Prolonged Low Doses of Methylprednisolone for Patients With COVID-19 Severe Acute Respiratory Syndrome

NCT04323592

March 23rd, 2020

MP-C19 – Study protocol

Background and rationale

The COVID-19 pandemic caused by the new coronavirus called SARS-CoV-2 is associated in about 20% of hospitalized cases in Italy with a severe acute respiratory syndrome with dramatic impact on the system organization and health of the population due to the high need for mechanical ventilation (MV), frequent hospitalization in the General Intensive Care Unit (ICU) and significant increase in mortality [1,2].

It is precisely the high concomitant number of cases of severe acute respiratory syndromes in very short times that is having an extraordinary impact on the health system with high consumption of precious resources such as beds of intensive care units and the need to quickly commit huge economic and human resources.

Due to the exceptional nature of the current situation that is being experienced in Italy, there is a desperate need for evidence to improve the therapeutic management of COVID-19 patients with severe acute respiratory syndrome.

A very recent Chinese report published on 13.March.2020 in JAMA Internal Medicine describes favourable data on the treatment with methylprednisolone (MP) in a series of 201 patients with COVID193 acute respiratory distress syndrome (ARDS) stating that the use of corticosteroids, in particular methylprednisolone, can have a beneficial effect on mortality.

The World Health Organization (WHO) advises against the use of steroids in COVID-19 based on retrospective MERS studies that have shown prolongation of viral clearance without however influencing the clinical outcome [5].

On the other hand, WHO itself through the Blueprint process has prioritized studies on steroids as an additional therapy that can improve outcomes in order to identify actions that can save lives throughout the COVID-19 pandemic [6].

In Italy, the use of corticosteroids is currently not recommended by official guidelines, but is routinely practiced in some respiratory centers with Semi-Intensive Respiratory Therapy Unit (UTIR) on the basis of positive results of randomized controlled trials on patients with severe community pneumonia [7] .

Corticosteroids, like any other drug, can have different effects based on the dosage schedule used, the timing of intervention and indications. Previous controversial studies on cortisone do not indicate the dosage regimen [5] or use a reduced time with rebound effect [8] and / or too high doses [9] and immunosuppressive effect, or are used in patients who are not too sick [10]. Here we want to propose the use of prolonged low para-physiological doses of MP as suggested several times in the studies of Prof. Umberto Meduri of Memphis in patients with ARDS [11]. Indeed, prolonged glucocorticoid treatment is a highly effective treatment in ARDS caused by severe bacterial pneumonia [7].

Acute respiratory distress syndrome (ARDS) is a catastrophic disease of multifactorial etiology characterized by severe and diffuse inflammatory exudate of the lung leading to hypoxemic respiratory failure (ARF) that requires mechanical ventilation (MV) [12,13]. Lung infections, including COVID-19, are the main cause of ARDS.

Translational research has established a strong association between dysregulated inflammation, pulmonary and systemic, and progression (maladaptive repair) or delayed resolution of ARDS. Randomized controlled trials (RCTs) have shown that prolonged

treatment of glucocorticoids (GCs) mediated by downregulation of systemic and pulmonary inflammation is essential to accelerate disease resolution and restore tissue homeostasis and can be significantly improved with a prolonged moderate dose of GC [15,16]. Since 1998, ten RCTs have studied prolonged GC treatment (methylprednisolone, hydrocortisone, dexamethasone) in ARDS for a total of 1093 patients. Compared to placebo, GC treatment was associated with statistically significant improvements (among those reported) in (i) markers of systemic inflammation (7 of 7), (ii) oxygenation (10 of 10), (iii) duration of MV (7 of 9) and length of stay in intensive care (7 of 7). Overall, cortisone treatment was effective despite disease-related heterogeneity (precipitating conditions, disease severity, ARDS timing, mechanical ventilation mode) and treatment (type of GC, start timing, dose, mode of administration, duration of treatment and titration). Importantly, with the exception of transient hyperglycaemia related to initial bolus administration, corticosteroid treatment was not associated with an increased risk of complications, and hyperglycaemia didn't affect the outcome. Table 1 shows the data of the ten RCTs [7, 17-25] conducted on the prolonged treatment with glucocorticoids started before the 14th day of ARDS (treatment vs. control) with the following outcome of interest: overall mortality, treatment mortality, improvement of the markers of systemic inflammation, oxygenation, duration of mechanical ventilation and stay in intensive care, and infection rate after entering the study.

