THE LANCET
Rheumatology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Cavalli G, De Luca, Campochiaro GC, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020; published online May 7. https://doi.org/10.1016/S2665-9913(20)30127-2.

ONLINE APPENDIX

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DEFINITION OF DISEASE STATES

Acute Respiratory Distress Syndrome

The Berlin definition of Acute Respiratory Distress Syndrome.
• Timing. Within one week of a known clinical insult or new or worsening respiratory symptoms
and
• Chest imaging (Chest radiograph or computed tomography scan). Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules
and
• Origin of edema. Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic edema if no risk factor present
and
• Oxygenation:
Mild. PaO2:FIO2 between 26.7 and 40.0 kPa (200–300 mmHg) with PEEP or CPAP ≥ 5 cmH2O. This may be delivered non-invasively in the mild acute respiratory distress syndrome group.
Moderate. PaO2:FIO2 between 13.3 and 26.6 kPa (100–200 mmHg) with PEEP ≥ 5 cmH2O
Severe. PaO2:FIO2 13.3 kPa (100 mmHg) with PEEP ≥ 5 cmH2O
If altitude is higher than 1000 m, a correction factor should be calculated (PaO2:FiO2 x [barometric pressure/101 kPa]).

Bacteremia

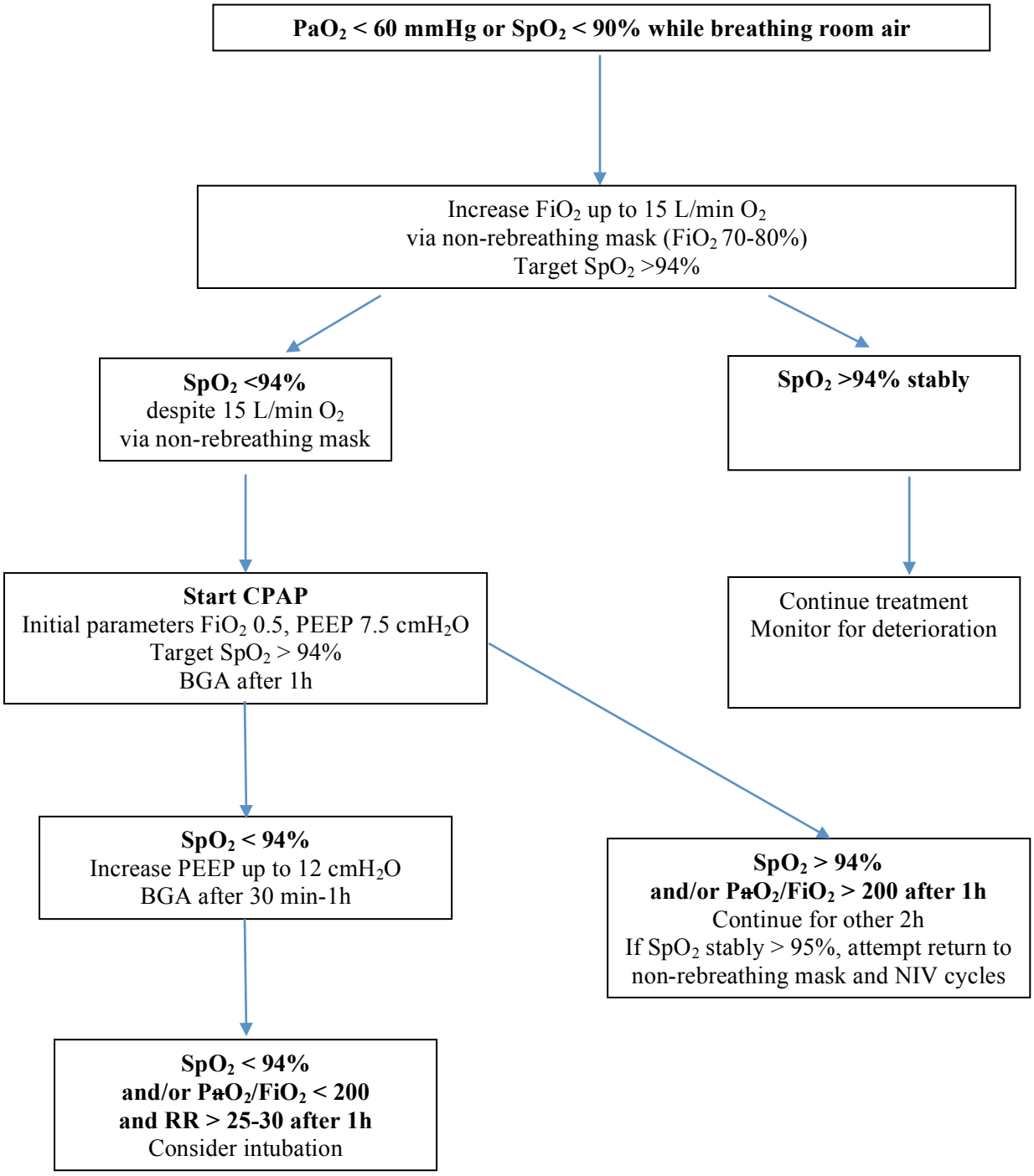
The CDC defines laboratory confirmed bloodstream infection as one which meets at least one of the following criteria which should not be related to infection at another site:

