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Management of SARS-CoV-2 pneumonia in intensive care unit: An observational retrospective study comparing two bundles

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ABSTRACT

Purpose: To compare the effects of two therapeutic bundles of management in SARS-CoV2 ICU patients.
Materials and methods: Our retrospective, observational study was performed in a university ICU from March to June 2020 (first wave) and from September 2020 to January 2021 (second wave). In first wave, patients received bundle 1 including early invasive ventilation, hydroxychloroquine, cefotaxime and azithromycin. In second wave, bundle 2 included non-invasive oxygenation support and dexamethasone. The main outcome was in-hospital mortality. Secondary outcomes included ICU and hospital length of stay, ICU supportive therapies, viral clearance and antimicrobial resistance emergence.
Results: 129 patients with SARS-CoV-2 pneumonia were admitted to our ICU. Thirty-five were treated according to bundle 1 and 76 to bundle 2. In-hospital mortality was similar in the two groups (23%, $p = 1$). The hospital ($p = 0.003$) and ICU ($p = 0.01$) length of stay and ventilator-free days at 28 days ($p = 0.03$) were significantly reduced in bundle 2. Increasing age, vasopressor use and PaO_2/FiO_2 ratio < 125 were associated with in-hospital mortality.
Conclusion: Within the limitations of our study, changes in therapeutic bundles for SARS-Cov-2 ICU patients might have no effect on in-hospital mortality but were associated with less exposure to mechanical ventilation and reduced hospital length of stay.

1. Introduction

Since the World Health Organization announced the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) outbreak [1], many antivirals and immunomodulatory drugs have been proposed [2] to improve outcomes of patients admitted to the hospital. In addition, strategies regarding oxygenation support have been discussed at length.

During the first wave lasting from March to May 2020, hydroxychloroquine (HCQ) and azithromycin (AZT) were extensively used to reduce the viral load of SARS-CoV-2 in patients with mild to severe disease [1] [2]. However, several studies suggested that HCQ use failed to improve the prognosis in SARS-CoV-2 intensive care unit (ICU) patients [3]. The RECOVERY study, a large trial that randomized 4717 patients, found no difference in 28-day mortality between the patients treated with and those who did not receive this drug [4]. In addition, several lines of evidence showed a low rate of bacterial infections in the ICU admission of patients with SARS-CoV-2, suggesting that early antibiotic treatment was not systematically required in those patients. From a ventilator-related standpoint, early invasive mechanical ventilation was suggested as safe with regard to the risks associated with the use of non-invasive respiratory supports [5].

In contrast, glucocorticoids [6,7] emerged as an interesting treatment in SARS-CoV-2 pneumonia. The administration of dexamethasone (DXM) has been associated with reduced in-hospital mortality [8]. In addition, practices have changed for correcting hypoxemia with a larger use of non-invasive respiratory supports.

Most of these treatments have been assessed as single interventions in many publications [9], but to our knowledge, studies comparing the effects of two different bundles of management are scarce. The first aim of our study was to compare the effects of two bundles of treatment in the management of SARS-CoV-2 pneumonia in ICU patients on in-hospital mortality rate. The secondary aim of this study was to

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determine if one of the two bundles was associated with a shorter duration of ICU and hospital stays.

2. Methods

2.1. Design

This single-center, retrospective, observational study was performed in the polyvalent ICU of the North University Hospital of Marseille. The first and second waves lasted from March 2020 to June 2020 and from September 2020 to January 2021, respectively. The study was compliant with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [10].

2.2. Ethical considerations

The study was approved by the Committee for Research Ethics of the French Society of Anesthesia & Intensive Care Medicine (CERAR no. IRB 00010254–2020 - 257). Patients were informed regarding the use of their data. The different treatment strategies being considered as standard care, informed consent was waived, according to French law [11].

2.3. Population

Confirmed Corona Virus disease 2019 (COVID-19) patients with acute respiratory failure were included if they completed the following criteria: i) adult patients with a SARS-CoV-2 infection confirmed by real-time reverse transcriptase polymerase chain reaction (RT-PCR) of nasopharyngeal samples upon ICU admission [12] and ii) respiratory support therapy (conventional oxygen therapy, high flow nasal oxygenation, non-invasive or invasive mechanical ventilation) for hypoxemia defined as an oxygen saturation below 90%. The exclusion criteria were as follows: patients with a known allergy or contraindication to HCQ, AZT, or DXM and those treated with other drugs (lopinavir/ritonavir). We identified two different groups: patients undergoing bundle 1 treatment during the first wave (HCQ plus AZT plus cefotaxime) and those undergoing bundle 2 treatment during the second wave (DXM alone).

