Initial experiences from patients with COVID-19 on ventilatory support in Denmark

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ABSTRACT

INTRODUCTION: The coronavirus disease 2019 (COVID-19) pandemic reached Denmark in early 2020. This paper presents initial intensive-care unit (ICU) experiences with COVID-19 patients at Roskilde Hospital, which was the primary recipient of COVID-19 patients in need of intensive care in the Zealand Region, Denmark.
METHODS: An evaluation was conducted of the COVID-19 patients admitted to the ICU due to respiratory failure from 11 March 2020 to 01 April 2020. The number of ICU beds was increased from eight to 22 beds during this period.
RESULTS: Sixteen patients (four women) were evaluated. The median age was 69.5 years (range: 56-84 years). All the patients were admitted to the ICU for hypoxemic respiratory failure and all needed mechanical ventilation by orotracheal intubation. By 16 April, six patients were still admitted to the ICU, four patients had been discharged from the ICU and seven had died. At present, the average length of ICU stay is 14 ± 9 days (mean ± standard deviation). One patient has remained on ventilatory support for 31 days. The evaluation revealed four key themes. COVID-19 patients 1) had greatly increased C-reactive protein levels, 2) needed a significant inspiratory O_2 fraction, 3) were highly positive end-expiratory pressure (PEEP) dependent on ventilatory support and 4) suffered highly fluctuating respiratory failure requiring ventilatory support for a significantly longer period of time than non-COVID-19 patients.
CONCLUSIONS: COVID-19 patients have characteristic reproducible laboratory findings and present a major challenge due to their illness severity and required treatment length.
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Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has developed into a pandemic and coronavirus disease 2019 (COVID-19) may become severe in some patients [1, 2]. Intensive-care unit (ICU) capacity has been increased as COVID-19 may cause respiratory failure [3] of varying adult respiratory distress syndrome (ARDS) severity. The severity of ARDS is described by the ratio of the arterial oxygen tension (PaO_2) to the inspiratory oxygen fraction (FiO_2) [4]. Recently, an international guideline on the treatment of COVID-19 was released by the Society of Critical Care Medicine [5]. However, the scientific evidence underpinning the treatment of COVID-19-associated respiratory failure is sparse [6]. This paper presents initial experiences with COVID-19 at ICU Zealand University Hospital Roskilde, which initially served as the primary COVID-19 unit in the Zealand Region, Denmark.

METHODS

This is a single-centre descriptive study with quality-like evaluation. Sharing our initial experiences with the treatment of COVID-19 patients in the ICU is essential in this early stage of the pandemic. The evaluation was conducted among COVID-19 patients admitted to the ICU due to respiratory failure between 11 March 2020 and 01 April 2020. The local guideline on COVID-19 treatment of ICU patients is shown in **Table 1**. The ICU capacity was increased from eight to 22 beds during this period. Initially, the ventilator capacity consisted of Hamilton mechanical ventilators exclusively. These were supplemented by ventilators allocated from the operating theatre. In addition, three older ventilator models of the Engstrom type were made available for the COVID-19 ICU. The study was presented to the Regional Ethical Committee that found the study to be a quality evaluation paper in a clinical setting without the need to go through a formal approval process. The management of the Department of Anaesthesia at Zealand University Hospital Roskilde granted its permission to extract data from the patient files to facilitate a retrospective quality study.

Trial registration: not relevant.

RESULTS

On 11 March 2020, the first COVID-19 patient was admitted to the ICU. The following days, another sixteen COVID-19 patients were admitted. The sixteen patients, of whom only four were women, had a median age of 69.5 years (range: 56-84 years). All patients presented with life-threatening hypoxic respiratory failure requiring acute intubation and ventilatory support. By 16 April, six patients remained in the ICU, four patients had been discharged from the ICU and seven had died. So far, the average length of ICU stay is 14 ± 9 days (mean ± standard deviation); and by 16 April, one of

