Supplementary Online Content 2

Dequin P-F, Heming N, Meziani F, et al; CAPE COVID Trial Group and the CRICS-TriGGERSep Network. Effect of hydrocortisone on 21-day mortality or respiratory support among critically-ill patients with COVID-19: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2020.16761

Statistical Analysis Plan

Centre d'Investigation Clinique
INSERM CIC 1415

INFLUENCE DE LA CORTICOTHERAPIE A DOSES FAIBLES SUR L'ÉVOLUTION DES PNEUMOPATHIES AIGUËS GRAVES DANS LE CADRE DE L EPIDEMIE COVID19.

Community-Acquired Pneumonia: Evaluation of Corticosteroids in COronaVIrus Disease

CAPE COVID19

Final analysis

V1 – 08.07.2020

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SOMMAIRE

I. Context

On 28 March 2020, 591 971 cases of coronavirus disease (COVID19) due to SARS-CoV-2 have been reported, of whom 27 090 died (fatality rate 4.6%). Over 175 countries have reported laboratory-confirmed cases. In France, at the same date, 37 575 patients were contaminated and 2 314 have died (fatality rate 6.1%). Although most patients progress well and do not require specific treatment, therapy of severe forms (which represent 15% of cases) remains a challenge, as there is a lack of effective drug in addition to supportive care. At this stage, ICU-mortality is estimated to be 50%. There is an urgent need for focusing funding into searching novel approaches to treat severe coronavirus-associated pneumonia. Chinese experience shows that 45% of patients with severe disease receive corticosteroids (CTx). In Severe Acute Respiratory Syndrome (SARS) as in Middle-East Respiratory Syndrome (MERS) - two viral pulmonary diseases due to other coronaviruses - pulmonary histology revealed inflammation and diffuse alveolar injury. In severe cases, COVID19 is associated with a cytokine storm. This excessive immune response leads to extensive lung damage. Theoretically, CTx could have a role to decrease lung inflammation in coronaviruses pneumonia. Our knowledge on clinical use of CTx in viral pneumonia is essentially based on observational cohorts. As clinicians use CTx in the most critically ill patients, careful attention must be paid to the interpretation of mortality. In SARS, adverse effects of CTx have been observed, generally linked to the use of high doses. Prolonged viremia has also been evocated, without clinical impact. In MERS, CTx did not influence D-90 mortality, but seemed to delay viral clearance. Although controversial, some Chinese experts recommend short courses of CTx at low-to-moderate doses in the treatment of severe SARS-CoV-2 pneumonia. In a recently-published observational cohort of 201 patients, CTx appears to decrease the risk of death in the sub-group of Acute Respiratory Distress Syndrome (ARDS) patients: hazard ratio 0.38; 95% CI, 0.20-0.72. The need for a randomized clinical trial is strongly advocated. We suggest adapting a trial already underway to test the efficacy and safety of moderate doses of CTx in COVID19 patients.

II. Objectives

1. Primary objective

Demonstrate that low-dose hydrocortisone started during the first 24 hours following the occurrence of the first severity criterion and administered for 8 to 14 day to patients admitted to the Intensive Care Unit (ICU) for severe CAP related to SARS-CoV-2 infection could decrease the rate of treatment failure at D21, failure being defined either by patients death or persistent use of ICU respiratory support.

2. Secondary objectives

Demonstrate that low-dose hydrocortisone started during the first 24 hours following the occurrence of the first severity criterion and administered for 8 to 14 day to patients admitted to the Intensive Care Unit (ICU) for severe CAP related to SARS-CoV-2 infection:

- could improve oxygenation parameters
- could decrease:
    - the need for intubation (for patients not-intubated at inclusion)
    - the need for rescue therapies: prone-position, extra-corporeal membrane oxygenation (ECMO), nitric oxide inhalation (iNO)
- will not increase the incidence of secondary infections

III. Methodology

1. Study design

The Cape-COVID19 trial is a multi-center, blinded, two parallel group trial with group sequential analysis.

2. Outcomes

a) Primary outcome

D21 failure, where a failure is defined as death or need of respiratory support (mechanical ventilation or high-flow oxygen therapy).

b) Secondary outcomes

Secondary outcomes :

- P/F ratio measured daily from D1 to D7, at D14 and at D21
- In patients non-invasively ventilated at inclusion, proportion of patients needing endotracheal intubation at D21
- Number of prone-position sessions at D21
- Days on ECMO, days on iNO at D21
- Proportion of patients experiencing secondary infection during their ICU-stay

c) Additional outcome

SOFA measured daily from D1 to D7.

3. Procedures

Hydrocortisone or placebo were given in a double-blind fashion for 8 or 14 full days. The intravenous route was used. The treatment course included 4 or 7 days of full dose (200 mg/day by continuous infusion), 2 or 4 days of half dose (100 mg/day by continuous infusion), and 2 or 3 days of tapering dose (50 mg/day by continuous infusion). Duration of treatment was chosen upon patient initial improvement.

4. Sample size

The event rate was assumed to be 30% in the control group. The trial was designed to demonstrate superiority of experimental treatment over control with an assumed event rate of 15% in the experimental group with 80% power. Asymmetric two-sided group sequential design requires sample size 290 for 6 interim analyses (5 during the trial and one final). Bounds were determined using a Kim-DeMets alpha spending function (Lan et al, Biometrika 1983;70:659-63; kim et al Biometrics 1987;4:857-64; DeMets et al Statist Medicine 1994;13:1341-52) with a conservative bound for efficacy and an aggressive bound for futility. That is, stopping for high evidence of superiority while

stopping early if the experimental treatment is not effective and can be potentially harmful for patients.
Due to uncertainty of the failure rate in the control group, we planned to re-calculate this sample size while the trial is going-on. Indeed, data about mortality rate of COVID patients in ICU are diverging and ranging from 50% to 5%. We choose to assume a 30% rate considering mortality or need of respiratory support for the control arm but this is uncertain. This is why sample size re-estimation could be necessary during the trial when up-dated knowledge will be available..

