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High-Dose Dexamethasone and Oxygen Support Strategies in Intensive Care Unit Patients With Severe COVID-19 Acute Hypoxemic Respiratory Failure
The COVIDICUS Randomized Clinical Trial

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IMPORTANCE The benefit of high-dose dexamethasone and oxygenation strategies vs standard of care for patients with severe acute hypoxemic respiratory failure (AHRF) caused by COVID-19 pneumonia is debated.

OBJECTIVES To assess the benefit of high-dose dexamethasone compared with standard of care dexamethasone, and to assess the benefit of high-flow nasal oxygen ($HFNO_2$) or continuous positive airway pressure (CPAP) compared with oxygen support standard of care (O_2SC).

DESIGN, SETTING, AND PARTICIPANTS This multicenter, placebo-controlled randomized clinical trial was conducted in 19 intensive care units (ICUs) in France from April 2020 to January 2021. Eligible patients were consecutive ICU-admitted adults with COVID-19 AHRF. Randomization used a 2 × 3 factorial design for dexamethasone and oxygenation strategies; patients not eligible for at least 1 oxygenation strategy and/or already receiving invasive mechanical ventilation (IMV) were only randomized for dexamethasone. All patients were followed-up for 60 days. Data were analyzed from May 26 to July 31, 2021.

INTERVENTIONS Patients received standard dexamethasone (dexamethasone-phosphate 6 mg/d for 10 days [or placebo prior to RECOVERY trial results communication]) or high-dose dexamethasone (dexamethasone-phosphate 20 mg/d on days 1-5 then 10 mg/d on days 6-10). Those not requiring IMV were additionally randomized to O_2SC, CPAP, or $HFNO_2$.

MAIN OUTCOMES AND MEASURES The main outcomes were time to all-cause mortality, assessed at day 60, for the dexamethasone interventions, and time to IMV requirement, assessed at day 28, for the oxygenation interventions. Differences between intervention groups were calculated using proportional Cox models and expressed as hazard ratios (HRs).

RESULTS Among 841 screened patients, 546 patients (median [IQR] age, 67.4 [59.3-73.1] years; 414 [75.8%] men) were randomized between standard dexamethasone (276 patients, including 37 patients who received placebo) or high-dose dexamethasone (270 patients). Of these, 333 patients were randomized among O_2SC (109 patients, including 56 receiving standard dexamethasone), CPAP (109 patients, including 57 receiving standard dexamethasone), and $HFNO_2$ (115 patients, including 56 receiving standard dexamethasone). There was no difference in 60-day mortality between standard and high-dose dexamethasone groups (HR, 0.96 [95% CI, 0.69-1.33]; P = .79). There was no significant difference for the cumulative incidence of IMV criteria at day 28 among O_2 support groups (O_2SC vs CPAP: HR, 1.08 [95% CI, 0.71-1.63]; O_2SC vs $HFNO_2$: HR, 1.04 [95% CI, 0.69-1.55]) or 60-day mortality (O_2SC vs CPAP: HR, 0.97 [95% CI, 0.58-1.61; O_2SC vs $HFNO_2$: HR, 0.89 [95% CI, 0.53-1.47]). Interactions between interventions were not significant.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial among ICU patients with COVID-19–related AHRF, high-dose dexamethasone did not significantly improve 60-day survival. The oxygenation strategies in patients who were not initially receiving IMV did not significantly modify 28-day risk of IMV requirement.

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Supplemental content

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While acute hypoxemic respiratory failure (AHRF) is the main manifestation of severe COVID-19, the most appropriate noninvasive respiratory support (NIRS) and the appropriate timing of invasive mechanical ventilation (IMV) remain to be defined.[1-4] The advantages of high-flow nasal oxygen therapy ($HFNO_2$)[5] and continuous positive airway pressure (CPAP)[6] in the management of COVID-19–related AHRF, with additional specificities related to the pandemic context, are still debated.[7,8]