**TABLE 1 /** The local guideline for treatment of coronavirus disease 2019 patients in the intensive-care unit.

Sedation	Remifentanil and propofol
Ventilation	Orotracheal intubation Mechanical ventilator with settings in controlled mandatory ventilation PEEP initially 13-15 cm H_2O and FiO_2 〉 0.6 Maintaining sufficient ventilation with a tidal volume 〈 6 ml/kg of ideal body weight Respiratory frequency at 15-30 breaths/min. PaO_2 〉 8-9 kPa I:E ratio 1:1.5 or 1:1
Circulation	Infusion of noradrenalin to maintain MAP at 60-65 mmHg Fluid restriction Haemoglobin level 〉 4.3 mmol/l
Nutrition	25-30 kcal/kg
Renal	Maintain diuresis until slightly negative fluid balance Consider dialysis if increase in serum creatinine level
Coagulation	Thrombosis prophylaxis
Systemic	Avoid routine administration of steroid: prednisolone
Blood tests	Daily

FiO_2 = inspired O_2 fraction; I:E = inspiratory:expiratory; MAP = mean arterial pressure; PaO_2 = arterial O_2 pressureM; PEEP = *positive end-expiratory pressure*.

the patients had been on ventilatory support for 31 days. Another four patients had successfully been weaned off ventilator support after needing respiratory support for up to 19 days. **Figure 1** shows the increase in the number of COVID-19 patients admitted to the ICU. Patient demographics are shown in **Table 2**. Except for three cases, the patients included in this report all had at least one co-morbidity related to the heart, lungs, diabetes, hypertension or cancer. Almost half of the patients had a history of smoking.

Patients presented with severe respiratory hypoxic failure progressing into mainly mono-systemic pulmonary failure and in several cases death. In a minimum of one case, concurrent rapid development of severe multi-organ failure of pulmonary, renal, circulatory

FIGURE 1 / The increase in number of admissions of coronavirus disease 2019 patients to the intensive-care unit between 11 March 2020 and 01 April 2020.
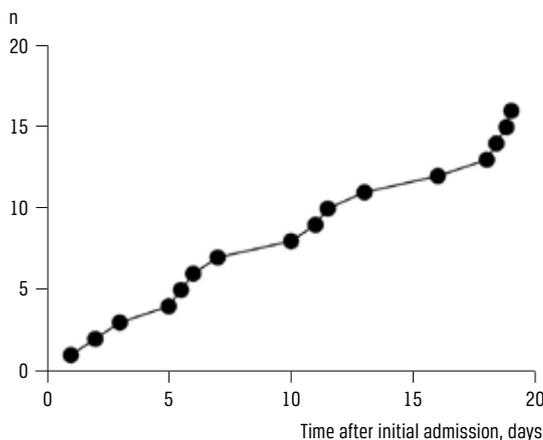
liver and coagulative origin was seen. BMI indicated overweight. In three patients, BMI was above 30 kg/m^2. Laboratory investigations showed elevated levels of haemophagocytosis indicators as well as markedly increased C-reactive protein (CRP) levels (see **Figure 2**) and most often without leucocytosis (Table 2). All COVID-19 patients admitted to the ICU had elevated lactate dehydrogenase (LDH) (> 300 U/l) at admission. In severely affected patients, ferritin levels were increased as well. D-dimer was markedly increased (in six patients, D-dimer levels exceeded 20 whereas data for coagulation competence (international normalised ratio, INR) were almost within normal limits. Chest X-ray of the thorax showed infiltrates in a classical ARDS pattern.

Experiences with ventilatory and circulatory support as well as the antimicrobial strategy are described below.

Ventilatory support

In accordance with ARDS guidelines [7], treatment aimed to:

- Maintain sufficient ventilation with a tidal volume (TV) below 6 ml/kg of ideal body weight
- Maintain the inspiratory plateau pressure below 30 cm H_2O.

In the initial phase, COVID-19 patients were considered to need a high positive end-expiratory pressure (PEEP; up to 15-18 cm H_2O) for several days to facilitate oxygenation of the blood. To achieve targets for PaO_2 and arterial haemoglobin O_2 saturation, our experience is that FiO_2 may reach 0.7-0.8 for several days (average 0.62 with a maximum of 1.00). It is also our experience that a PEEP reduction should be initiated with caution and should not exceed 1-2 cm H_2O per day. Initial ventilatory settings are shown in Table 2. Our patients demonstrated an average ARDS score of 17 ± 5 kPa, indicating severe respiratory failure.

It is considered that ventilation in prone position, if needed, should be initiated early and be maintained for 14-16 hours a day for at least three days. In five patients, ventilation in prone position was needed. Ventilation dyssynchrony may occur and the patient may be unable to accept ventilatory settings despite deep sedation. Muscle relaxation with rocuronium may be necessary.