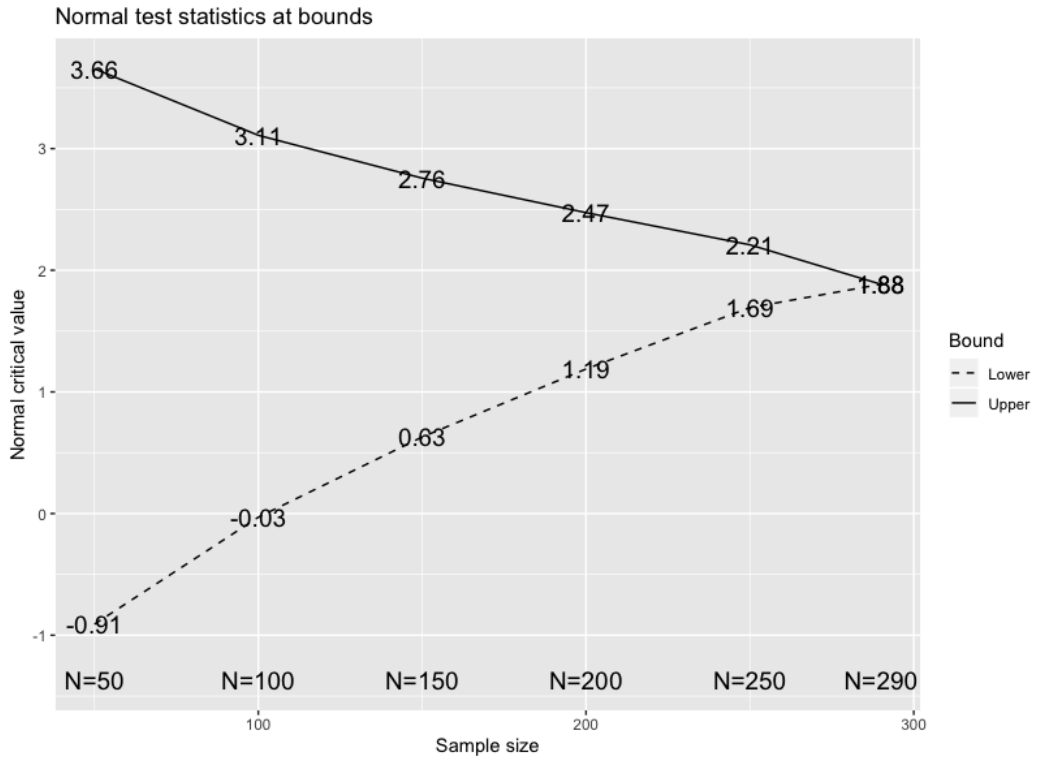
IV. Statistical analysis

1. General principles

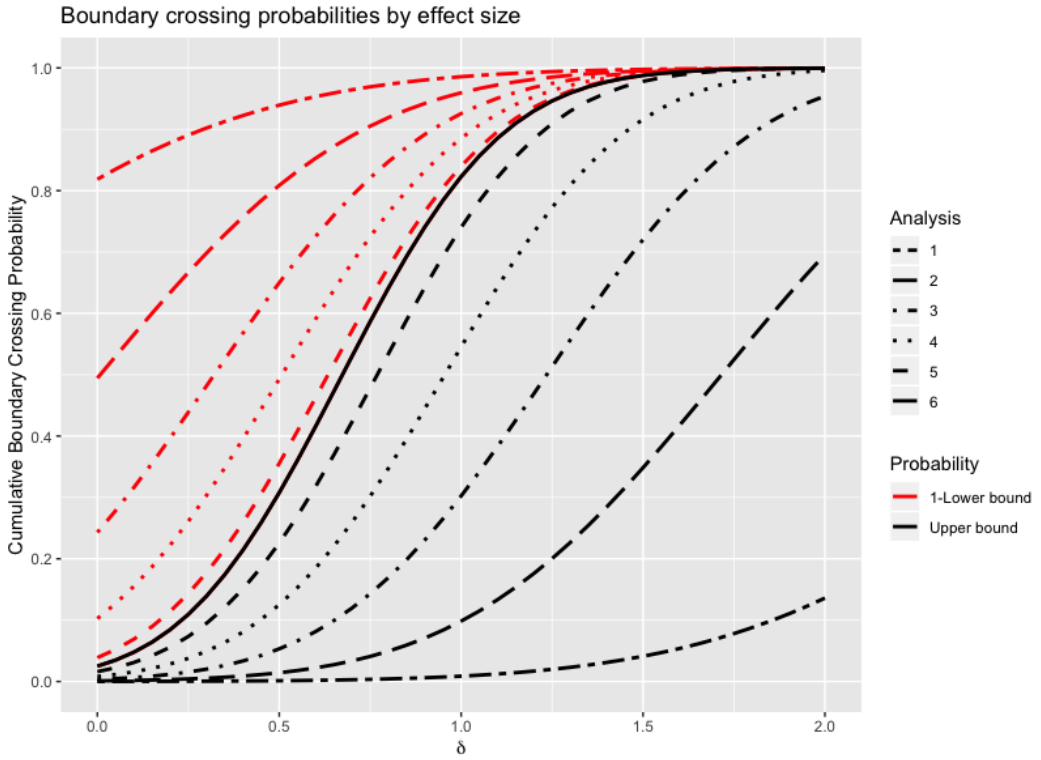
The statistical analyses were performed by the INSERM CIC 1415 unit. SAS 9.4 and R 3.6.3 (package gsDesign version 3.0-1) softwares were used. A statistical report were written in agreement with the standards as specified in the CONSORT Statement (http://www.consort-statement.org/). The statistical analyses were conducted according to the intention to treat (ITT) principle.

The statistical design for this phase III two arms clinical trial followed a group sequential design with a total of 6 analyses (5 interim analyses and a final). The group sequential used a Kim-DeMets alpha spending function with a conservative bound for efficacy and an aggressive bound for futility. That is, a conservative O'Brien Fleming type of bound for superiority bound and an aggressive futility boundary with "rho"=1.5 for futility design.

At each interim analysis, the Z statistic (for a difference of binary endpoints) was computed from the data of the two arms and was compared to the efficacy and futility bounds given in the figure bellow:



If the value of Z was higher than the interim analysis specific upper bound (or lower than the lower bound), the trial should be stopped for reasons of demonstrated efficacy (or futility); otherwise the trial should continue. Under these assumptions are given in the figure bellow the probabilities of crossing the boundaries at each interim analysis according to the effect size.