When the RECOVERY trial showed that dexamethasone 6 mg/d for 10 days reduced 28-day mortality in patients with the most severe COVID-19,[9] low-dose corticosteroids became a standard of care. A meta-analysis of randomized clinical trials (RCTs) in patients with severe COVID-19 showed that corticosteroids treatment was associated with lower all-cause mortality vs usual care or placebo.[10] An RCT by Villar et al described the benefit of dexamethasone 20 mg/d in acute respiratory distress syndrome,[11] but a study among patients with severe COVID-19 by Munch et al[12] found no difference between dexamethasone 12 mg/d and 6 mg/d for 28-day mortality (−5.2%; P = .10) or days alive without life support at day 28. Therefore, use of high-dose dexamethasone for COVID-19–related AHRF was deemed worthy of further investigation. We report the results of the COVIDICUS trial that tested the benefit of high-dose dexamethasone, compared with standard of care, and of NIRS strategies based on CPAP or $HFNO_2$ in intensive care unit (ICU) patients with COVID-19 AHRF.

Key Points

Question What are the effects of high-dose vs low-dose dexamethasone on 60-day time to all-cause mortality, and oxygenation strategies vs standard oxygen support on 28-day time to fulfilling invasive mechanical ventilation (IMV) criteria in patients with COVID-19 and severe acute hypoxemic respiratory failure (AHRF)?

Findings In this randomized clinical trial among 546 patients with COVID-19 and severe AHRF, no difference was observed in 60-day mortality according to dexamethasone dose or in 28-day cumulative need for IMV according to oxygenation strategy.

Meaning These findings suggest that in patients with COVID-19 and AHRF, high-dose dexamethasone or different oxygenation strategies did not significantly modify 60-day mortality or 28-day requirement for IMV criteria.

Methods

The trial protocol for this RCT was approved by the institutional review board of the Comité de Protection des Personnes Ile-de-France-XI and the French Health Authorities, in initial and amended versions, as provided in Supplement 1 and the eMethods in Supplement 2. This study was conducted in accordance with Helsinki Declaration.[13] Consents were obtained in adherence with the French law for emergency inclusion, with signed informed consent obtained from conscious patients and an emergency consent procedure with the patient's legal guardian or relatives implemented for those unable to consent. An independent data safety monitoring board (DSMB) reviewed the trial data. This study is reported following the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Trial Design and Goal

This multicenter RCT tested 2 interventions, high-dose dexamethasone vs standard of care dexamethasone, and CPAP or $HFNO_2$ vs standard of care O_2 (O_2SC) support. For patients not receiving IMV eligible to any oxygenation strategies, both interventions were assessed using a 2 × 3 factorial design (**Figure 1**). Patients receiving IMV at randomization or for whom any 1 oxygenation strategy was contraindicated were randomized with a 1:1 ratio for the dexamethasone interventions only, resulting in 2 other treatment groups: standard of care dexamethasone and high-dose dexamethasone.

Changes in Standard of Care for Dexamethasone

The initial version of the trial investigated the efficacy of high-dose corticosteroid therapy compared with placebo. After the publication of results from the RECOVERY trial,[9] the French Health Authorities recommended modifying the standard of care for administering low-dose dexamethasone (6 mg/d) to patients with COVID-19 who were hypoxemic (eMethods in Supplement 2).[14] The amended protocol was approved on September 17, 2020 (eFigure 1 in Supplement 2).

