Early corticosteroid therapy may increase ventilator-associated lower respiratory tract infection in critically ill patients with COVID-19: a multicenter retrospective cohort study

Balcaen M. , Mesland J.B. , Carlier E. , François B., Serck N. , Gerard L. , Briat C. , Piagnerelli M. , Laterre P.F.

- INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has put significant pressure on hospitals, and in particular on intensive care units (ICU). Some patients develop acute hypoxemic respiratory failure with profound hypoxia, which likely requires invasive mechanical ventilation during prolonged periods. Corticosteroids have become a cornerstone therapy for patients with severe COVID-19, though only little data are available regarding their potential harms and benefits, especially concerning the risk of ventilator-associated lower respiratory tract infection (VA-LRTI).

- OBJECTIVES

The primary objective of this study was to compare in patients undergoing MV for severe SARS-CoV2 pneumonia the occurrence of VA-LRTI between patients who received and those who did not receive early corticosteroid therapy (<7 days since hospital admission). Secondary objectives were to identify potential risk-factors for VA-LRTI, along with the microbiology of this events.

- METHODS

This retrospective multicenter study included patients admitted in four ICUs from Belgium and France for severe COVID-19, who required invasive mechanical ventilation (MV). We compared clinical and demographic variables between patients that received or not corticosteroids, using univariate, multivariate, and Fine and Gray analyses to identify factors influencing VA-LRTI occurrence.

- RESULTS

From March 2020 to January 2021, 341 patients required MV for acute respiratory failure related to COVID-19, 322 of whom were included in the analysis, with 60.6% of them receiving corticosteroids. The patient characteristics at baseline, in addition to adjuvant therapies, respiratory variables and outcomes, are summarized in **Tables 1**. Clinical outcomes did not differ according to corticosteroid treatment including ICU length of stay, duration of ventilation, and ventilatory free days at Day 28, whereas there was a non-significant trend towards higher ICU mortality (51.3% *vs*. 40,2%, p=0.051) among patients receiving corticosteroids. The VA-LRTI proportion was significantly higher in the corticosteroid group (63.1% *vs*. 48.8%, p = 0.011), reflected in both early VA-LRTI (11,8% in the non-corticosteroid group *vs*. 18,5% in the

corticosteroid group) and late VA-LRTI (37% in the non-corticosteroid group *vs*. 44,6% in the corticosteroid group) subpopulations. Time to the first VA-LRTI episode was 7.4 days +/- 4.6 days *vs*. 8.9 +/- 5.7 days (p=0.06) in the corticosteroid *vs.* non corticosteroid group respectively.

In addition, we compared the incidence of first episode of VA-LRTI between patients with and without corticosteroids using Fine and Gray competing risk model, while considering the competing risks of death and extubation. As shown in Figure 1, VA-LRTI incidence was still significantly higher in the corticosteroids group (p = 0.0077). The same results as for VA-LRTI occurrence (66% *vs*. 48%, p = 0.0025) were observed after excluding the patients in whom steroids were started after intubation, in order to avoid the risk of immortal time bias.

Multivariable Fine and Gray modeling considering death and extubation as competing events revealed that the factors independently associated with VA-LRTI occurrence were male gender (adjusted sHR:1.7, p = 0.0022) and corticosteroids (adjusted sHR: 1.44, p = 0.022).

During the first 30 days of ventilation, overall 227 VA-LRTI episodes were documented in the 185 patients with VA-LRTI during this period. Of these, 19,8% were considered as early VA-LRTI (<5 days from intubation), and 80,2% as late VA-LRTI (≥5 days from intubation). Overall, 73.2% of isolates for VA-LRTI were *Gram-negative bacilli*, 26.2% *Gram-positive cocci*, and 0.6% *Gram-negative cocci*. The predominant pathogen was *Staphylococcus aureus* in 22.4% of VA-LRTI, followed by *Pseudomonas aeruginosa* (15.1%), and *Escherichia Coli* (13.2%)

- CONCLUSIONS

In our multicenter retrospective cohort of COVID-19 patients undergoing MV, early corticosteroid therapy was independently associated with VA-LRTI.

Figure 1. Cumulative incidence of Ventilatory-Associated Lower Respiratory Tract infection within 30 days of mechanical ventilation, using Fine and Gray model, considering extubation or death within 30 days as competing events .VA-LRTI: ventilator-associated respiratory tract infection.