Table 1 (see below) also shows the median increase in free days from MV to day 28 in the aggregated data of patients randomized to three cortisone compounds (methylprednisolone, hydrocortisone and dexamethasone) and the effective reduction in the duration of MV for methylprednisolone and dexamethasone. The significant reduction in the duration of MV reported in the last RCT by Villar et al. [22] (14.1 1.7 vs. 23.6 2.9; p = 0.006) is similar to the one reported in the other RCT [26] (From -8.7 to - 10.6 days) on methylprednisolone (median 8 days in each group).

Table 1. Prolonged glucocorticoid treatment in ARDS (treated vs. control): overall mortality, mortality for treatment initiated before day 14 of ARDS, improvement in markers of systemic inflammation, oxygenation, duration of mechanical ventilation and ICU stay, and infection rate after study entry.

Study **RCTs = 10** **N = 1043**	**Hospital mortality* for treatment started before ARDS day 14** Comparisons are reported as glucocorticoid-treated vs. control.	**Reduction in inflammation**	**Improvement in PaO_2:FiO_2**	**Reduction in MV duration**	**Reduction in ICU stay**	**Rate of infection**
Early ALI-ARDS (< 3 d; n=899)	31.4% vs. 44.3%	5 of 5	8 of 8	5 of 7	5 of 5	22% vs. 27%
Confalonieri, 2005 (n=34)† ‡ ADDIN EN.CITE [7]	0% vs. 36.8%	Yes	Yes	Yes	Yes	0% vs. 21%
Annane, 2006 (n=177) ADDIN EN.CITE [25]	63.5% vs. 72.8%	Yes	Yes	No	NR	14% vs. 13%
		Yes	Yes	Yes	Yes	

Meduri, 2007 (n=91)† ADDIN EN.CITE [17]	23.8% vs. 42.9%					63% vs. 143%
Sabry, 2011 (n=60) ‡ [18]	7.7% vs. 17.6%	Yes	Yes	Yes	NR	0% vs 10%
Liu, 2012 (n=26) ADDIN EN.CITE [19]	16.7% vs 50.0%	NR	Yes	NR	Yes	7% vs. 9%
Rezk, 2013 (n=27)[20]	0% vs. 33.3%	Yes	Yes	Yes	Yes	0% vs 33%
Tongyoo, 2016 (n=197) ADDIN EN.CITE [21]	22.4% vs. 27.3%	NR	Yes	No	NR	17% vs. 19%
Villar, 2020 (n=277) ADDIN EN.CITE [22]	23.7% vs. 36.2%	NR	Yes	Yes	Yes	24% vs. 25%
Late ARDS (≥ 5 d; n=154)	21.3% vs. 37.8%	2 of 2	2 of 2	2 of 2	2 of 2	42 vs. 40%
Meduri, 1998 (n=22) ADDIN EN.CITE [24]	14.3% vs. 62.5%	Yes	Yes	Yes	Yes	150% vs. 125%
Steinberg, 2006 (n=132) ADDIN EN.CITE [23]	22.7% vs. 34.8%	Yes	Yes	Yes	Yes	22.5 vs. 33%
Early and Late ARDS	35% vs. 54%	7 of 7	10 of 10	7 of 9	7 of 7	26% vs. 30%

Legend: NA = not available or not applicable; NR = not reported; d = days; MV = mechanical ventilation; ICU = intensive care unit. Rate of infection = number of infections divided by number of patients.

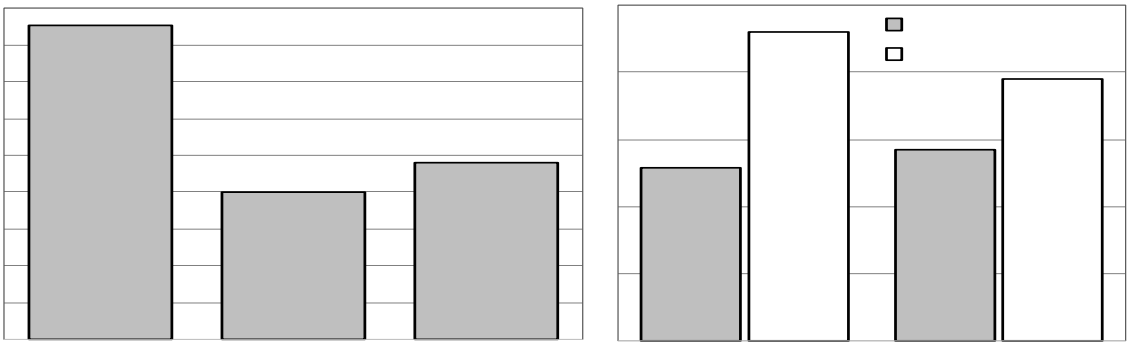
* Mortality data for Liu et al ADDIN EN.CITE [19] are reported as 28-day mortality.