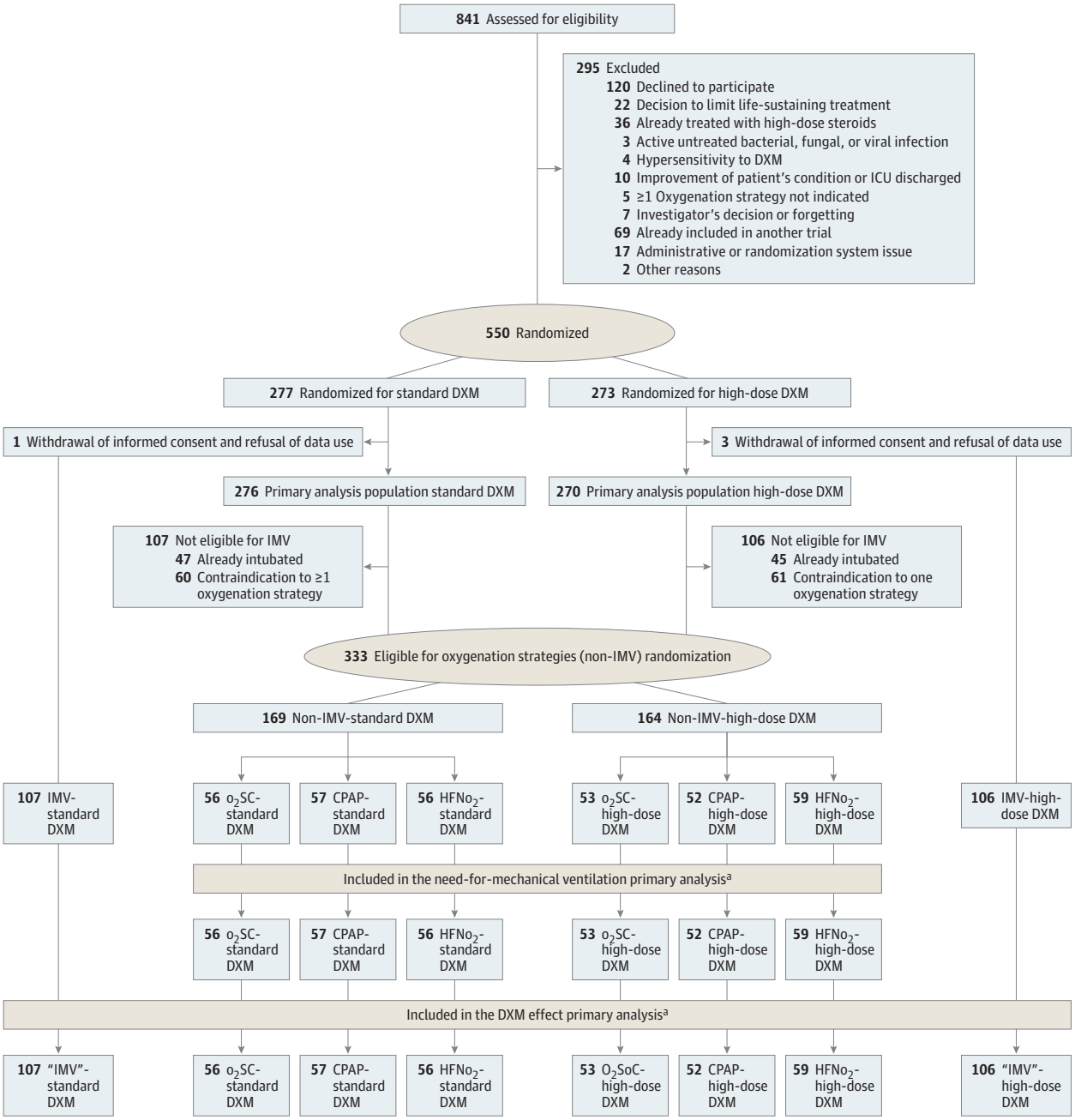
Patients

Study participation was proposed to all consecutive patients with COVID-19 admitted to participating ICUs. Eligible patients were adults aged at least 18 years admitted to an ICU within the last 48 hours for confirmed or highly suspected COVID-19, with AHRF (defined as arterial partial pressure of oxygen, [PaO_2] <70 mm Hg, transcutaneous oxygen saturation as measured by pulse oximetry [SpO_2] <90% on room air, tachypnea with >30 breaths/min, labored breathing, respiratory distress, or need for O_2 flow ≥6 L/min), and who could receive any available treatment targeting COVID-19. Those with ongoing IMV at inclusion or with anatomical factors precluding the use of nasal cannula, hypercapnia indicating noninvasive ventilation ($PaCO_2$ ≥50 mm Hg), or intolerance at admission to any of the oxygenation strategies, ie, the IMV population, were only eligible to the dexamethasone randomization. The main exclusion criteria were decision to limit life-sustaining treatment, corticosteroid therapy of 0.5 mg/kg/d or more of prednisone equivalent for 3 weeks or longer; active untreated bacterial, fungal, or parasitic infection; and hypersensitivity to dexamethasone.