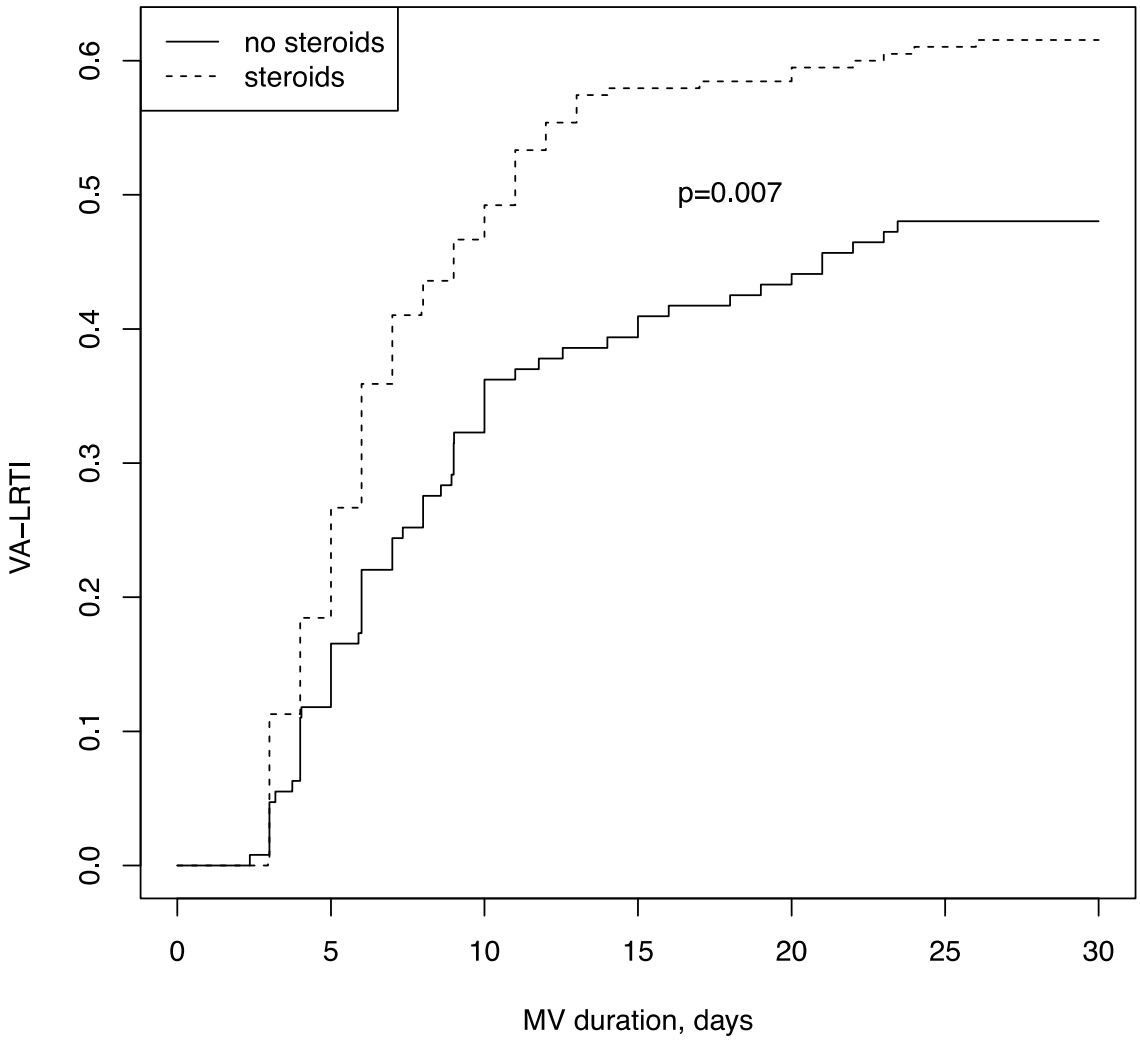

Table 1. Characteristics between patients receiving early corticosteroid therapy and those who did not.