† In two positive trials ADDIN EN.CITE [7, 17] improvement in lung function (PaO2:FiO2 or lung injury score) was the primary outcome variable.

‡ Data for the Confalonieri et al. ADDIN EN.CITE [7] and Sabry et al.[18] are limited to patients receiving mechanical ventilation.

Figure 1 shows the median increase in free days from the MV to the 28th day in the aggregated data of all the clinical trials described above (Reproduced with permission from reference [15]).

Figure 1. Impact of long-dose cortisone treatment on ventilation dependence.



The Faculty of Intensive Care Medicine (FICM) and the Intensive Care Society (ICS) have recently published [26] their "Guidelines on the management of acute respiratory distress syndrome (ARDS)". These guidelines used the GRADE methodology in developing evidence -based recommendations for the management of ARDS in adult ICU patients. The task force suggested that methylprednisolone should be administered to patients with moderate to severe early ARDS (1 mg / kg / day) (recommendation based on moderate quality of evidence). The treatment protocol recommended by the guidelines is the one adopted in this proposal. Importantly, the task force suggested that methylprednisolone should be weaned slowly (6-14 days) and not stopped quickly (2-4 days) or abruptly since deterioration may occur from the development of a reconstituted inflammatory response [26]. The methylprednisolone dose of 1 mg / kg / day in the first ARDS is similar to that commonly used in other forms of interstitial lung disease and in the individual patient data the metanalysis (IPDMA) was associated - compared to placebo - with a triple increase rate of extubation by day 28 (HR 3.48, 95% CI 2.07-5.85; p <0.0001) [26].

Prolonged treatment with methylprednisolone in ARDS caused by COVID19: a desperate need for evidence.

Given the SARS-CoV-2 virus pandemic and the dramatic Italian situation, we think that the efficacy of cortisone for patients with ARDS from COVID-19 should be urgently clarified, as WHO requires.

The dramatic rate of progression of the infection in Italy and the high simultaneous number of hospitalizations for severe pneumonia from COVID-19 provides the opportunity and the need to start quickly to collect important public health data in a short time.

Particular concern raises the high number in Italy of COVID-19 subjects suffering from severe acute respiratory failure with extensive need for hospitalization in general intensive care (16% of all hospitalized in Italy) with very frequent (79%) need for mechanical ventilation invasive (IMV) and high mortality (in Italy it was estimated to be 5.8% in mid-March 20), sometimes even in young adults and without serious co-morbidities [1, 30].

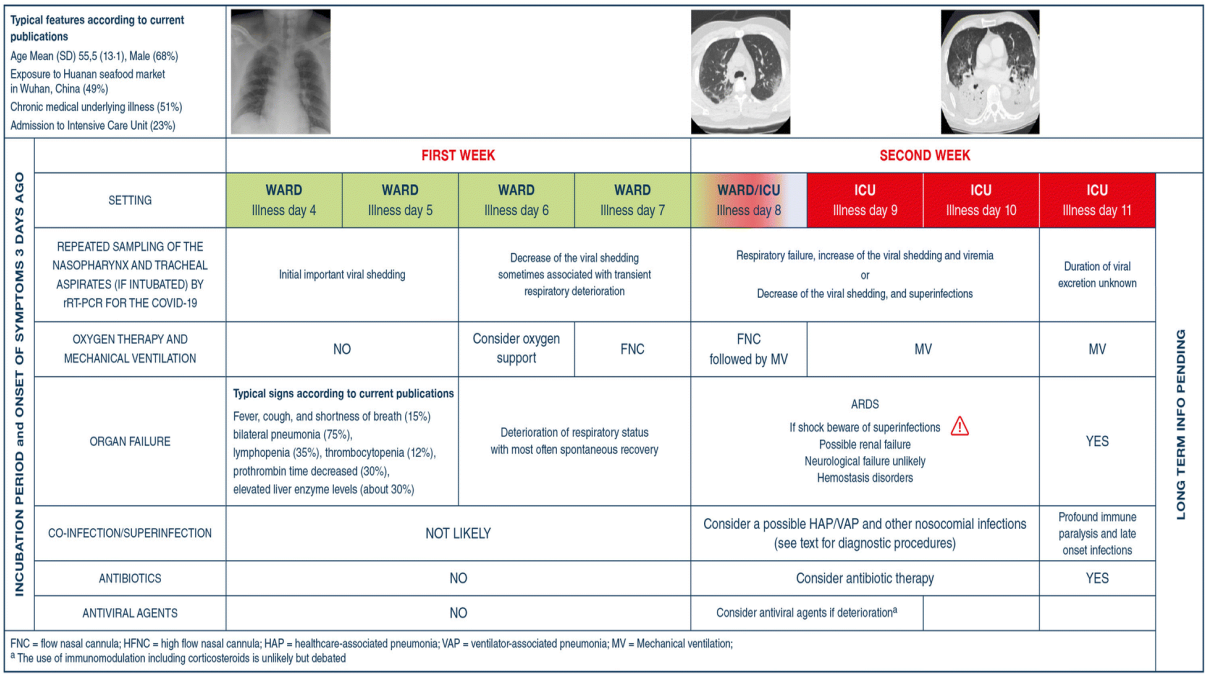
Many RCTs have shown evidence of the use of low prolonged corticosteroids in bacterial community-acquired pneumonia as the main cause of ARDS [7,25]. Evidence and studies are lacking in patients with ARDS from viral pneumonia. ARDS caused by bacteria or COVID-19 viruses is associated with a massive inflammatory response and is potentially responsive to cortisone-type anti-inflammatory treatment. It is therefore not surprising that many Chinese researchers have suggested the use of corticosteroids in patients with ARDS from viral pneumonia due to COVID-19 virus.