All tests performed were bilateral. P values of 0·0452 or less were taken as indicating a significant difference in the primary outcome because of the three planned interim analyses and values of 0·05 or less as indicating statistical significance for the secondary outcomes.

2. Baseline characteristics

Baseline characteristics were reported per group using descriptive statistics. No statistical test was performed.

3. Primary outcome

D21 failure was analyzed using a two-proportion z-test based on normal approximation. Analyses were performed on complete case and after imputation of missing data by failure. Difference of proportions was estimated with its 95.48% confidence interval.

4. Secondary outcomes

- All components of the primary outcome were studied using two-proportion z-tests based on normal approximation. Differences of proportions were estimated with its 95% confidence intervals.

- In patients non-invasively ventilated at inclusion, proportion of patients needing endotracheal intubation was estimated in each group with descriptive statistics due to the number of events.
- The incidence of patient with at least one prone-position session was estimated using a competing risk approach (with death and end of ICU stay as competing events).
- The extra-corporeal membrane oxygenation (ECMO) and nitric oxide inhalation (iNO) will be studied with descriptive statistic due to the weak number of events.
- The number of prone position sessions, days on ECMO, iNO were estimated in each group.
- P/F ratio and SOFA measured daily were described using box plots and analyzed in the framework of mixed models.
- Proportion of patients experiencing secondary infection during their ICU-stay was estimated in the framework of a competing risk model with death and end of ICU stay considered as competing events.