	All population (n = 322)	No steroid (n = 127)	Steroid (n = 195)	p value
Baseline characteristics				
Age, years (+/- SD)	64.8 (+/- 10.4)	65 (+/- 10)	64.6 (+/- 10.7)	0.71
Male (%)	219/322 (68)	90/127 (70.9)	129/195 (66.2)	0.38
BMI (+/- SD)	29.7 (+/- 6.2)	29 (+/- 4.8)	30.2 (+/- 6.9)	0.081
Hypertension (%)	204/322 (63.3)	78/127 (61.4)	126/195 (64.6)	0.62
Diabetes mellitus (%)	132/322 (41)	46/127 (36.2)	86/195 (44.1)	0.18
Cardiomyopathy (%)	49/322 (15.2)	19/127 (14.6)	30/195 (15.4)	0.94
Chronic kidney disease (%)	33/322 (10.2)	8/127 (6.3)	25/195 (12.8)	0.062
Immunosuppression (%)	30/322 (9.3)	6/127 (4.7)	24/195 (12.3)	0.024
COPD (%)	28/322 (8.7)	9/127 (7.1)	19/195 (9.74)	0.42
Neoplasia <2 years (%)	21/322 (6.5)	5/127 (4)	16/195 (8.2)	0.13
Admission characteristics				
SOFA (+/- SD)	5,6 (+/- 2.4)	5,4 (+/- 2.4)	5,7 (+/- 2.5)	0.26
APACHE II (+/- SD)	16 (+/- 5.5)	16,1 (+/- 4.5)	15,9 (+/- 5.8)	0.73
PaO2/FiO2, mmHg (+/- SD)	93,7 (+/- 47.8)	104,2 (+/- 54)	86,8 (+/- 42)	0.0014
Mild ARDS (PaO2/FiO2 < 300 mmHg)	10/322 (3.1)	6/127 (4.7)	4/195 (2.1)	0.17
Moderate ARDS (PaO2/FiO2 < 200 mmHg)	89/322 (27.6)	43/127 (33.9)	46/195 (23.6)	0.044
Severe ARDS (Pa02/FiO2 < 100 mmHg)	219/322 (68)	76/127 (59.8)	143/195 (73.3)	0.011
Ferritin, mcg/L (+/- SD), *(n=165)*	2041 (+/-1794)	2051 (+/- 1808)	2035 (+/- 1794)	0.95
CRP, mg/L (+/- SD)	172.9 (+/- 101.5)	186.1 (+/- 103.5)	165,2 (+/- 99.7)	0.082
Lymphocytes, /mcL (+/- SD)	840 (+/- 996)	780 (+/- 427)	878 (+/- 1231)	0.39
Shock (%)	53/322 (16.4)	18/127 (14.2)	35/195 (18)	0.37
Prior antibiotic treatment (%)	143/322 (44.7)	73/127 (57.5)	70/195 (35.8)	0.0002
Treatment				
Hydroxychloroquine (%)	64/322 (19.9)	59/127 (46.4)	5/195 (2.6)	<0.0001
Azythromycin (%)	19/322 (5.9)	15/127 (11.8)	4/195 (2.1)	0.0003
Remdesivir (%)	13/322 (4)	6/127 (4.7)	7/195 (3.6)	0.61
Immunomodulating therapies, IL6 & IL1 antagonist (%)	12/322 (3.7)	2/127 (1.6)	10/195 (5.1)	0.10
ECMO (%)	44/322 (13.7)	12/127 (9.5)	32/195 (16.4)	0.076
Prone positionning (%)	271/322 (84.2)	108/127 (86.4)	163/195 (83.6)	0.78
Sedation, days (+/- SD)	14.4 (+/-13.2)	12.9 (+/- 9.9)	15.3 (+/- 14.9)	0.11
Hospital admission to intubation, days (+/- SD)	4.2 (+/- 5.8)	4.2 (+/- 6.6)	4.2 (+/- 5.2)	0.96
Outcomes				
ICU mortality (%)	151/322 (46.9)	51/127 (40.2)	100/195 (51.3)	0.051
ICU Day-28 mortality (%)	120/322 (37.3)	40/127 (31.5)	80/195 (41)	0.084
ICU length of stay, days (+/- SD)	23.1 (+/- 20.9)	22.9 (+/- 15.9)	23.2 (+/- 23.7)	0.89
Duration of ventilation, days (+/- SD)	18.3 (+/- 17)	17.9 (+/- 14)	18.5 (+/-18.7)	0.73
Ventilatory free day D28 (+/- SD)	6.8 (+/- 8.7)	7.6 (+/- 8.3)	6.3 (+/- 9)	0.19
Blood stream-infection (%)	73/322 (22.6)	23/127 (18.1)	50/195 (25.6)	0.11
Ventilator-associated lower respiratory tract infection (%)	185/322 (57.5)	62/127 (48.8)	123/195 (63.1)	0.011

ICU: Intensive care unit, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, SOFA: Sequential organ failure assessment, APACHE II Acute Physiology And Chronic Health Evaluation II, ARDS: Acute Respiratory Distress Syndrome, ECMO: Extra-corporeal membrane oxygenation.