Randomization

In patients eligible for the 3 O_2 support strategies (the non-IMV population), randomization used a factorial design with a 1:1:1 ratio across oxygenation groups, and a 1:1 ratio across the dexamethasone intervention. The IMV population was only randomized 1:1 for the dexamethasone interventions. Randomization was centralized and stratified by center (eMethods in Supplement 2).

Figure 1. Patient Recruitment Flowchart



[a] Consent withdrawal occurred before the date of day 60 of follow-up in no patients receiving standard of care oxygen (o_2SC), 8 patients receiving continuous positive airway pressure (CPAP), and 1 patient receiving high-flow nasal oxygen ($HFNo_2$) in the non-invasive mechanical ventilation (IMV) group. In patients with IMV or contraindication to any 1 o_2 support strategy, 3 patients withdrew consent. These patients were censored at the date of consent withdrawal.

DXM indicates dexamethasone; ICU, intensive care unit.

Trial Interventions and Blinding Procedures

In France, dexamethasone is administered as dexamethasone-phosphate, thus patients administered with dexamethasone-phosphate 20 mg/d actually received dexamethasone 16.6 mg/d. Initially, the standard dexamethasone group received a nondexamethasone placebo. From the amendment implementation, the standard of care moved to an intravenous administration of dexamethasone-phosphate 6 mg/d on days 1 to 10 to all patients. In addition, all patients received an additional infusion of placebo if they were allocated to standard dexamethasone or of dexamethasone-phosphate 14 mg/d on days 1 to 5, then 4 mg/d on days 6 to 10 if allocated to high-dose dexamethasone. A 7-day treatment with hydrocortisone or fludrocortisone was allowed for septic shock that fulfilled predefined criteria.

Regarding oxygenation strategies (eTable 1 in Supplement 2), patients allocated to CPAP received periods of CPAP in addition to the standard O_2 treatment (eMethods in Supplement 2). For $HFNO_2$, gas flow was delivered at 30 L/min and increased up to 60 L/min, based on clinical response. In all groups, O_2 flow or inspired O_2 fraction (FiO_2) were adjusted for a targeted SpO_2 of at least 92%. Oxygenation was pursued until death, fulfillment of endotracheal intubation criteria, or predefined cessation criteria (eMethods in Supplement 2).

Study Assessments

Participants were assessed daily in the ICU and at predefined time points after ICU discharge up to day 60 (SD, 14) days. Safety data were collected until day 28. At days 1 and 7, nasopharyngeal swabs were obtained for SARS-CoV-2 detection; if possible, subglottic samples (bronchoalveolar lavage, plugged telescopic catheter, or tracheal aspiration) were also collected.

For high-dose dexamethasone evaluation, the primary end point was time-to-death from all causes up to day 60. For oxygenation strategies evaluation, the primary end point was time to IMV criteria fulfillment within the first 28 days after randomization, based on the fulfillment of previously described IMV criteria[5]: worsening respiratory failure, hemodynamic instability, and neurological status deterioration (eMethods in Supplement 2).

Prespecified secondary end points were health care–associated infection at day 28, number of IMV-free days alive at day 28, and ICU and hospital lengths of stay (LOS). For dexamethasone interventions, additional end points were the change in Sequential Organ Failure Assessment (SOFA) score and change in viral load, and the number of days alive without kidney replacement therapy at day 28. For O_2 supply interventions, additional end points included overall survival at day 60, severe hypoxemia (SpO_2 <80%) within the 2 minutes following induction of tracheal intubation, and cardiac arrest within the hour following tracheal intubation. The 28-day cumulative incidence of actual IMV was added at the request of the DSMB. Viral load was determined by real-time semiquantitative reverse transcriptase–polymerase chain reaction (RT-PCR) (eMethods in Supplement 2).