V. Results

1. Flow chart

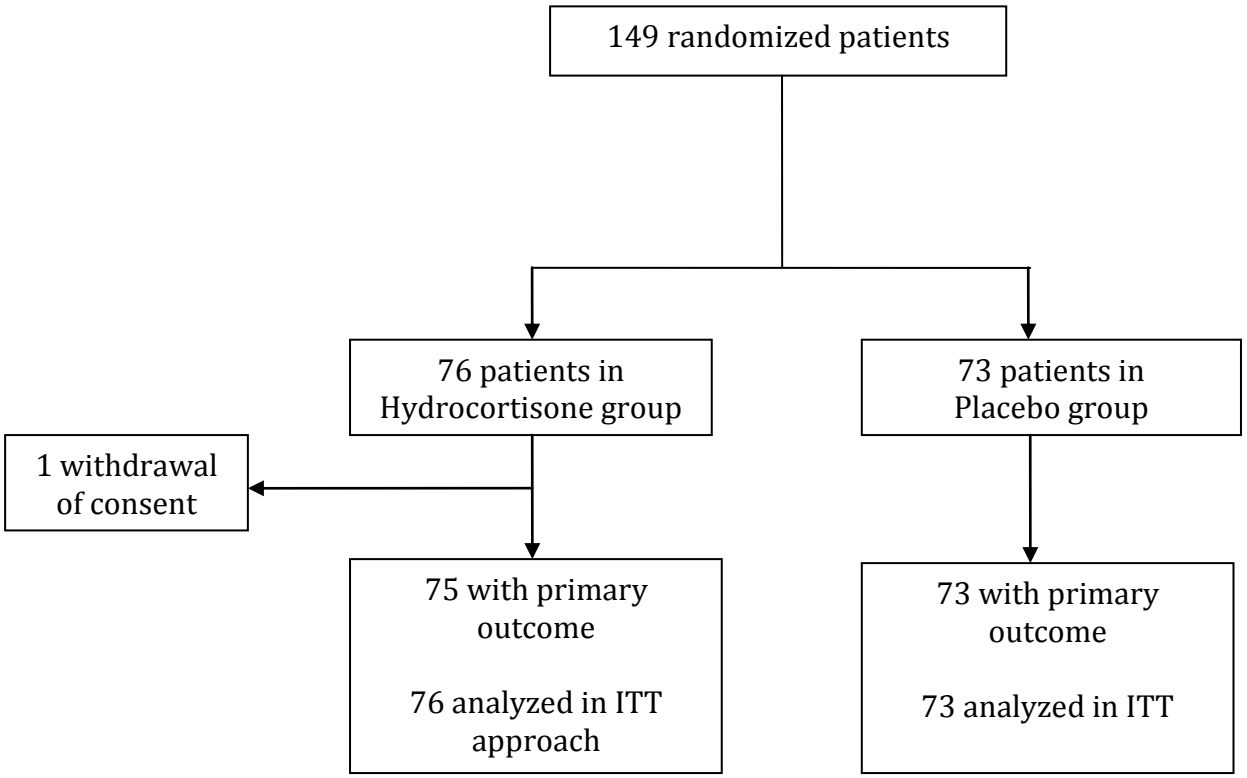


Fig.1 Flow chart

2. Baseline characteristics

Table I – Baseline characteristics

	Hydrocortisone group (n_1=76)	**Placebo Group (n_2=73)**
Clinical examination and demographics		
Men	54 (71.1)	50 (68.5)
Age, *years*	61.9 ± 11.8	62.5 ± 13.4
	63.1 [51.5 ; 70.8]	66.3 [53.5 ; 72.7]
Smoking status, *n_1=75, n_2=72*		
Current smoker	1 (1.3)	0 (0.0)
Ex-smoker	17 (22.7)	15 (20.8)
Never smoker	57 (76.0)	57 (79.2)
BMI, *$Kg.m^{-2}$, n_1=59, n_2=61*	29.6 ± 6.6	29.3 ± 5.4
	27.5 [25.3 ; 32.4]	28.4 [26.0 ; 31.2]
Heart rate, *bpm, n_1=55, n_2=57*	84.9 ± 20.6	85.9 ± 21.1
	85.0 [68.0 ; 100.0]	81.0 [72.0 ; 100.0]
Systolic blood pressure, *mmHg, n_1=59, n_2=56*	118.8 ± 28.2	127.5 ± 26.4
	112.0 [104.0 ; 133.0]	126.5 [111.0 ; 145.0]
Diastolic blood pressure, *mmHg, n_1=59, n_2=56*	63.7 ± 12.5	65.0 ± 11.5
	64.0 [54.0 ; 70.0]	67.0 [58.0 ; 71.0]
Respiratory rate, */min, n_1=60, n_2=64*	27.2 ± 6.9	27.1 ± 6.9
	26.0 [24.0 ; 31.5]	25.0 [22.5 ; 30.0]
Temperature, *°C, n_1=66 n_2=66*	37.7 ± 1.1	37.7 ± 1.2
	37.7 [36.8 ; 38.6]	37.8 [36.9 ; 38.6]
PCR	75 (98.7)	73 (100.0)
Positive results	72 (96.0)	72 (98.6)
Quantitative results, *n_1=6 n_2=2*	30.2 ± 5.9	13.0 ± 17.0
	32.5 [25.0 ; 33.0]	13.0 [1.0 ; 25.0]
Symptom start, *days, n_1=76 n_2=72*	9.0 [7.0 ; 11.5]	10.0 [8.0 ; 12.0]
Medical history		
COPD	4 (5.3)	2 (2.7)
Asthma	3 (3.9)	2 (2.7)
Diabetes mellitus treated	13 (17.1)	14 (19.2)
Immunosuppression	6 (7.9)	3 (4.1)
Neoplastic disease , *n_1=43 n_2=51*	2 (4.7)	3 (5.9)
Liver disease , *n_1=43 n_2=51*	1 (2.3)	1 (2.0)
Congestive heart failure, *n_1=43 n_2=51*	3 (7.0)	3 (5.9)
Cerebrovascular disease, *n_1=43 n_2=51*	1 (2.3)	1 (2.0)
Renal disease, *n_1=43 n_2=51*	2 (4.7)	2 (3.9)
Altered mental status, *n_1=43 n_2=51*	0 (0.0)	1 (2.0)
Pleural effusion, *n_1=43 n_2=51*	0 (0.0)	0 (0.0)
Graft	1 (1.3)	1 (1.4)

n (%) for qualitative variables ; Mean ± standard deviation; median [1st quartile; 3rd quartile] for continuous variables

	Hydrocortisone group (n_1=76)	**Placebo Group (n_2=73)**
Biology		
Potassium, *mmol/L*, n_1=71, n_2=69	3.9 [3.7 ; 4.2]	3.8 [3.5 ; 4.1]
Glucose *mmol/L*, n_1=51 n_2=56	7.4 [6.4 ; 9.9]	7.8 [6.3 ; 10.5]
Creatine Phosphokinase, *UI/L*, n_1=45, n_2=43	194.0 [79.0 ; 421.0]	157.0 [90.6 ; 416.0]
CRP, *mg/L*, n_1=57, n_2=53	154.0 [113.0 ; 271.0]	185.0 [119.0 ; 237.0]
Procalcitonin, *ng/mL*, n_1=52, n_2=46	0.4 [0.2 ; 0.7]	0.4 [0.2 ; 0.8]
Cortisol, *nmol/L*, n_1=26, n_2=23	526.0 [336.0 ; 613.0]	493.0 [355.0 ; 620.0]
Platelet count, *Giga/L*, n_1=64, n_2=63	217.0 [170.0 ; 279.0]	229.0 [167.0 ; 281.0]
White blood cells count, *Giga/L*, n_1=64, n_2=63	8.3 [6.6 ; 10.2]	8.2 [6.2 ; 10.4]
Lymphocyte, *Giga/L*, n_1=65, n_2=57	0.9 [0.5 ; 1.4]	0.7 [0.6 ; 1.3]
Arterial blood gas		
PH, n_1=75, n_2=72	7.4 ± 0.1	7.4 ± 0.1
	7.4 [7.3 ; 7.5]	7.4 [7.3 ; 7.5]
PAO_2, *mmHG*, n_1=75, n_2=72	116.4 ± 60.0	107.3 ± 50.8
	97.0 [74.1 ; 137.0]	92.0 [71.2 ; 126.5]
$PACO_2$, *mmHG*, n_1=74, n_2=72	40.5 ± 8.7	40.2 ± 9.0
	39.0 [34.0 ; 47.0]	38.9 [34.0 ; 45.4]
Lactate, *mmol/L*, n_1=73, n_2=64	1.1 [0.9 ; 1.4]	1.1 [0.9 ; 1.6]
SpO_2, *%*, n_1=32 n_2=29	95.2 ± 3.4	95.6 ± 3.0
	96.0 [94.0 ; 97.5]	96.0 [94.0 ; 98.0]
Ventilation		
Mechanical ventilation	62 (81.6)	59 (80.8)
Invasive	60 (96.8)	57 (96.6)
PEEP, cmH_2O	10.4 ± 2.9	10.1 ± 3.2
	10.0 [8.0 ; 12.0]	10.0 [8.0 ; 12.0]
FIO_2, *%*	80.8 ± 22.1	80.8 ± 20.7
	95.0 [60.0 ; 100.0]	90.0 [60.0 ; 100.0]
High flow oxygen therapy	10 (13.2)	9 (12.3)
Oxygen therapy with rebreathing-mask with a reservoir bag	4 (5.3)	5 (6.8)
P/F ratio, *mmHg*, n_1=75, n_2=72	151.4 ± 79.4	139.3 ± 61.4
	130.0 [96.7 ; 188.0]	133.0 [89.8 ; 174.8]
SDRA, n_1=75, n_2=72		
No SDRA (P/F ratio >300)	3 (4.0)	1 (1.4)
Mild (200<P/F ratio ≤ 300)	14 (18.7)	11 (15.3)
Moderate (100<P/F ratio ≤ 200)	37 (49.3)	38 (52.8)
Severe (0<P/F ratio ≤ 100)	21 (28.0)	22 (30.6)
Patient placed on mechanical ventilation (invasive or not) for acute respiratory failure, with a PEEP level of 5 cm of water or more	62 (81.6)	59 (80.8)
Patient treated by high-flow oxygen therapy with a FiO2 of 50% or more and a P/F ratio less than 300	10 (13.2)	9 (12.3)

Patient treated by oxygen therapy with a partial rebreathing-mask with a reservoir bag, provided that the PaO2 is less than:	5 (6.6)	5 (6.8)

Oxygen flow (L/min)	6	7	8	9	10 or more
PaO2 (mmHg) less than	180	210	240	270	300

Inclusion in another trial	20 (26.3)	24 (32.9)

n (%) for qualitative variables ; Mean ± standard deviation; median [1st quartile; 3rd quartile] for continuous variables