With patients ventilated at a low TV, it is our experience that hypercapnia needs to be accepted despite ventilation at 10-12 l/min. In the initial phase, it was possible to maintain the TV within the aim without provoking severe hypercapnia (Table 2). We aimed for ventilatory support in a controlled ventilatory setting until the clinical condition stabilised so that ventilation in adaptive support ventilation mode was considered

TABLE 2 / Patient demographics, initial ventilatory settings[a] and selected blood variables.

Differentialdiagnose	Symptomer
BMI, mean ± SE, kg/m^2	28.9 ± 8.5
Diabetes, n (%)	2 (13)
Hypertension, n (%)	9 (56)
Heart disease, n (%)	3 (19)
Lung disease, n (%)	3 (19)
Previous cancer, n (%)	3 (19)
Smoking, n (%)	7 (44)
Alcohol, n (%)	1 (6)
FiO$_2$, mean ± SE	0.62 ± 0.20
PaO$_2$, mean ± SE, kPa	9.8 ± 1.3
PaCO$_2$, mean ± SE, kPa	5.9 ± 1.1 kPa
Tidal volume/kg, mean ± SE, cm H$_2$O	5.6 ± 1.0
MAP, mmHg	74 ± 7
Lactate level, mean ± SE, mmol/l	1.3 ± 0.8
pH, mean ± SE	7.36 ± 0.05
CRP level, mean ± SE, mg/l	343 ± 110
Ferritin level, mean ± SE, µg/l	2,744 ± 2,211
LDH level, mean ± SE, U/l	614 ± 233
D-dimer level, mean ± SE, mg/l	13.4 ± 8.2
INR, mean ± SE	1.2 ± 0.1

CRP = C-reactive protein; FiO$_2$ = inspired O$_2$ fraction; INR = international normalised ratio, coagulation competence; LDH = lactate dehydrogenase; MAP = mean arterial pressure; PaCO$_2$ = arterial CO$_2$ pressure; PaO$_2$ = arterial O$_2$ pressure; SE = standard error.
a) Ventilatory settings are those obtained within the 1st day after respiratory failure was stabilised with the patient on a ventilator via orothracheal intubation.

possible. In selected patients, a so-called lung recruitment manoeuvre seems to have a transient effect on oxygenation levels in the blood. Our impression, however, is that respiratory failure is related to inflammation and subsequent oedema of the alveolo-capillary membrane without significant atelectasis formation. In support of this, bronchoscopy revealed oedema and inflammation in the epithelium. When patients are to be weaned off ventilator support, administration of methadone is useful for treatment of abstinences following a prolonged period of sedation, but it may also be helpful for treatment of cough that seems to be present even several days after tracheotomy has been performed.

Our experience is that tracheotomy should be postponed until a need for ventilation in the prone position is less likely. Our experience also is that, in the initial phase of respiratory failure, COVID-19 patients may have highly fluctuating respiratory support requirements. Recurrence of respiratory failure was seen up to 5-7 days after initiation of mechanical ventilation. Low-dose prednisolone therapy was used in patients with more severe ARDS only. Transfer of patients to specialised thoracic surgery units for extracorporeal membrane oxygenation therapy is available, but has not yet

been utilised. The highly variable course of respiratory failure is a clinical challenge demanding that treatment needs be re-evaluated frequently and on a highly individualised basis.

Circulatory support
It is our experience that in COVID-19 patients, systemic vasodilatation is not as severe as for patients in systemic inflammatory response syndrome. In most patients, administration of noradrenaline infusion (a modest dose) was needed to maintain blood pressure. In the initial phase of COVID-19, serum lactate levels were within normal limits for most patients and metabolic acidosis was absent (Table 2). We have maintained patients on fluid restriction to limit the accumulation of fluid in the lungs. However, at the same time, it is ensured that patients do not become hypovolaemic. Impaired renal function led to a need for continuous renal replacement therapy in five patients. Unfortunately, dialysis failed to be life saving. Severe and rapidly increasing hyperthermia within 24 hours of admission was recorded for two patients. Both subsequently died.