Statistical Analysis

Regarding the dexamethasone interventions, the 60-day cumulative incidence of all-cause death was assumed at 60%.[15-17] Thus, a sample size of 550 participants (275 per group) would achieve 80.1% power at an $\alpha = .05$ significance level to detect a hazard ratio (HR) of 0.75 for a survivor proportion of 0.40 in the control group (2-sided log-rank test). In the non-IMV population, 2 comparisons of each intervention (CPAP or $HFNO_2$) against the O_2SC group (with an assumed incidence at 80% for IMV criteria fulfillment at day 28) were designed, with an expected similar benefit of each experimental arm of HR, 0.65. A 2-sided log-rank test with an overall sample size of 220 participants (110 per group) would achieve 80.0% power to detect such an effect, using an adjusted type I error rate of 0.025, given the multiple comparisons. Therefore, 330 patients overall were required to evaluate the O_2 support strategies (ie, the non-IMV population).

All analyses were based on the intention-to-treat principle. Summary statistics used frequencies and percentages for categorical variables or medians and IQRs for continuous or discrete variables. Three bayesian interim analyses were presented to the DSMB during the study (eTable 2 in Supplement 2).

The primary end points were analyzed using survival methods assuming noninformative right-censoring of data at days 28 or 60. Survival curves were estimated in each randomization group using the Kaplan-Meier method then compared using the log-rank test. Cox models stratified on the patient populations (IMV and non-IMV) quantified the effect size by HR with 95% CIs. Proportional hazards assumptions were assessed using Grambsch and Therneau statistics.[18] Subsets by treatment interactions were tested by Gail and Simon statistics. Period effect (ie, before vs after the protocol amendment for standard dexamethasone) was tested using fixed covariate in the regression models. Secondary planned analyses of primary outcomes were performed on the as-treated populations, defined as patients analyzed in the group of treatment actually received at randomization. The changes in RT-PCR results and SOFA scores were modeled and compared using linear mixed models. The proportions of health care–associated infections at days 28 and 60 were compared using a Fisher exact test. The number of days alive without IMV or kidney replacement therapy and ICU and hospital LOS were compared using a Wilcoxon rank sum test.

We conducted 3 sensitivity analyses of the primary end point. First, we assessed whether the change in the standard dexamethasone group affected the 60-day mortality or 28-day need for IMV. Second, we explored the impact of the IMV population heterogeneity on the dexamethasone effect, as no patients from that population were actually receiving IMV. Third, we investigated for potential center effect in the assessment of CPAP and $HFNO_2$ effects, due to some imbalance in treatment adherence, using frailty models. Because of the potential for type I error owing to multiple comparisons, findings of analyses of other end points than the primary end point should be interpreted as exploratory.

All analyses were conducted blinded to treatment assignment. Statistical analyses were performed using R software version 4.0.3 (R Project for Statistical Computing). All tests were 2-sided, with $P = .05$ denoting statistical significance. Data were analyzed from May 26 to July 31, 2021.

Results

Patients

From April 10 to September 17, 2020, 73 patients were randomized between placebo (37 patients) and high-dose dexamethasone (36 patients), including 53 patients in the non-IMV population (O_2SC: 15 patients; CPAP: 20 patients; $HFNO_2$: 18 patients). Thereafter, 473 patients were randomly allocated between standard dexamethasone (239 patients) or high-dose dexamethasone (234 patients), including 280 in the non-IMV population (O_2SC: 94 patients; CPAP: 89 patients; $HFNO_2$, 97 patients). Four patients eventually withdrew their participation consent and declined the use of their data and thus were

excluded from the analysis. Therefore, the primary analysis dealt with 546 patients (median [IQR] age, 67.4 [59.3-73.1] years; 414 [75.8%] men) enrolled in 19 ICUs (Figure 1). The DSMB recommended to continue the study to completion. Main baseline characteristics of patients according to dexamethasone groups are in **Table 1** and according to the oxygen support strategy are in **Table 2**.