	Hydrocortisone group (n_1=76)	**Placebo Group (n_2=73)**
Pneumonia severity index, *n_1=43 n_2=51*	103.4 ± 32.4	101.0 ± 33.4
	101.0 [82.0 ; 121.0]	102.0 [80.0 ; 120.0]
SAPS II	34.3 ± 11.5	33.1 ± 12.1
	32.5 [25.0 ; 38.5]	32.0 [27.0 ; 39.0]
SOFA, *n_1=74 n_2=72*	6.3 ± 3.2	5.7 ± 2.6
	6.0 [4.0 ; 8.0]	6.0 [4.0 ; 7.5]
neurological	0.0 [0.0 ; 4.0]	0.0 [0.0 ; 4.0]
cardiovascular	1.0 [0.0 ; 3.0]	0.0 [0.0 ; 1.0]
respiratory	3.0 [2.0 ; 3.0]	3.0 [2.5 ; 4.0]
renal	0.0 [0.0 ; 0.0]	0.0 [0.0 ; 0.0]
hematological	0.0 [0.0 ; 0.0]	0.0 [0.0 ; 0.0]
hepatic	0.0 [0.0 ; 0.0]	0.0 [0.0 ; 0.0]
Catecholamine	18 (23.7)	13 (17.8)
At least one treatment administered	52 (68.4)	51 (69.9)
At least one specific COVID treatment	44 (57.9)	47 (64.4)

n (%) for qualitative variables ; Mean ± standard deviation ; median [1stquartile; 3rd quartile] for continuous variables

Treatment administered prior /at /after inclusion	**Hydrocortisone group (n_1=92* treatments)**	**Placebo Group (n_2=93* treatments)**
ATB aminoglycoside	2 (2.2)	4 (4.3)
ATB Azithromycin	3 (3.3)	2 (2.2)
ATB C3G	26 (28.6)	21 (22.6)
ATB C4G	0 (0.0)	1 (1.1)
ATB Piperacillin/ Tazobactam	3 (3.3)	3 (3.2)
ATB Spiramycin	5 (5.5)	6 (6.5)
ATB cotrimoxazole	0 (0.0)	1 (1.1)
ATB meropenem	1 (1.1)	0 (0.0)
ATB roxithromycin	1 (1.1)	0 (0.0)
ATB vancomycin	0 (0.0)	1 (1.1)
Eculizumab	3 (3.3)	2 (2.2)
Hydroxychloroquine/ Azithromycin	23 (25.2)	28 (30.1)
Hydroxychloroquine/ Spiramycin	1 (1.1)	0 (0.0)
Hydroxychloroquine	10 (11.0)	8 (8.6)
Methylprednisolone	1 (1.1)	0 (0.0)
Remdesivir	2 (2.2)	3 (3.2)
Ritonavir/lopinavir	10 (10.9)	11 (11.8)
Tocilizumab	1 (1.1)	2 (2.2)

*n (%) for qualitative variables ; *Several treatments for a same patient.*

Treatment administered prior or at the time of randomization	**Hydrocortisone group (n_1=76)**	**Placebo Group (n_2=73)**
Patients treated with remdesevir	1 (1.3)	0 (0.0)
Patients treated with lopinavir/ritonavir	8 (10.5)	9 (12.3)
Patients treated with favipravir	0 (0.0)	0 (0.0)
Patients treated with hydroxychloroquine	29 (38.2)	32 (43.8)
Patients treated with azithromycin	19 (25.0)	24 (32.9)
Patients treated with convalescent plasma	0 (0.0)	0 (0.0)

n (%) for qualitative variables

Median [1stquartile; 3rd quartile]	**Hydrocortisone group (n_1=76)**	**Placebo Group (n_2=73)**
Duration of experimental treatment, *days*	10.5 [6.0 ; 14.0]	12.0 [8.0 ; 13.0]

3. Primary outcome

Table II – D21 failure

D21 failure (death or need of respiratory support: mechanical ventilation or high-flow oxygen therapy*), n (%)*	**Hydrocortisone group (n_1=76)**	**Placebo Group (n_2=73)**	**Z statistic**	**Difference of proportions and 95.48%CI**	**p**
Complete case,*n_1=75, n_2=73*	31 (41.3)	37 (50.7)	1.14	-9.4 [-25.7 ; 7.0]	0.25
Missing data imputed by failure (ITT approach)	32 (42.1)	37 (50.7)	1.05	-8.6 [-24.9 ; 7.7]	0.29