In the absence of RCT, WHO [4] does not recommend treatment with glucocorticoids in ARDS associated with COVID-19 partly based on concern about the risk of decreased viral clearance from a single study [5]. There are no quality data indicating an increase in morbidity or mortality with prolonged low to moderate dose glucocorticoid therapy in severe viral pneumonia. Furthermore, there are multiple factors that influence the interpretation of observational studies conducted without a standard protocol, that create conflicting results and confusion [27]. However, WHO believes that promoting RCT is a priority to study the anti-inflammatory treatment of glucocorticoids in COVID-19 pneumonia [4]. Preliminary Italian data in some patients indicate improvement with the use of a new selective interleukin -6 blocker, tocilizumab, indicating that anti-inflammatory interventions could be of benefit [unpublished].

Due to the methodological limitations in previous studies, the Chinese Thoracic Society developed an expert consensus statement [28] on the use of corticosteroids in pneumonia 2019-nCoV. According to this experts consensus statement, the following basic principles must be followed when using corticosteroids: (1) the benefits and harms must be carefully weighed before using corticosteroids; (2) corticosteroids should be used with caution in critically ill patients with pneumonia 2019-nCoV; (3) for patients with hypoxemia due to underlying diseases or who regularly use corticosteroids for chronic diseases, further use of corticosteroids should be prudent; and (4) the dosage should be low to moderate (0.5–1 mg / kg per day of methylprednisolone or equivalent) and the duration should be short (7 days) [28].

The organization, supervision and conduct of RCTs add further levels of complexity and commitment by institutions that are in extreme conditions. In today's reality, our intensive care units do not have the ability to administer complex RCT in patients with highly lethal disease. Support for our proposal is provided by a new observational study of 201 patients with confirmed COVID-19 pneumonia admitted to Wuhan Jinyintan hospital in China [December 25, 2019 and January 26, 2020] [3]. In this study, among ARDS patients, of those who received methylprednisolone treatment, 23 of 50 (46.0%) patients died, while of those who did not receive methylprednisolone treatment, 21 of 34 (61.8%) died. Methylprednisolone administration appears to have reduced the risk of death in patients with ARDS (HR, 0.38; 95% CI, 0.20-0.72; P = 0.003) (Figure 2) [3]. The protocol used during the study was not reported. Further observational studies reported that the sickest patients received "high-dose" glucocorticoid treatment (without specific details) with higher mortality (48% vs. 23%), while two other observational studies found a reduction in mortality with glucocorticoid treatment [29].

Figure 2 - Progression from hospital entry to development of ARDS from COVID-19 [32]



Study acronym: MP-C19

Primary aim:

Evaluate the efficacy of methylprednisolone (MP) at prolonged low doses in severe acute respiratory syndrome (SARS) with ARDS from COVID-19.

Primary outcome: proportion of patients experiencing one or more of the following events: admission to a General Intensive Care Unit (ICU), need of invasive mechanical ventilation (intubation), death.

Based on data from the recent study by Wu C, et al. [3] on MP in the ARDS COVID-19 related and from the studies on ARDS secondary to community pneumonia, we expect a strong difference in the proportion of patients who will encounter at least one of the events included in the primary outcome mentioned above in the group treated with MP compared to the controls (no MP treatment).

Secondary objectives:

- Assess the impact of the MP in terms of changing the values of the reactive Protein C (PCR) and PaO2/FiO2 ratio
- Assess the impact of the MP on intra-hospital mortality
- Assess the impact of the MP on the use of intubation and on days free from mechanical ventilation (VM)

Study design: multi centers, observational prospective cohort study in patients with severe acute respiratory syndrome due to COVID-19.