2.4. Study protocol

At ICU admission, each patient's demographic, clinical, and biological data were collected, and the Simplified Acute Physiology Score II (SAPS II) and the Sepsis-related Organ Failure Assessment (SOFA) score were calculated. COVID-19 features, such as the duration of symptoms and the onset of disease, were reported. The use of vasopressors, the use of antibiotics, and the duration of mechanical ventilation were also recorded. The viral load was determined from nasopharyngeal swab samples collected at ICU admission and every 72 h by polymerase chain reaction (PCR). The follow-up of each patient lasted 28 days.

The first bundle consisted of an 800 mg loading dose of HCQ on the first day of treatment and a maintenance dose of 400 mg for nine days. The additional treatment consisted of a 500 mg loading dose of AZT followed by a 250 mg maintenance dose associated with cefotaxime (6 g a day administered by continuous infusion) for five days. Then, antibiotics were provided if a bacterial infection was documented. High-dose steroids (methylprednisolone 2 mg/kg) were administered in patients developing prolonged acute respiratory distress syndrome with elevated serum and alveolar concentrations of procollagen type III [13]. In those patients, tracheal intubation and mechanical ventilation were performed early in case of desaturation (pulse oximetry below 90% under maximal oxygen support). The second bundle consisted of the use of DXM at a dose of 6 mg per day for 10 days. Neither antivirals nor antibiotics were used with the exception of suspected or documented bacteria pneumonia, based on evaluative image of the chest X-ray, increase in inflammatory biomarkers (CRP and procalcitonin), hemodynamic instability requiring the introduction of norepinephrine, and identification of bacteria on directed samples. The second wave patients received oxygen by the use of non-invasive respiratory supports, recourse to intubation being required only in case of desaturation after non-invasive respiratory support failure. Anticoagulation protocols did not differ between the two groups, according to international guidelines [14] (e-Table 1).

2.5. Outcomes

The first endpoint was in-hospital mortality rate in the two groups. The secondary endpoints were ICU mortality rate, length of ICU and hospital stays, duration of mechanical ventilation (ventilator free-days), vasopressor use, antibiotic use, the number of patients with negative PCR at Day 15, and ICU-acquired infection rates.

2.6. Statistical analysis

The necessary number of patients to be included was not calculated *a priori*; all the patients admitted to our ICU during the study period were eligible. Categorical variables were reported as absolute frequencies and proportions. Continuous variables were reported as median (interquartile range) or mean (standard deviation) when needed. Normal distribution was evaluated using the Kolmogrov-Smirnov test and skewness and kurtosis coefficients. The Mann-Whitney *U* test was used to compare continuous variables between groups in the case of non-normally distributed data, and the Student *t*-test was used in the case of normal distribution. Chi-squared test (X^2) was used to compare qualitative variables between groups, except for variables in which the expected number of variable occurrences was <5, where Exact Fisher

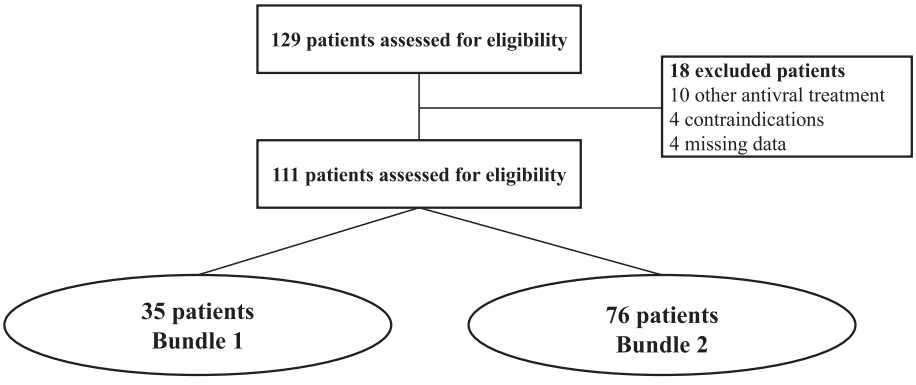

Fig. 1. Flow chart.

test was used. Bivariate logistic regression was performed on qualitative variables and quantitative variables of interest after binarization around their median or a validated threshold. Age was binarized around its median (66 years-old), ratio of arterial oxygen partial to fractional inspired oxygen (PaO_2/FiO_2) around its median (125 mmHg) and admission cycle threshold (Ct) of PCR assay around its median [29].

Statistical significance was defined as $p < 0.05$. Analyses were performed using R software 4.0.4 for Windows (R Core Team, R Foundation for Statistical Computing, Vienne, Austria, 2021).