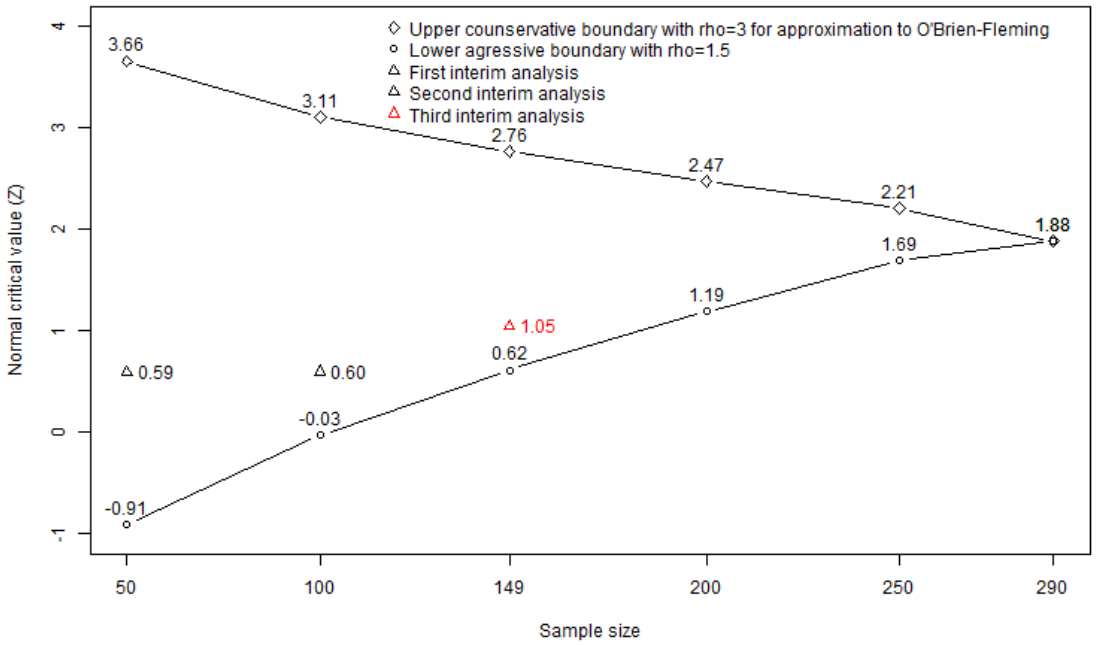


Fig.2 Z statistic

4. Secondary outcomes

a) Primary outcome components

D21 Status, *n*	**Hydrocortisone group (n_1=75)**	**Placebo Group (n_2=73)**	**Difference of proportions and 95%CI**	**p**
Death	11 (14.7)	20 (27.4)	-12.7 [-25.7 ; 0.3]	0.057
Mechanical ventilation	17 (22.7)	17 (23.3)	-0.6 [-14.2 ; 12.9]	0.93
High-flow oxygen therapy	3 (4.0)	0 (0.0)	-	-
Simple oxygen therapy	1 (1.3)	4 (5.5)	-	-
ICU discharge	43 (57.3)	32 (43.8)	13.5 [-2.5 ; 29.5]	0.10

b) <u>P/F ratio</u>

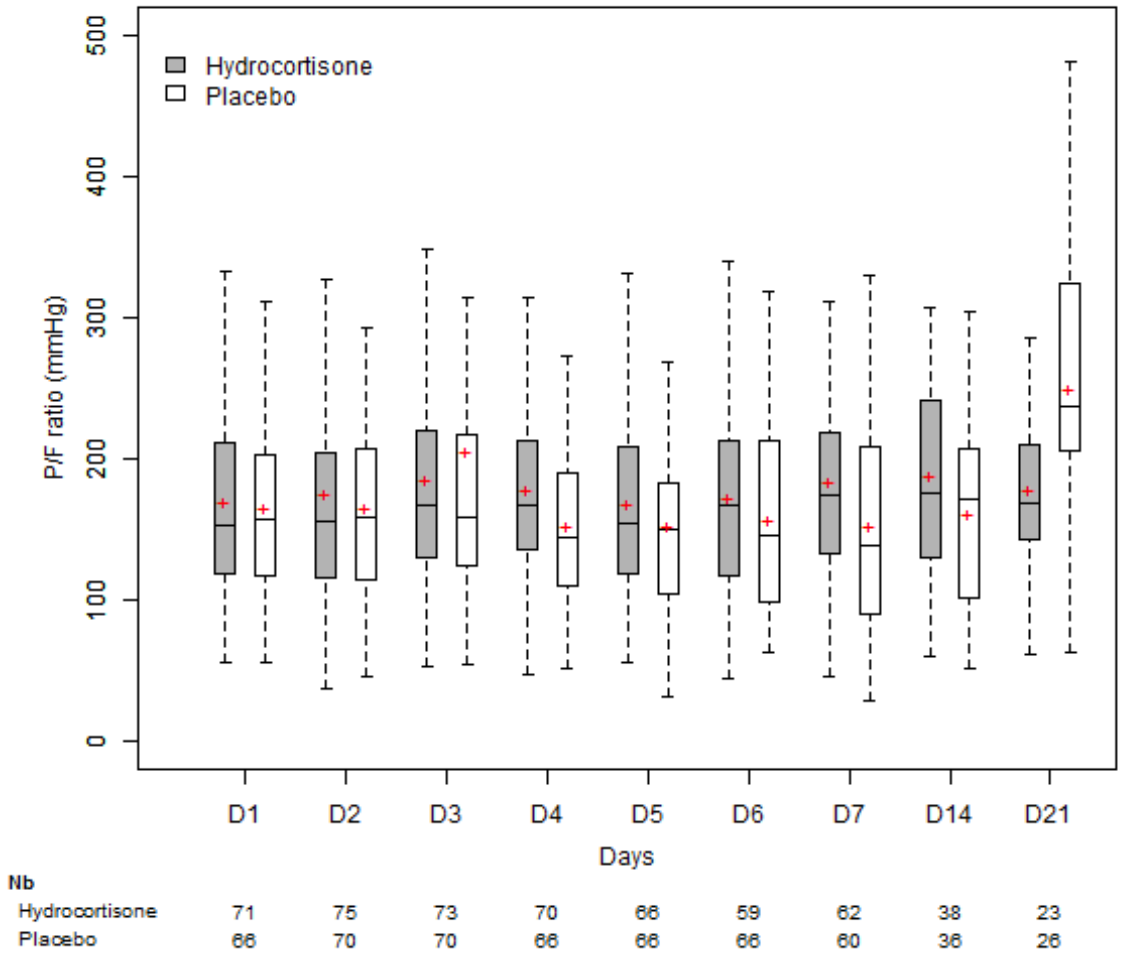


Fig.3 Evolution of P/F ratio

Effect	Parameter & 95%CI	p
Intercept	158.05 [140.72 ; 175.38]	<.0001
Time, *days*	1.96 [0.03 ; 3.89]	0.046
Group Hydrocortisone *versus* placebo	15.92 [-8.33 ; 40.18]	0.19
Interaction between time and group	**-1.26 [-4.01 ; 1.48]**	**0.37**