Comparison of two groups of patients SARS-CoV-2 positive with severe acute respiratory syndrome:

1. Exposed to low prolonged doses of Methylprednisolone
2. Not exposed to corticosteroids (standard of care alone)

The two group will be weighted by means of a propensity score according to:

a. Sex
b. Age
c. C-reactive Protein (CRP) at baseline
d. SOFA score at baseline
e. PaO2/FiO2 ratio at baseline

Study population: patients admitted to respiratory/UTIR departments of the centers participating in the study who meet the following inclusion criteria.

Inclusion criteria:

1. SARS-CoV-2 positive (on swab or bronchial wash)
2. Age >18 years and <80 years
3. PaO2/FiO2 <250 mmHg
4. Diffuse interstitial pneumonia or bilateral infiltrates
5. CRP (C-reactive protein) > 10mg / dL (or> 100mg / L)
6. As an alternative to criteria 4.-5.-6. diagnosis of ARDS according to the Berlin definition [31]

Exclusion criteria:

- Left heart failure as the main cause of acute respiratory failure
- Decompensated liver cirrhosis
- Cancer in progress
- Organ transplantation
- HIV
- Dialysis
- Home oxygen therapy
- Idiopathic Pulmonary Fibrosis
- Progressive neuromuscular diseases (e.g. ALS, Duchenne dystrophy, etc.)
- Dementia or decompensated psychiatric diseases
- Immunosuppressant drugs in use

- Chronically used oral steroid
- Use of tocilizumab
- Known pregnancy

Groups/Cohorts	Interventions
Exposed to Methylprednisolone Consecutive SARS-CoV-2 positive patients with severe acute respiratory syndrome treated with methylprednisolone (MP) at low prolonged dose, fulfilling inclusion and exclusion criteria.	Drug: Methylprednisolone Usual standard of care plus Methylprednisolone (MP) 80 mg/kg IV bolus, followed by MP infusion of 80 mg/day in 240 mL normal saline at 10 mL/h. The infusion is continued for at least eight days and until achieving either a PaO2:FiO2 > 350 mmHg or a CRP < 20 mg/L. Treatment is then switched to oral administration of Methylprednisolone 16 mg or 20 mg IV twice daily until CRP returns to < 20% of normal range and/or PaO2:FiO2 > 400 or SatHbO2 95%. The decision to apply the protocol to Covid-19 is left to the discretion of the treating team for each individual patient. standard care usual standard of care: • oxygen therapy (regular or high-flow) and monitoring • empiric antibiotic therapy • mechanical ventilation (invasive or noninvasive) • ECMO when needed and available • pronation when possible • other treatment which can be used are: antivirals, chloroquine, vitamins
Non-exposed to Methylprednisolone Concurrent patients fulfilling the same inclusion and exclusion criteria, never treated with steroids.	standard care usual standard of care: • oxygen therapy (regular or high-flow) and monitoring • empiric antibiotic therapy • mechanical ventilation (invasive or noninvasive) • ECMO when needed and available

	• pronation when possible • other treatment which can be used are: antivirals, chloroquine, vitamins

Study variables and timing of data collection

Outcome measures:

- PaO2/FiO2, mmHg
- PCR, mg / L (or mg / dL)
- Platelets, n / mm3
- Total bilirubin, mg / dL
- Blood pressure (Max / Min mmHg)
- Creatinine mg / dL
- Glasgow Come Scale (score)
- SOFA score (https://www.mdcalc.com/sequential-organ-failure-assessment-sofa-score)
- Number of days free from VM of any type (CPAP, NIV, IMV, number of days until the 28th day of admission to Respiratory Unit / UTIR)
- Number of days free from invasive VM (number of days until the 28th day of admission to Respiratory Unit / UTIR)

Follow up: 28 days from hospital admission

Measures timepoints: UTIR = Semi-Intensive Respiratory Therapy Unit

- Day 0-1 from entry into UTIR / Respiratory Unit
- Day 3 from entry into UTIR / Respiratory Unit
- Day 7 from entry into UTIR / Respiratory Unit
- Day 14 from entry into UTIR / Respiratory Unit
- Day 28 from entry into UTIR / Respiratory Unit

Additional data to be collected:

- Intra-hospital Medications, type and dosages
- Pre-hospital Medications, type and dosages
- Pre-hospital co-morbidity
- In-hospital adverse events

- Date of death
- ICU Admission date
- ICU and Hospital dates of discharge
- COVID-19 test negative date

EXPECTED RESULTS:

In the group treated with MP compared to the group without MP:

- Reduction of the proportion of patients who undergo ICU admission, intubation, or death within 28 days of admission to Respiratory Unit / UTIR
- Increase in days free from VM of all types on day 28 of admission to Respiratory Unit / UTIR
- Increase in days free from invasive VM on day 28 of admission to Respiratory Unit / UTIR
- In-hospital mortality reduction
- Reduction of PCR values on day 7 and 14 of admission to Respiratory Unit / UTIR
- Improvement of PaO2/FiO2 on day 7 and 14 of admission to Respiratory Unit / UTIR

Primary Outcome:

Difference between the two study groups in the proportion of patients experiencing one or more of the following events within 28 days of admission to Respiratory Unit / UTIR:

a) hospitalization in Intensive Care Unit

b) intubation and use of invasive mechanical ventilation

c) death in hospital for any reason.