Treatment and Interventions

Overall, 276 patients were allocated to the standard dexamethasone group and 270 patients were allocated to the high-dose dexamethasone group, including 213 patients from the IMV population solely randomized for dexamethasone interventions, while 333 patients from the non-IMV population were additionally randomized for the oxygenation interventions (Figure 1). Among 546 patients, 541 (99.1%) were administered at least 1 day of study drugs (dexamethasone-phosphate or placebo [standard dexamethasone]: 273 patients [98.9%]; high-dose dexamethasone: 268 patients [99.3%]). Adherence was unbalanced between allocated oxygenation groups: 77 patients in the O_2SC group (70.6%) were adherent (29 patients received $HFNO_2$); 89 patients in the CPAP group (81.7%) were adherent (12 patients received $HFNO_2$); and 110 patients in the $HFNO_2$ group (95.7%) were adherent. Nonadherence in oxygenation supply varied from 0.3% up to 27% across centers.

Primary Outcomes

Median (IQR) follow-up was 60 (27-69) days. A total of 43 patients (7.9%) were discharged from the hospital prior to their 60-day follow-up (IMV population: 13 patients; non-IMV population: 30 patients).

Dexamethasone Interventions

Dexamethasone-phosphate was administered for a median (IQR) of 9 (6-10) days in both groups. Overall, 144 patients died within 60 days after randomization (standard dexamethasone: 74 patients [26.8%]; high-dose dexamethasone: 70 patients [25.9%]; absolute risk difference, −0.8% [95% CI, -8.3 to 6.5]; HR, 0.96 [95% CI, 0.69 to 1.33]; P = .79) (**Figure 2** and **Table 3**). No evidence of any violation of the proportional hazards assumption was found. No significant interaction with the randomization strata was observed in hazard of death (non-IMV: HR, 0.88 [95% CI, 0.58 to 1.29] vs IMV population: HR, 1.08 [95% CI, 0.64 to 1.83]; P for interaction = .55) (eFigure 2 in Supplement 2). The analysis on the as-treated population did not markedly affect the results (HR, 0.95 [95% CI, 0.69 to 1.32]; P = .77).

Oxygen Support Intervention

In the non-IMV population, the 28-day cumulative incidence of IMV criteria fulfillment was 41.4% (95% CI, 32.0% to 50.4%) for O_2SC, 43.0% (95% CI, 33.3% to 52.2%) for CPAP (cause-specific HR, 1.08 [95% CI, 0.71 to 1.63]; P = .71), and 43.8% (95% CI, 34.5% to 52.6%) for $HFNO_2$ (cause-specific HR, 1.04 [95% CI, 0.69 to 1.55]; P = .85), with no significant difference between groups (Figure 2; eTable 3 in Supplement 2). Proportional hazards assumption was checked either for the CPAP effect or for $HFNO_2$, and no significant interaction with the dexamethasone interventions was observed, neither with CPAP, nor $HFNO_2$ (eFigure 3 in Supplement 2). Results in the as-treated population were not significantly modified (CPAP vs O_2SC: HR, 1.39 [95% CI, 0.88-2.19]; P = .15; $HFNO_2$ vs O_2SC: HR, 0.98 [95% CI, 0.64-1.50]; P = .93.

Secondary Outcomes

Secondary outcomes regarding the effects of dexamethasone and of oxygenation strategies are presented in Table 3, eTable 3, eFigure 4, and eFigure 5 in Supplement 2. Overall, none of the interventions elicited any significant differences in secondary end points vs standard of care.

In post hoc analysis, the estimated effect of dexamethasone on 60-day mortality was not mediated by the type of control received by patients (high-dose dexamethasone vs standard dexamethasone/placebo: HR, 0.99 [95% CI, 0.47 to 2.07]; high-dose dexamethasone vs standard dexamethasone/dexamethasone-phosphate 6 mg/d: HR, 0.95 [95% CI, 0.66 to 1.36]; Gail and Simon P = .92). Similarly, the type of population either actually with IMV (HR, 1.18 [95% CI, 0.64 to 2.16]) or without IMV (HR, 0.88 [95% CI, 0.59 to 1.30]) did not significantly modify these findings (Gail and Simon P = .73). There was no heterogeneity across the oxygenation groups (eFigure 6 in Supplement 2). The as-treated population yielded similar results (eTable 4 in Supplement 2).