c) <u>SOFA</u>

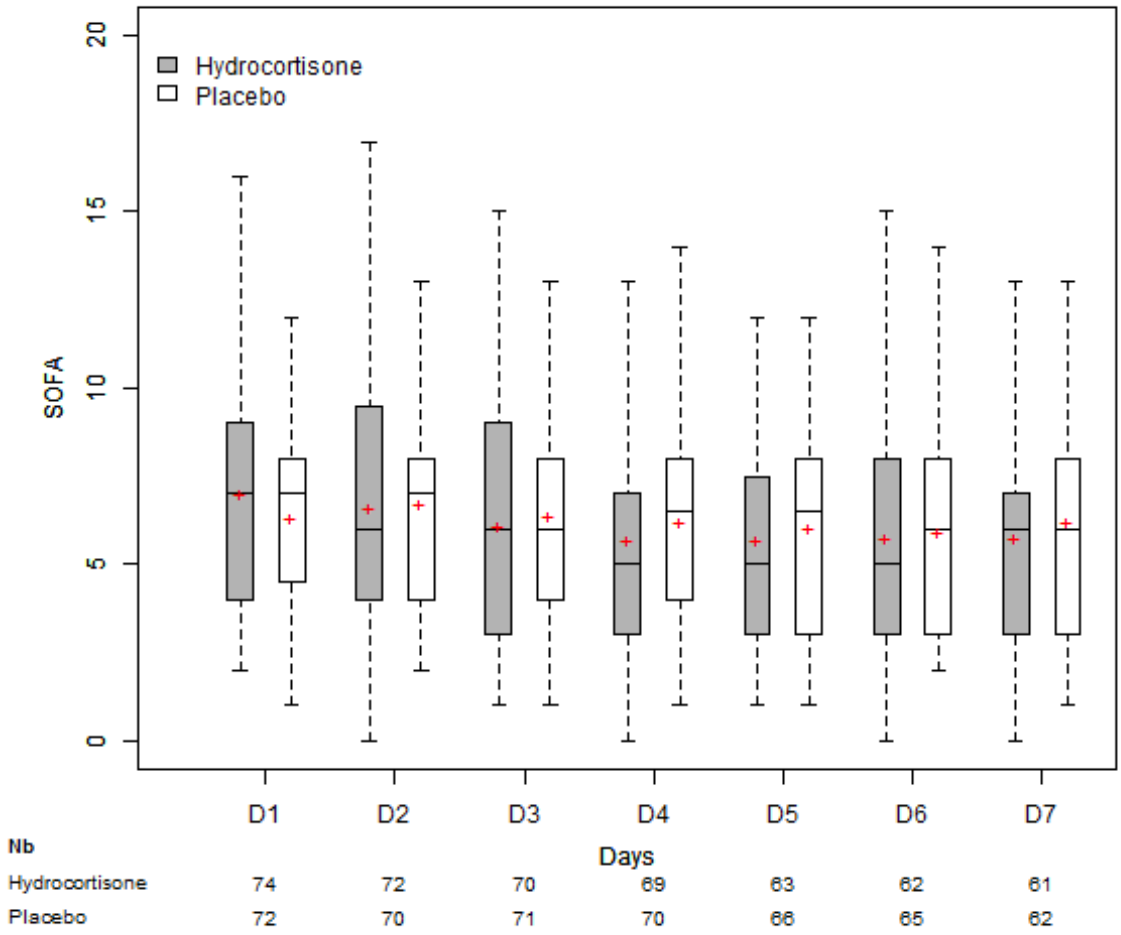


Fig.4 Evolution of SOFA

Effect	Parameter & 95%CI	p
Intercept	6.53 [5.87 ; 7.20]	<.0001
Time, *days*	-0.05 [-0.18 ; 0.06]	0.37
Group Hydrocortisone *versus* placebo	0.51 [-0.41 ; 1.44]	0.28
Interaction between time and group	**-0.21 [-0.39 ; -0.04]**	**0.015**

d) <u>Endotracheal intubation after inclusion</u>

Table III – Endotracheal intubation

Patients non-invasively ventilated at inclusion	**Hydrocortisone group (n_1=16/149)**	**Placebo Group (n_2=16/149)**
Patients needing endotracheal intubation	8	12

e) <u>Need for rescue therapies</u>

Seventy five patients had at least one prone-position session during the first 21 days of follow-up (36 in the Hydrocortisone group *vs* 39 in the Placebo group), 9 died without prone-position session before day 21 (4 in the Hydrocortisone group *vs* 5 in the Placebo group), 48 left ICU without prone-position session before day 21 (29 in the Hydrocortisone group *vs* 19 in the Placebo group) and 17 are censored (1 for withdrawal consent and 6 are stil in ICU at day 21 in the Hydrocortisone group *vs* 10 still in ICU at day 21 in the Placebo group).