Patients who on day 0 fall into one of the 3 previous conditions or leave the study on day 0 are excluded from the primary outcome analysis.

Secondary Outcomes:

Difference between the two groups compared to:

- Proportion of patients with PCR reduction on day 7 and day 14 of admission to Respiratory Unit / UTIR
- Proportion of patients with PaO2/FiO2 improvement (> 350 mmHg) on day 7 and on day 14 of admission to Respiratory Unit / UTIR
- Proportion of intubated patients with invasive VM on day 28 of admission to Respiratory Unit / UTIR
- Total number of days free from VM or non-invasive CPAP (helmet, mask) on day 28 of admission to Respiratory Unit / UTIR
- Total number of days free from invasive VM on day 28 of admission to Respiratory Unit / UTIR
- In-hospital mortality, expressed both in terms of the proportion of patients with death within 28 days of admission to Respiratory Unit / UTIR, both in terms of survival (calculated as time from the date of admission to Respiratory Unit / UTIR until the

first of the following dates: date of death, date of hospital discharge or end of study follow-up).

SAMPLE SIZE

The Chinese observational study published on 13/3/2020 in JAMA Intern Med3 showed that the use of MP leads to a reduction of about 15% percentage points of mortality (30-day mortality: 46.0% in 50 treated patients vs. 61.8 % in 34 untreated patients; survival median: 25 days vs. 10 days, HR 0.4, 95% CI: 0.2-0.7). Furthermore, the same study shows a proportion of ICU admissions of patients with ARDS of 63% and use of intubation and invasive VM in 79% of ARDS cases.
Given a study power (1-beta) of 80% and a probability of type 1 error (alpha) of 0.05, we calculated a sample size of 98 patients (49 for each group) using a proportional test, Z-test (pooled), 2-code. Considering the primary outcome, from the literature data it is expected for ARDS patients a proportion equal to about 70% of patients intubated and / or hospitalized in ICU and / or deceased that would be reduced by at least 40% (i.e. from 70% to 42%) with the MP-based intervention in Respiratory Unit / UTIR.
Considering a 5% drop-out, a total of at least 104 patients will need to be enrolled (52 per group).

Statistical analysis plan

See statistical analysis plan document.

ETHICAL CONSIDERATIONS FOR THE MP-C19 STUDY:

1. The highly virulent epidemic Covid19 is reaping victims in Italy even among people without particular co-morbidities despite every type of respiratory support.
2. The results of the most recent Chinese study published on March 13, 2020 in JAMA Intern Med suggests testing of methylprednisolone as a possible therapy in patients with severe COVID-19 pneumonia is needed.
3. The Chinese observational study shows an important 30-day mortality change with methylprednisolone. In addition, the impact on the health system with high number of simultaneous accesses to the hospital by patients with ARDS requires the need to find feasible solutions in a short time.
4. The size of the problem does not allow us to think of a randomized study, so we opted for a prospective case-control study with a control group selected from "contemporary" and not "historical" cases
5. Written informed consent is not necessary in these clinical situations according to the law.
6. There are robust justifications for a well-designed controlled study based on strong pharmacological and physiological principles.
7. A multicenter study is proposed that includes several centers directly involved in patient care in geographical areas with a high incidence of cases with acute respiratory failure and severe COVID-19 pneumonia in order to enroll large numbers of patients in a short time.

8. The study will be conducted in accordance with the Good Clinical Practice guidelines, the ethical principles deriving from the Helsinki declaration and the current legislation on observational studies.
9. The study follows the guidance of AIFA regarding "Management of clinical studies in Italy during an emergency COVID-19 (coronavirus disease 19)" (see https://www.aifa.gov.it/web/guest / - / management-of-clinical-studies-in-italy-in-course-of-emergency-covid-19-coronavirus-disease-19-)

CONSENT AND PRIVACY STATEMENT

Consistent with the need to inform the subjects to be included in the research, and the applicable right of patients to receive personalized information, it is believed that the conditions of extreme clinical severity and urgent care foreseen in the protocol could, for the most part, be incompatible with the application of the procedures required for the formulation of an informed consent prior to the start of the Study. This issue also applies to the presumed possibility of being able to appoint and have any legal representatives available.