3. Results

From March 2020 to January 2021, 129 patients with SARS-CoV-2 pneumonia were admitted to our ICU. Among them, 35 patients were treated according to bundle 1 and 76 patients according to bundle 2 (Fig. 1). The demographic characteristics, clinical features, and severity scores did not differ between both groups, with the exception of age (62 [52–72] years in bundle 1 *vs.* 67 [60–73] years in bundle 2, $p = 0.03$) and viral load at admission (31 [28–33] Ct in bundle 1 *vs.* 24 [24–32] Ct in bundle 2, $p = 0.02$).

3.1. Primary outcome

Eight patients (23%) from the bundle 1 group and 16 (21%) patients from the bundle 2 group did not survive to hospital discharge ($p = 0.97$) (Fig. 2).

3.2. Secondary outcomes

The hospital length of stay (25 [13–44] *vs.* 13 [9–24] days, $p = 0.003$) and the ICU length of stay (16 [5–32] *vs.* 7 [3–15] days, $p = 0.01$) were shorter in the bundle 2 group (see Table 1). The use of vasopressors and mechanical ventilation was similarly distributed in both groups ($p = 0.31$ and $p = 0.14$, respectively, Table 1). At day 28, the number of ventilator-free days was reduced in the bundle 1 group, as compared with the bundle 2 group ($p = 0.03$). High flow nasal cannula oxygenation was mostly used in the bundle 2 group ($p = 0.03$). No statistical difference was found for ICU-acquired infections (12 (34%) *vs.* 26 (34%), $p = 1$) (Table 1). There was no difference in antibiotics use after excluding those given for prophylaxis ($p = 0.56$) but and high-dose steroid uses ($p = 1$) between the two groups (Table 1).

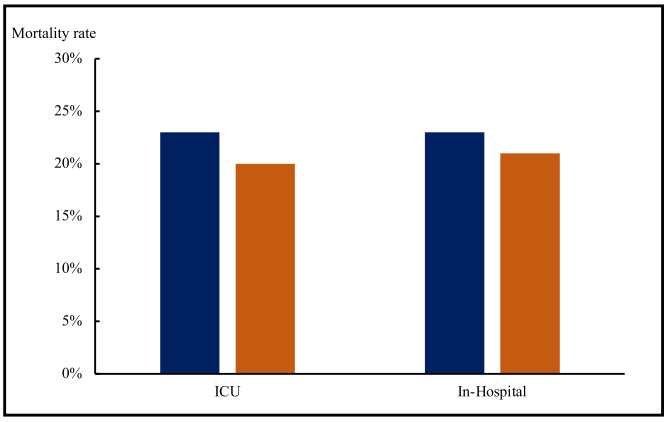

Fig. 2. ICU and in-hospital mortalities between the two groups. Bundle 1 and Bundle 2 are represented in dark blue and dark orange respectively.
ICU mortality: $p = 0.91$ and in-hospital mortality: $p = 0.97$.

Table 1
Demographic and clinical findings.

