exogenous surfactant preparations, utilizing surfactant as a carrier for other drugs and, finally, using exogenous surfactant in combination with other therapies. With respect to the latter, the use of surfactant is compatible with most other (potential) COVID-19 treatment strategies. Considering the wide array of approaches under investigation, we will limit our focus on the surfactant-relevant enhancements in therapy.

3.4.1. The next generations of exogenous surfactants

Although a variety of synthetic surfactants have been developed and tested over the last three decades, current evidence still favors the animal-derived material for most clinical indications [13,36]. As noted above, the two hydrophobic proteins of surfactant, SP-B and SP-C, have been difficult to produce synthetically and protein-free surfactants have limited functionality. Producing effective synthetic exogenous surfactants

would provide theoretical benefits at several levels. First, it would limit the potential resource limitations of animal-derived surfactants as well as potential natural variations in preparations associated with a natural product. Second, synthetic surfactant could be preferred over porcine or bovine surfactant for personal or religious reasons. Third, with the appropriate building blocks, synthetic surfactant could be cheaper, and custom-designed for specific indications or situations. For example, one could envision an inexpensive, synthetic surfactant with enhanced stability over natural surfactants, for distribution to third world countries. Finally, it is theoretically possible to produce a synthetic surfactant containing a human version of the hydrophilic protein SP-A. Removed from all animal-derived surfactants for immunological reasons, an SP-A containing surfactant may have better functionality in certain disease conditions. For example, the presence of SP-A in surfactant reduces the inhibitory effects of serum proteins or reactive oxygen species [80–82]. This would obviously impact the functionality in conditions such as severe ARDS associated with COVID-19.

Based on this potential, several approaches to generating new synthetic surfactant have been reported, with others likely ongoing. Currently, the most advanced new synthetic surfactant is CHF5633 produced by Chiesi Farmaceutici S.p.A. (Parma, Italy), which has already been utilized in premature infants with good efficacy [83]. In contrast to the other synthetic surfactants reported to date, which have been based on either SP-B or SP-C like peptides or other novel constituents to support its biophysical function, this synthetic surfactant is enriched by peptide analogs of both hydrophobic surfactant proteins. Another alternative is the production of peptoid-based protein mimics [59]. Although this approach with stable peptoid versions of SP-B and SP-C is not as far advanced as CHF5633, promising results have been obtained [59]. With respect to COVID-19, future pandemics and treatment of ARDS and other lung injuries in general, it will be of great interest to see how synthetic surfactants develop in the years to come.

3.4.2. Surfactant as a drug delivery vehicle

As COVID-19 is initiated through the respiratory system, delivery of drugs directly to the lung is appealing. Such localized delivery could yield highly effective doses of a drug at the required site for clinical efficacy. Furthermore, it would avoid potential issues associated with systemic administration, such as hepatic drug metabolism, renal clearance, and off-target effects, which could negatively impact the effectiveness of a particular drug [84]. Unfortunately, localized delivery becomes more difficult when targeting the deeper areas of the lung, due to its extensive branching structure and large surface area. Existing areas of lung injury would provide a further hurdle for direct pulmonary delivery. One solution to overcome these obstacles would be the utilization of exogenous surfactant for delivering COVID-19-relevant drugs to the lung [85–87].

The mechanism by which exogenous surfactant by itself may have beneficial effects in COVID-19 is supportive in nature: helping to maintain lung function while the body fights off the viral infection. The basic concept behind surfactant as

a delivery vehicle is that it would still function to help maintain lung compliance and oxygenation but also, *via* surfactant's ability to spread throughout the lungs, allow the delivery of COVID-19 relevant therapeutics deep inside the lung to further improve patient outcomes. This approach could apply to existing or new drugs [88], especially those hydrophobic in nature.

A variety of potential COVID-19 drugs can be considered suitable for delivery *via* exogenous surfactant. In general, research into the development of such fortified surfactant preparations should focus on the ability of surfactant to transport the drug to the alveolar region of the lung and to ensure that the preparation maintains functionality of the delivered drug as well as the surfactant. With respect to COVID-19, one could consider drugs that either target pathophysiological pathways associated with the development of the disease, or therapeutics that directly target the viral infection or replication pathways. The former could include glucocorticoids to downregulate pulmonary inflammation, DNase to reduce the debris associated with NETosis, fibrinolytics to limit fibrin deposition, β 2 agonist to mitigate edema, or anti-oxidants to counteract oxidative stress [39,89,90]. Intratracheal instillation of budesonide using Survanta as a delivery vehicle has shown efficacy in preventing chronic lung disease in premature infants [91]. The optimal combinations and mixing ratios between different surfactant preparations and glucocorticoids have been studied [92,93]. The recent report of a successful trial using systemic administration of dexamethasone attests to the potential effectiveness of this approach [94]. Targeting the viral infection could also involve existing host defense peptides, currently tested drugs like remdesivir or novel designer molecules. Although it is unlikely that all of these drugs will prove suitable for use with exogenous surfactant, they represent logical targets for at least pre-clinical studies to determine potential efficacy.