In the logic outlined above, ad hoc forms (Information on Data Processing and Informed Consent for participation in the Study) are attached to this protocol which will also be presented to those patients who survive, after resuming the cognitive, functional and emotional functions to validly participate in the information process.

Therefore this clinical study will be conducted in compliance with the provisions of the Privacy Guarantor n. 146 of 5 June 2019, which recalls the previous authorization n. 9/2016 - general authorization for the processing of personal data carried out for scientific research purposes - 15 December 2016, which allows the processing of data suitable for revealing the state of health, sexual life and racial and ethnic origin, even in the absence of the consent of the interested parties, for scientific research purposes in the medical, biomedical or epidemiological field in compliance with the limits and conditions set out in the authorization itself.
The a'forementioned authorization, in fact, also allows Healthcare Companies to process the data of subjects to be included in the research, if it is not possible to contact them, in order to provide the information, if there is, among others, the following exceptional circumstance, documented in the protocol:
the intervention is necessary for the conduct of studies carried out with data referring to people who, due to the seriousness of their clinical status, are unable to understand the indications given in the information and to give valid consent.

The obligation to collect consent to the participation and processing of data [*] [**] of the interested parties enrolled in the research remains valid in all cases in which, during the study, it is possible to provide them with adequate information, as in the case in which the patient initially in critical or unconscious conditions, recovers the ability to validly give his consent to the participation to the study and gathering/usage/disclosure of data already collected and / or to the continuation of the study.

[*] for the prospective part of the study: "*After adequate information and signing of the informed consent form and the ICF form, in accordance with the current legislation on data processing (Regulation (EU) 2016/679 of 27 April 2016 , Legislative Decree 10.08.18 No. 101 GU 205-18) and subsequent amendments, and to comply with the provisions of the Guidelines for the treatment of personal data in the context of clinical trials of medicines, adopted on 24 July 2008 of Guarantor for the protection of personal data, or to comply with the provisions of Resolution no. 85 of 01 March 2012, OJ General Series n.72 of 26-3-2012), the patient data that will be affiliated with our Center, will be collected anonymously at the source and will be kept until the conclusion of the study* ".

[**]
for the part of the controls: "(...) *it should be noted that in the condition of samples / retrospective data of patients found to be deceased or unavailable, the right enshrined in art. 110, paragraph 1, and 41 of the Code, to process the data and carry out the operations strictly indispensable and pertinent to the conduct of the study, even in the absence of their informed consent. Data will be collected for all patients relating to the diagnosis, the therapy they underwent and the clinical course. Biological samples and clinical data will be immediately anonymised, before proceeding with the subsequent analysis* ".

RETENTION OF DOCUMENTS

The documentation will be available, for inspection, for at least 7 years from the formal closure of the study

SCIENTIFIC DATA OWNER

The owner of the collected data will be the promoter of the study

PUBLICATION POLICIES AND COMMUNICATION OF RESULTS

The scientific director of the study will undertake to write a final report and a scientific article and to publish the results at the end of the study. The data will be anonymous and presented in aggregate mode.

The study is promoted by ASUGI (Giuliano Isontina University Health Authority)

COORDINATING CENTER

Struttura complessa Pneumologia, ASUGI - Ospedale di Cattinara, strada di Fiume 447, 34149 Trieste

Director: Prof Marco Confalonieri, phone 040/3994667, email mconfalonieri@units.it)

For information:

Dr Francesco Salton (email: francesco.salton@gmail.com),

Prof Marco Confalonieri (email mconfalonieri@units.it, ph 0403994667)