Microbiological support
Following guidance from the Departments of Microbiology and Infectious Diseases, the first five COVID-19 patients were given an empirical treatment with meropenem and clarithromycin, whereas all subsequent patients were given piperacillin-tazobactam and clarithromycin. Clarithromycin was discontinued following negative cultures for atypical bacteria from tracheal fluid. Meropenem and piperacillin-tazobactam were continued for a minimum total of eight days or until treatment was deemed sufficient. In some cases, piperacillin-tazobactam was changed to meropenem when

FIGURE 2 / Changes in C-reactive protein concentration (CRP) in a coronavirus disease 2019 patient, who was discharged from the intensive-care unit (ICU) to a department of infectious diseases following 24 days of intensive care.
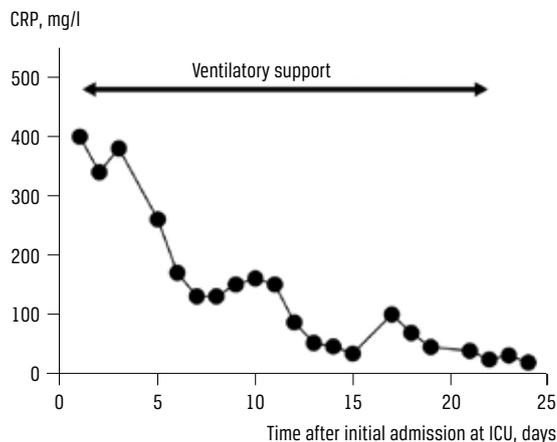
Bronchoscopic recording of a coronavirus disease 2019 patient.

suspected bacterial superinfection seemed uncontrolled and positive microbiology was absent. Vancomycin was used as a supplement in selected cases. The number of positive cultures has been limited for COVID-19 patients in the ICU. Ventilator-associated pneumonia (with *Enterobacter cloacae*) was verified only in one COVID-19 patient. Pro-calcitonin levels were measured regularly to guide the antibiotic strategy.

DISCUSSION

Treatment of COVID-19 patients is a new situation for most clinicians. This paper describes our initial experiences with COVID-19 patients requiring ventilatory and circulatory support in our ICU at Zealand University Hospital Roskilde. So far, the experience is that ventilatory support may need to be maintained for more than four weeks and that a prolonged period of rehabilitation is to be expected in recovering patients, as severe critical illness peripheral neuropathy is likely. COVID-19-associated respiratory failure is a challenge due both to its severity and duration.

The clinical course of our COVID-19 patients is similar to that described in small and large case series from other countries [1-3, 8, 9]. The age of COVID-19 patients in ICU is as expected. The significant overrepresentation of males is somewhat surprising. The highly abnormal CRP and LDH values are of particular interest. In addition, markedly increased D-dimer levels also reflect severe infection. However, in COVID-19 patients, the risk of arterial thromboembolism should be considered. Thus, pulmonary embolism was the most frequent thrombotic complication in a Dutch report counting 184 ICU patients with proven COVID-19 pneumonia [10]. An echocardiographic evaluation of the right ventricle may visualise a systemic influence of pulmonary embolism as well as myocarditis secondary to COVID-19 [11].

The need for PEEP is well known in the treatment of ARDS [4, 6, 7], but it is somewhat surprising that COVID-19 patients are PEEP-dependent for several days and highly sensitive to changes in PEEP levels. High levels of PEEP are also one of the main baseline characteristics of patients infected with SARS-CoV-2 admitted to ICUs in the Lombardy Region, Italy [8]. One explanation for the PEEP dependence may be that normal production of surfactant is influenced by SARS-CoV-2 [12]. On the other hand, it may be that the initial use of high levels of PEEP is detrimental to lung function as is the case for prolonged use of hyperoxia [13]. Therefore, the needed FiO_2 level should be re-evaluated daily. As the alveolo-capillary membrane is a main problem in COVID-19, assessment of the alveolar-arterial O_2 difference as well pulmonary O_2 diffusion capacity measurement could be considered as a supplementary investigation in the ICU.

Clinical concerns have developed as to whether patients in angiotensin-converting enzyme (ACE) blockade are at greater risk for SARS-CoV-2 infection [14]. Nine of our patients had been diagnosed with hypertension, and only in two cases had patients been prescribed ACE inhibitors prior to admission. Based on our cases, it seems unlikely that antihypertensive treatment comprising ACE blockade had an effect on the clinical course of COVID-19.

Centralisation of the ICU treatment of COVID-19 patients was appropriate and enabled early knowledge sharing and experience gathering.

This paper supports the claim that COVID-19-associated respiratory failure is difficult to treat.

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