Variables	Bundle 1 ($n = 35$)	Bundle 2 ($n = 76$)	p
Demographics and severity			
Age, median [IQR], (years)	62 [52–72]	67 [60–73]	0.03
Sex			
Men, n (%)	27 (77)	55 (72)	0.76
Comorbidities, n (%)			
BMI > 25 kg/m^2	29 (83)	62 (82)	1
Pregnancy	3 (9)	1 (1)	0.09
Coronary disease	9 (26)	15 (20)	0.64
Hypertension	24 (69)	40 (53)	0.16
COPD	4 (11)	11 (15)	0.77
Cancer	4 (11)	13 (17)	0.63
Immunosuppression[a]	2 (6)	10 (13)	0.33
Chronic kidney disease	1 (3)	5 (7)	0.66
Liver disease	1 (3)	1 (1)	0.53
Active smoker	8 (23)	11 (15)	0.41
Diabetes	15 (43)	22 (29)	0.21
SAPS II at admission, median [IQR][b]	31 [23–38)	34 [30–42]	0.12
SOFA at admission, median [IQR]	3 [2–5]	3 [2–4]	0.37
PaO_2/FiO_2 ratio at admission, median [IQR] (mmHg)	145 [108–190]	123 [93–165]	0.15
Duration of symptoms before hospital admission, mean ± SD (days)	5 ± 3	5 ± 6	0.86
Duration of symptoms before ICU admission, mean ± SD (days)	6 ± 4	7 ± 6	0.37
Duration of symptoms before mechanical ventilation, median [IQR] (days)	1 (1–3)	1 (0–4)	0.72
Viral load at admission, median [IQR] (Ct of PCR assay)	31 [28–33]	24 [24–32]	0.02
Interventions and clinical findings			
Mechanical ventilation, n (%)	23 (66)	37 (48)	0.14
High flow nasal oxygen, n (%)	25 (71)	67 (88)	0.06
Ventilator-free days (28 days), median [IQR] (days)	13 [0–28]	28 [1–28]	0.03
Vasopressors use, n (%)	20 (57)	34 (44)	0.31
Thrombosis, n (%)	9 (26)	10 (13)	0.17
Antibiotic use*, n (%)	18 (51)	33 (43)	0.56
Antibiotic-free days (including prophylaxis), median [IQR] (days)	18 [16–23]	28 [21–28]	< 0.001
Antibiotic-free days (excluding prophylaxis), median [IQR] (days)	23 [21–28]	28 [21–28]	0.3
High dose of steroids	2 (6)	5 (7)	1
Methylprednisolone 2 mg/kg, n (%)			
ICU-acquired infections, n (%)	12 (34)	26 (34)	1
Pneumonia	9	15	
Bacteremia	3	2	
Intra-abdominal	0	3	
Other site	0	5	
Bacteria			
Gram-negative bacteria	5	13	
Gram-positive cocci	4	7	
Others	0	5	
Multidrug resistant bacteria during ICU stay, n (%)	7 (20)	9 (12)	0.39
Renal replacement therapy, n (%)	3 (9)	2 (3)	0.32
ECMO recourse, n (%)	3 (9)	2 (3)	0.32
Outcomes			
Length of hospital stay, median [IQR] (days)	25 [13–44]	13 [9–24]	0.003
Length of ICU stay, median [IQR] (days)	16 [5–32]	7 [3–15]	0.01
Negative PCR Day 15	25 (71)	55 (72)	1

Abbreviations: BMI, Body mass index; SAPS II, Simplified acute physiology score II; SOFA, Sepsis-related organ failure assessment; PaO2/FiO2, ratio of arterial oxygen partial to fractional inspired oxygen; PCR, Polymerase Chain reaction; Ct, Cycle threshold; ECMO, Extracorporeal membrane oxygenation; ICU, Intensive care unit; IQR, Interquartile range; SD, Standard derivation.

[a] Immunosuppression: HIV patients, transplant patients, patients undergoing immunosuppressive treatment.

[b] The SAPS II ranges from 0 to 163, with higher scores indicating a higher risk of mortality. A patient with a score of 30 has an estimated mortality risk of 10%.

* Except with antimicrobials administered systematically according to bundle 1.

Table 2
Bivariate analyses of variables in association with in-hospital mortality.

	Univariate analysis			
	In-hospital survival n (%) $n = 88$	In-hospital mortality n (%) $n = 23$	OR (95% CI)	p
Age > 66 years old	29 (33)	21 (91)	19.4 (4.4–123.4)	<0.001
PaO_2/FiO_2 ratio < 125 mmHg	32 (36)	18 (78)	5.8 (1.9–17.7)	<0.001
Viral load at admission >29 (Ct of PCR assay)	36 (41)	16 (70)	3 (1.1–9.3)	0.03
SAPS II at ICU admission >33	33 (38)	18 (78)	5.5 (1.8–16.8)	<0.01
SOFA score at ICU admission >3	31 (35)	12 (52)	1.9 (0.7–4.8)	0.23
Bundle 1	27 (31)	8 (35)	1.1 (0.4–3.2)	0.8
Coronary disease	15 (17)	8 (35)	2.4 (0.8–7.1)	0.09
COPD	9 (10)	5 (22)	2.3 (0.7–8.3)	0.17
Cancer	11 (13)	6 (22)	2.3 (0.7–7.2)	0.19
Mechanical ventilation	38 (43)	18 (78)	4.3 (1.4–13.2)	0.01
Vasopressors use	32 (36)	19 (83)	7.6 (2.2–26.3)	<0.001
ICU-acquired infections	24 (27)	11 (48)	2.3 (0.9–5.9)	0.13
Antibiotic use	32 (36)	15 (65)	3 (1.1–8)	0.03
Women	24 (27)	4 (17)	0.5 (0.2–1.7)	0.4
Obese (BMI > 25 kg/m^2)	32 (36)	8 (35)	0.9 (0.3–2.4)	0.8

Abbreviations: BMI, body mass index; COPD, chronic obstructive lung disease; Ct, Cycle threshold; ICU, intensive care unit; PaO_2/FiO_2, ratio of arterial oxygen partial to fractional inspired oxygen; PCR, polymerase chain reaction; SAPS, severity acute physiology score; SOFA, sequential organ failure assessment; OR, odds ratio; CI, confidence interval.