***Ethic committee**: CEUR F.V.G. – C/o C.R.O. di Aviano (PN)- Italy*

References

1. Grasselli G, Pesenti A, Cecconi M. Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy: Early Experience and Forecast During an Emergency Response. *JAMA* 2020 Mar 13. doi: 10.1001/jama.2020.4031. [Epub ahead of print]
2. Yang X, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Whuan, China: a single-centered, retrospective, observational study. *Lancet Resp Med* 2020; published online Feb 21, 2020. https://doi.org/10.1016/S2213-2600(20)379-5
3. Wu C, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020; Online published March 13, 2020. doi: 10.1001/jamainternmed.2020.0994
4. WHO Interim Guidance 13 March 2020. Clinical management of severe acute respiratory infectin (SARI) when COVID-19 disease is suspected. WHO/2019-nCoV/clinical/2020.4
5. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. Am J Respir Crit Care Med. 2018;197(6):757-767. doi: 10.1164/rccm.201706-1172OC. PMID: 29161116
6. WHO. COVID 19 – Public health emergency of international concern. Global https://www.who.int/blueprint/priority-diseases/key-action/Global_Research_Forum_FINAL_VERSION_for_web_14_feb_2020.pdf?ua=1
7. Confalonieri M, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. Am J Respir Crit Care Med 2005; ;171(3):242-8.
8. Dinsen S, Baslund B, Klose M, Rasmussen AK, Friis-Hansen L, Hilsted L, Feldt-Rasmussen U: Why glucocorticoid withdrawal may sometimes be as dangerous as the treatment itself. *European journal of internal medicine* 2013, 24(8):714-720.
9. Bone RC. Corticosteroids for septic shock and adult respiratory distress syndrome. Prog Clin Biol Res 1989; 308: 857-65
10. Stern A, et al. Corticosteroids for pneumonia. Cochrane Database Syst Rev 2017 Dec 13;12:CD007720. doi: 10.1002/14651858.CD007720.pub3
11. Meduri GU, Bridges L, Shih MC, Marik PE, Siemieniuk RAC, Kocak M: Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. *Intensive Care Med* 2016, 42(5):829-840.

12. Meduri GU, Annane D, Chrousos GP, Marik PE, Sinclair SE: Activation and regulation of systemic inflammation in ARDS: Rationale for prolonged glucocorticoid therapy. *Chest* 2009, 136:1631-1643.
13. Meduri GU, Eltorky MA: Understanding ARDS-associated fibroproliferation. *Intensive Care Med* 2015, 41(3):517-520.
14. Annane D, et al. Critical illness-related corticosteroid insufciency (CIRCI): a narrative review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). Intensive Care Med (2017) 43:1781–1792
15. Zhao Q, et al. Effect of glucocorticoids on mortality in patients with acute respiratory distress syndrome: A meta-analysis. Exp Ther Med 2019; 18: 4913-20.
16. Torres A, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. JAMA 2015; 2015 Feb 17;313(7):677-86.
17. Meduri GU, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, Gibson M and Umberger R: Methylprednisolone infusion in early severe ARDS: Results of a randomized controlled trial. Chest 131: 954-963, 2007.
18. Sabry NA, Omar EE-D. Corticosteroids and ICU course of community acquired pneumonia in Egyptian settings. Pharmacol Pharm. 2011;2:73–81.
19. Liu L, Li J, Huang YZ, Liu SQ, Yang CS, Guo FM, Qiu HB, Yang Y. The effect of stress dose glucocorticoid on patients with acute respiratory distress syndrome combined with critical illness-related corticosteroid insufficiency. Zhonghua Nei Ke Za Zhi. 2012;51(8):599–603.
20. Rezk N, Ibrahim A. Effects of methylprednisolone in early ARDS. Egypt J Chest Dis Tuberc. 2013;62(1):167–72.
21. Tongyoo S, Permpikul C, Mongkolpun W, Vattanavanit V, Udompanturak S, Kocak M, Meduri GU. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: results of a randomized controlled trial. Crit Care. 2016;20(1):329.
22. Villar J, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med 2020 Mar;8(3):267-276.
23. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, Thompson BT, Ancukiewicz M. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med. 2006;354(16):1671–84.
24. Meduri GU, Headley AS, Golden E, Carson SJ, Umberger RA, Kelso T and Tolley EA: Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: A randomized controlled trial. JAMA 280: 159-165, 1998
25. Annane D, S bille V, Bellissant E and Ger-Inf-05 Study Group: Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress

syndrome. Crit Care Med 34: 22-30, 2006.

26. Meduri GU, et al. Prolonged low-dose methylprednisolone treatment is highly effective in reducing duration of mechanical ventilation and mortality in patients with ARDS. *J Intensive Care* 6, 53 (2018). https://doi.org/10.1186/s40560-018-0321-9
27. FICM. Guidelines on the management of acute respiratory distress syndrome. Version 1, July 2018. https://www.ficm.ac.uk/sites/default/files/ficm_ics_ards_guideline_-_july_2018.pdf
28. Ni Y-N, et al. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis.*Crit Care.* 2019; 23: 99
29. Shang L, et al. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet 2020; 683-4. Published Online February 11, 2020 https://doi.org/10.1016/ S0140-6736(20)30361-5
30. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet 2020; published online March 13. DOI:https://doi.org/10.1016/S0140-6736(20)30627-9
31. Ranieri MV. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012 Jun 20;307(23):2526-33
32. Bouadma L, Lescure FX, Lucet JC, Yazdanpanah Y, Timsit JF: Severe SARS-CoV-2 infections: practical considerations and management strategy for intensivists. *Intensive Care Med* 2020:1-4.