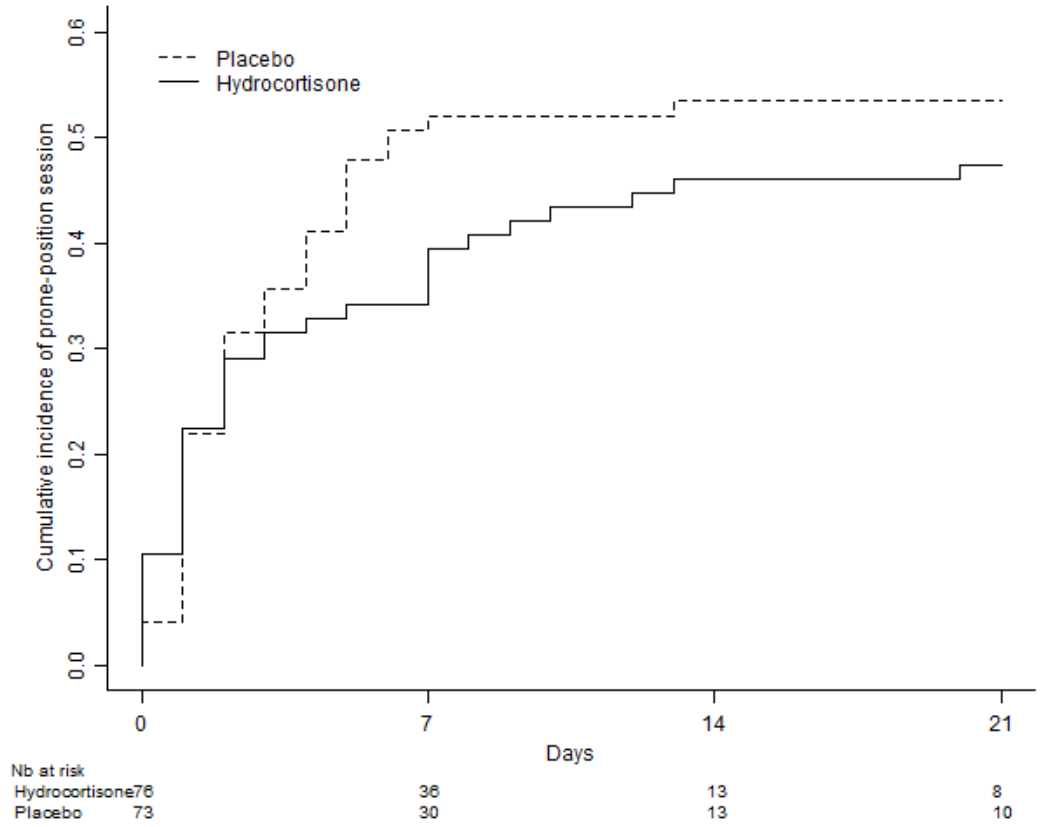


Fig.4 Cumulative incidence of prone position session

The cumulative incidence of prone position session at day 21 is 47.4% in the hydrocortisone group versus 53.4% in the placebo group (HR=0.85 [0.55; 1.32], p=0.47).

Table IV – Rescue therapies

	Hydrocortisone group (n_1=76)	**Placebo Group (n_2=73)**
Patients needing prone-position	36	39
Number of sessions, *median [1st quartile; 3rd quartile]*	2.0 [1.0 ; 3.0]	2.0 [2.0 ; 4.0]
Patients needing extra-corporeal membrane oxygenation	2	2
Number of days	8.0 [7.0 ; 9.0]	10.0 [2.0 ; 18.0]
Patients needing nitric oxide inhalation	5	11
Number of days	3.0 [1.0 ; 5.0]	2.0 [1.0 ; 8.0]

f) Nosocomial infection

Fifty eight patients had at least one nosocomial infection during ICU stay (28 in the Hydrocortisone group *vs* 30 in the Placebo group), 18 died without nosocomial infection (8 in the Hydrocortisone group *vs* 10 in the Placebo group), 67 left ICU without nosocomial infection (37 in the Hydrocortisone group *vs* 30 in the Placebo group) and 6 are censored (1 for withdrawal consent and 2 are in still in ICU without nosocomial infection in the Hydrocortisone group *vs* 3 still in ICU in the Placebo group).

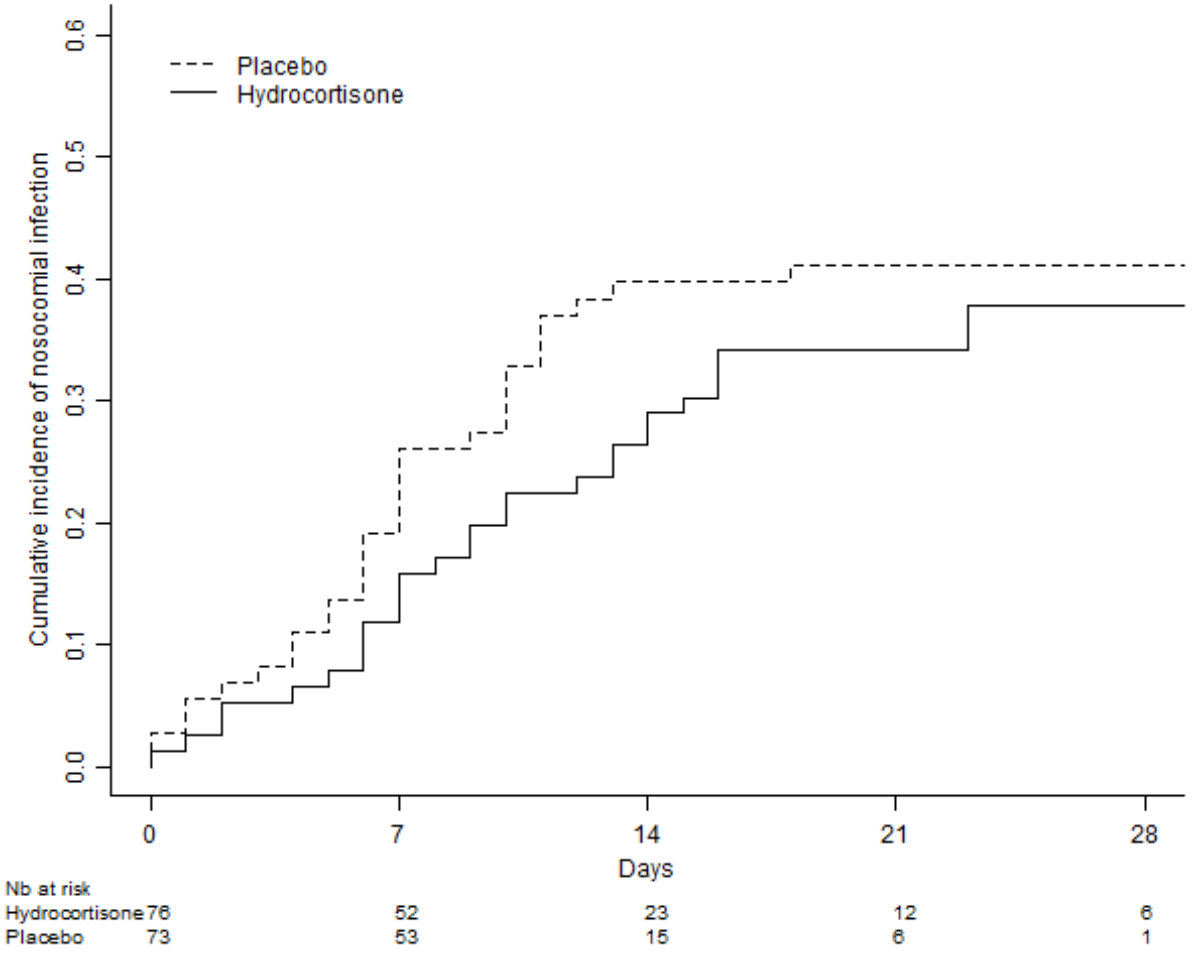


Fig.5 Cumulative incidence of nosocomial infection

The cumulative incidence of nosocomial infection at day 28 is 37.7% in the hydrocortisone group *vs* 41.1% in the placebo group (HR=0.81 [0.49 ; 1.35],p=0.42).