In the non-IMV population, there was no period × treatment interaction for the time to need for IMV against the O_2SC group for the CPAP or the $HFNO_2$ groups. Similarly, the 28-day cumulative incidence of time to fulfillment of IMV criteria was not significantly affected by any potential center effect (eTable 5 in Supplement 2).

By contrast, there was some heterogeneity across centers either on the 60-day survival (eFigure 7 and eFigure 8 in Supplement 2). However, there was no heterogeneity across centers in the dexamethasone effect on 60-day survival (eFigure 7 in Supplement 2) or in the CPAP and $HFNO_2$ effect on the need for IMV (eFigure 8 in Supplement 2).

Safety Data

The prevalence of adverse events was not significantly different across intervention groups (Table 3; eTable 6 and eTable 7 in Supplement 2). There were no clinically or statistically significant differences between arms, including no significant difference in the rates of infectious and noninfectious complications of dexamethasone-phosphate treatment.

Discussion

The COVIDICUS randomized clinical trial showed neither any benefit of high-dose dexamethasone on 60-day survival compared with standard of care for patients with COVID-19 and severe AHRF, nor any significant benefit of $HFNO_2$ or CPAP compared with standard O_2 therapy regarding the IMV criteria fulfillment within 28 days after ICU admission. Our trial had several strengths, such as its multicenter and placebo-controlled design, a sealed randomization to the

Table 1. Baseline Characteristics of Patients According to the Dexamethasone Arm

Variables	No. (%)		Standardized mean difference
	Standard of care dexamethasone (n = 276)	High-dose dexamethasone (n = 270)	
Age, median (IQR), y	66.3 (58.9-73.8)	68.1 (60.1-72.9)	0.015
Sex			
Women	79 (28.6)	53 (19.6)	0.211
Men	197 (71.4)	217 (80.4)	
BMI[a]			
Median (IQR)	29.4 (26.0-33.7)	28.6 (25.5-32.0)	0.184
25-30	94 (34.1)	98 (36.3)	0.183
>30	114 (41.3)	110 (40.7)	
Comorbidities			
Any	227 (82.2)	214 (79.3)	0.076
Cancer	28 (10.1)	33 (12.2)	0.130
Solid organ transplantation	8 (2.9)	3 (1.1)	0.128
Diabetes	108 (39.1)	94 (34.8)	0.092
Hypertension	160 (58.0)	143 (53.0)	0.101
Dexamethasone administration prior to the inclusion[b]			
Any	33 (11.9)	40 (14.8)	0.084
Duration, median (IQR), d	1 (1-2)	2 (1-3)	0.511
Oxygenation ventilation status			
IMV	48 (17.4)	50 (18.5)	0.170
o_2 standard of care	64 (23.2)	61 (22.6)	
CPAP	59 (21.4)	55 (20.4)	
$HFNo_2$	101 (36.6)	98 (36.3)	
Noninvasive ventilation	4 (1.4)	6 (2.2)	
COVID-19-specific treatment			
Any	182 (65.9)	168 (62.2)	0.073
Remdesivir	46 (16.7)	47 (17.4)	0.020
Lopinavir/ritonavir	6 (2.2)	6 (2.2)	0.003
Hydroxychloroquine	4 (1.4)	2 (0.7)	0.068
Tocilizumab	1 (0.4)	3 (1.1)	0.088
Hydrocortisone HS	1 (0.4)	3 (1.1)	0.088
Prednisone/prednisolone[c]	2 (0.7)	4 (1.5)	0.072
Clinical status at baseline			
Time since symptoms onset, median (IQR), d[d]	9 (7-11)	9 (6-11)	0.101
Time since ICU admission, median (IQR), d	1 (0-1)	0 (0-1)	0.148
Vasopressor use	22 (8.0)	29 (10.7)	0.099
SOFA score, median (IQR)	3 (2-4)	3 (2-4)	0.060
Positive results on first PCR test[e]	253 (91.7)	237 (87.8)	0.031
Biochemistry data, median (IQR)[f]			
White blood cells, /µL	8000 (5700-10 700)	8200 (6000-11 300)	0.086
Lymphocytes, /µL	600 (400-900)	700 (400-1000)	0.118
Platelets, $\times 10^3$/µL	236 000 (175 000-307 000)	234 000 (175 000-302 000)	0.032
Creatinine, mg/dL	0.84 (0.67-1.09)	0.86 (0.70-1.15)	0.137
C-reactive protein, mg/dL	12.6 (8.5-18.6)	13.6 (7.1-20.5)	0.035
D-dimers, µg/mL	1030 (573-1948)	804 (496-1516)	0.278
Troponin, ng/mL	20 (10-110)	20 (10-370)	0.006
Ferritin, ng/mL	915 (518-1801)	1240 (642-1946)	0.031