During the ICU stay, no significant differences were observed in the emergence of multidrug resistant bacteria ($p = 0.39$) (Table 1). The ICU mortality rate did not differ between the two groups ($p = 0.9$) (Fig. 2).

The type of management bundle was not associated with in-hospital mortality (OR: 1.1, 95% CI: 0.4–3.2; $p = 0.8$ for Bundle 1 *vs.* Bundle 2). Age > 66 years (OR: 19.4, 95% CI: 4.4–123.4; $p < 0.001$), vasopressors use (OR: 7.6, 95% CI: 2.2–26.3; $p < 0.001$), PaO_2/FiO_2 ratio < 125 (OR: 5.8, 95% CI: 1.9–17.7, $p < 0.001$) were associated with in-hospital mortality, as well as high viral load at the ICU admission, mechanical ventilation, SAPS II > 33 and antibiotics use (Table 2).

4. Discussion

Our study compared two bundles to manage severe SAR-CoV-2 patients admitted to a single ICU. Although no difference was found in-hospital mortality rate, the patients in the bundle 2 group were less exposed to mechanical ventilation, ICU, and hospital length of stay than those in the bundle 1 group. During a pandemic, due to the high need for ICU beds [15,16], the reduction in the duration of length of stay in ICU should be regarded as a significant finding. This result may favor higher rotation of patients in both ICU and hospital beds. Regarding the burden of care, the difference between the two groups did not seem irrelevant because more ICU beds and staff members were available during the second wave. Therefore, the workload was equal for both medical and nursing staff.

As we compared bundles retrospectively, no conclusion can be drawn on the effects of each single intervention. However, we note that the systematic use of prophylactic antibiotics was not associated with a reduction in ICU-acquired infection. We previously showed that therapeutic serum concentrations of HCQ were not associated with improved viral clearance and improved outcomes [2]. Thus, our present findings are in line with our previous finding [2], re-enforcing the lack of efficacy of HCQ in severe cases requiring ICU admission. Considering everything, we suggest that the different strategies regarding oxygenation may have played a major role in the differences in ICU stays between the two groups, although, once again, it is difficult to identify the role of a single intervention.

Our study has limitations that need to be acknowledged. It is a single-center study involving a small number of patients, which cannot be generalized. As such, the results from bivariate analysis should be interpreted with caution regarding the small number of events (in-hospital deaths) in some variables. Another study has suggested a decrease in mortality during the second wave [17]. As we compared several interventions including management of respiratory support, it is unclear which of them may have influenced our final findings on outcome. Finally, the bundles were not randomized, and a time effect cannot be ruled out.

During the first wave, physicians were reluctant to use non-invasive oxygenation support for fear of spreading an airborne virus [18], whereas in the second wave non-invasive support use was encouraged [19] [20]. Our data on respiratory management lacked sufficient granularity to allow us to understand whether this approach led to delayed intubations (higher oxygen demand or lower PaO_2/FiO_2 before intubation) in the second wave. This might be a limitation of our study. Another limitation of our study can be related to the lack of data regarding the specific elements of COVID-19 disease severity (such as imaging data [21]) as disease severity was only assessed by general severity scores in our cohort. Other factors such as knowledge on COVID-19 physiopathology and improvement in hospital organization may have impacted in-hospital mortality and were not measured in this study.

In conclusion, within the limitations of this study, our results suggest that changes in treatment strategies in SARS-CoV-2 ICU patients might not affect in-hospital mortality rate but were associated with less exposure to mechanical ventilation and reduced use of resources. These findings need to be confirmed in large and multicentric randomized controlled trials.

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Conflicts of interest

ML served as lecturer for MSD, Aspen and consultant for Gilead, Amomed. All other authors report no conflicts of interest.

Credit authorship contribution statement

Alexandre Lopez: Conceptualization, Methodology, Writing - original draft. **Ines Lakbar**: Conceptualization, Writing - original draft. **Louis Delamarre**: Methodology, Writing - review editing, Software. **Aurélien Culver**: Data curation, Investigation. **Charlotte Arbelot**: Investigation. **Gary Duclos**: Investigation. **Emmanuelle Hammad**: Investigation. **Bruno Pastene**: Investigation, Data curation. **François Antonini**: Formal analysis. **Laurent Zieleskiewicz**: Writing - review editing. **Marc Leone**: Writing - review editing, Supervision, Validation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2021.06.014.

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