3.5. Postulate 5: Surfactant therapy is cost-effective

Suggesting that exogenous surfactant therapy is cost-effective is, of course, highly dependent on the clinical outcomes. In addition, the cost per individual patient will vary between different preparations, doses administered either by instillation or aerosolization and health-care costs in different countries. Nevertheless, as a starting point of discussion, it is estimated that an exogenous surfactant treatment would cost US\$6,000–10,000 per patient [95]. Adding to these direct costs would be additional expenses related to increased personal protective equipment, personnel, and ICU procedures. If surfactant treatment provides a mortality benefit, these costs are obviously appropriate. However, improvements in additional outcomes, such as ventilator free days and fewer days of ICU stay would have a positive impact, both on cost as well as on the capacity of an individual hospital to deal with the large number of patients requiring intensive care.

4. Conclusion

Despite recent advances in the care of COVID-19 patients resulting in diminished mortality and encouraging preliminary reports on vaccines, it appears evident that we are into a second phase



and COVID-19 will continue to be an important health hazard for the foreseeable future. Thus, the search for appropriate treatment approaches, from prevention, supportive measures, and cures remains an important focus of research. This review has summarized the data on exogenous surfactant as one potential supportive therapy for the mechanically ventilated lung injured COVID-19 patients. It should be noted that several related aspects of the disease and patient management such as prone positioning, oxygen administration, more thorough details of different lung phenotypes and the development of multiple organ failure, fell outside the relatively narrow scope of the review, but are important for a broader context. The main message of this review is illustrated in [Figure 2](#), including how disease severity may influence specific surfactant treatment strategies and the hope that this therapy may result in improved outcomes.

5. Expert opinion

The above information provides a strong rationale for various surfactant treatment strategies in COVID-19 patients. Treatment of severely injured patients, such as those reported by Busani *et al.* with promising results [6], is based on the pathophysiology of the disease and the role of surfactant therapy in lung compliance. In this approach, exogenous surfactant aims to improve lung function. Despite a strong scientific rationale for additional studies employing this strategy, the authors' interpretation of the current literature favors an approach targeting treatment early in the disease process. The rationale for this opinion, as well as some of the practical considerations associated with this approach toward exogenous surfactant treatment for COVID-19 patients, is outlined below.

The majority of clinical and pre-clinical evidence indicates that surfactant therapy is mainly suited to mitigating the development or progression of injury; thus, the optimal timing for surfactant treatment in COVID-19 patients would be immediately at the onset of mechanical ventilation. Realistically, during a pandemic, in an ICU setting with patients with a highly infectious disease, with a process that requires involvement of the pharmacy, clinical trial coordinators, respiratory therapists, nurses and ICU physicians, a reasonable timeframe would be within 24 hours of the onset of mechanical ventilation. At the current stage of our knowledge, the authors consider an intratracheal bolus instillation of an animal derived surfactant at 50–100 mg/kg the most logical treatment strategy. This approach would ensure the delivery of an adequate dose of highly functional surfactant. It should be noted however, that this approach comes with some hurdles as it requires expertise in surfactant delivery, movement of the patients to ensure adequate distribution, and a brief halting of the mechanical ventilator. The process should also be optimized to avoid any increased risk in the safety and potential exposure of health-care workers involved in surfactant administration and patient monitoring. Considering these limitations, aerosol delivery, in which the delivery technique could be incorporated in the ventilation circuit, has distinct theoretical advantages. For the purpose of a clinical trial however, the lack of confidence in knowing the amount of surfactant deposited in the lung is a major concern that limit the authors enthusiasm for this approach. With recent improvements in aerosol devices for surfactant, the authors

deem further research on aerosol delivery of surfactant in the adult injured lung an important area of further research.

The goal of surfactant administration is aimed at maintaining lung function rather than targeting the infection itself. Success of this therapy would include maintaining or improving blood oxygenation, reducing mechanical ventilation dependency, shorter ICU stays, and, hopefully, reducing mortality. However, the supportive nature of the therapy also implies that it can be combined with additional approaches that will target the viral infection specifically. In addition to the complementing surfactant therapy with distinct other therapeutic approaches currently being investigated, the authors consider the possibility of combining surfactant with potential COVID-19 related drugs for direct pulmonary delivery particularly interesting for further preclinical studies. Paralleling research into this concept should be the further development of synthetic exogenous surfactants, since a major advantage of such products would be the ability to optimize the exogenous surfactant for drug delivery.

Overall, as more mechanistic and clinical insight into COVID-19 is being obtained, and results of the many clinical trials are reported, a clearer picture of the optimal treatment for an individual infected patient will emerge. The authors suggest that surfactant therapy has the potential to be beneficial in a subset of the COVID-19 patient population. However, as we have outlined in our review, there are existing barriers and limitations to our understanding that may affect this therapeutic approach and requires additional research. It is hoped that this information provides a context for interpreting the results of the ongoing exogenous surfactant trials in COVID-19 patients but also lead to further scientific understanding and improved treatment strategies for this and other cases of ARDS.

Declaration of interest

R Veldhuizen contributed to the design of the 'LESS-COVID' trial for testing exogenous surfactant in COVID-19 (ClinicalTrials.gov Identifier: NCT04375735), this therapy is being reviewed in this paper. J Lewis is the lead investigator of the 'LESS-COVID' trial for testing exogenous surfactant in COVID-19 (ClinicalTrials.gov Identifier: NCT04375735), this therapy is being reviewed in this paper. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

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