- Patient has a recognized pathogen cultured from one or more blood cultures and the organism cultured from blood is not related to an infection at another site; or
- Patient has at least one of the following signs or symptoms: fever >38.8°C, chills or hypotension, and at least one of the following:
    - common skin contaminant cultured from two or more blood cultures drawn on separate occasions; or
    - common skin contaminant cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy.

CLINICAL MANAGEMENT PROTOCOL

Our hospital implemented the following general management protocol for patients with COVID-19 respiratory failure.

Flow-chart for initial management of respiratory failure



Pharmacologic treatment

Antiviral therapy
All patient included in this study received:

- Hydroxychloroquine 200 mg BD orally
- Lopinavir/Ritonavir, 400/100 mg BD orally

At the time of conduction of this study, we routinely administered Lopinavir/Ritonavir 400/100 mg BD orally to all patients without contraindications. The duration of the treatment course was 7-10 days, as recommended by National guidelines. Following completion of this study, and after publication of a randomized controlled trial showing no benefit in patients with COVID-19,[1] administration of Lopinavir/Ritonavir was interrupted.

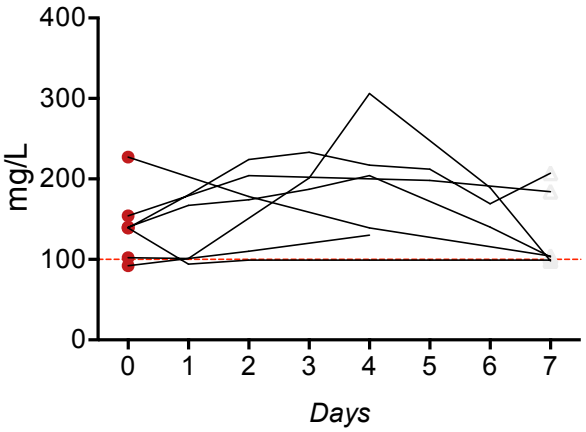
Glucocorticoids
Patients enrolled in this study did not receive glucocorticoids. Treatment with methylprednisolone is administered to selected COVID-19 patients hospitalized in our Hospital, but administration of other anti-inflammatory agents is mutually exclusive.

Antibiotic coverage
All patients received an initial empiric antibiotic coverage for community acquired/hospital acquired pneumonia.
For patients admitted from home, without previous antibiotic exposure:

- Ceftriaxone 2 g i.v. daily
- Azithromycin 500 mg i.v daily.

Antibiotic coverage could eventually be discontinued in the absence of bacterial isolates and clinical signs of bacterial infection, as per clinical judgment.

SUPPLEMENTAL FIGURES AND TABLES



Supplemental Figure 1. Before-after graph showing serum CRP measurements in patients receiving low-dose subcutaneous anakinra (n=7), collected for 7 days or until death or mechanical ventilation, whichever came first. A red line marks the 100 mg/L threshold, which was used to define hyper-inflammation.

Supplemental Table 1. Baseline clinical and laboratory features of patients treated with high-dose anakinra who were alive and mechanical ventilation-free at day 21, compared to those who were either dead or on mechanical ventilation at the same time point. Continuous variables are reported as mean and SD. Categorical variables are reported as numbers and percentage. COPD: chronic obstructive pulmonary disease; C-reactive protein; LDH: lactate dehydrogenase; PaO_2**:**FiO_2: ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2 expressed as a fraction), calculated with arterial blood gas while the patient was on CPAP (positive end expiratory pressure = 10 cm H_2O).

Clinical characteristic	**Alive and mechanical ventilation-free (n=21)**	**Dead or on mechanical ventilation (n=8)**
Age, y – mean (SD)	59 (±10)	61 (±10)
Tobacco smoking, n (percentage)	2 (10)	1 (12)
Arterial hypertension, n (percentage)	12 (52)	3 (37)
Coronary artery disease, n (percentage)	1 (5)	2 (25)
Diabetes mellitus, n (percentage)	5 (24)	1 (12)
COPD, n (percentage)	0 (0)	1 (12)
Chronic kidney disease, n (percentage)	2 (10)	0 (0)
CRP, mg/L – mean (SD)	143 ± 71	211 ± 89
Ferritin, ng/mL – mean (SD)	1556 ± 1010	2012 ± 1624
LDH, u/L – mean (SD)	399 ± 117	652 ± 189
PaO_2:FiO_2, mean (SD)	92 ± 21	72 ± 20

REFERENCES

1. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *New England Journal Of Medicine* 2020.