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); $HFNo_2$, high-flow nasal oxygen; HS, hydrocortisone hemisuccinate; ICU, intensive care unit; IMV, invasive mechanical ventilation; PCR, polymerase chain reaction; OFA, sequential organ failure assessment.

SI conversion factors: To convert white blood cells and lymphocytes to $\times 10^9$/L, multiply by 0.001; platelets to $\times 10^9$/L, multiply by 1; creatinine to micromoles per liter, multiply by 88.4; C-reactive protein to milligrams per deciliter, multiply by 10; D-dimer to nanomoles per L, multiply by 5.476; troponin to micrograms per liter, multiply by 1; and ferritin to nanograms per liter, multiply by 1.

[a] Data missing for 19 participants.

[b] Among 73 patients. Of note, 3 patients (2 in the standard dexamethasone group, and 1 in the high-dose dexamethasone group) received corticosteroids for at least 10 days (for 33, 14 and 12 days, respectively). The median (IQR) dose of dexamethasone-phosphate received before inclusion was 6 (6-6) mg/d, with only 2 patients who received 20 mg (1 in standard dexamethasone group, for 4 days, and 1 in the high-dose dexamethasone group, for 6 days).

[c] Long-term treatment with prednisone/prednisolone <0.5 mg/kg/d.

[d] Missing data for 10 patients.

[e] Patients with negative PCR results at randomization had positive PCR results just before.

[f] Missing data for 20 patients for white blood cell count, 152 patients for lymphocytes, 18 patients for platelets, 13 patients for creatinine, 152 patients for C-reactive protein, 200 patients for D-dimers, 224 patients for troponin, and 304 patients for ferritin.

Table 2. Baseline Characteristics of Patients Without Invasive Mechanical Ventilation at Randomization and Eligible for Any Oxygen Support Strategy, According to the Oxygen Support Provided

Characteristic	Patients, No. (%)			SMD	
	Standard care o_2 (n = 109)	CPAP (n = 109)	$HFNo_2$ (n = 115)	CPAP vs standard	$HFNo_2$ vs standard
Age, median (IQR), y	67.4 (60.8-72.3)	69.1 (59.4-76.3)	66.8 (58.9-71.9)	0.109	0.123
Sex					
Women	25 (22.9)	32 (29.4)	24 (20.9)	0.147	0.050
Men	84 (77.1)	77 (70.6)	91 (79.1)		
BMI[a]					
Median (IQR)	29 (26-31.8)	28.7 (24.5-32.9)	28.7 (26.0-32.9)	0.027	0.177
25-30	41 (38.7)	33 (31.4)	44 (39.3)	0.503	0.258
>30	44 (41.4)	40 (38.0)	46 (41.0)	0.221	0.082
Comorbidities					
Any	95 (87.2)	84 (77.1)	88 (76.5)	0.266	0.278
Cancer	15 (13.8)	8 (7.3)	17 (14.8)	0.102	0.042
Solid organ transplant	4 (3.7)	2 (1.8)	4 (3.5)	0.112	0.010
Diabetes	39 (35.8)	38 (34.9)	37 (32.2)	0.019	0.076
Hypertension	64 (58.7)	63 (57.8)	58 (50.4)	0.019	0.166
Oxygenation status, median (IQR)					
Respiratory rate, breaths/min	24 (20-29)	26 (21-30)	24 (20-28)	0.216	0.070
Gas flow rate, L/min[b]	15 (15-15)	20 (15-30)	50 (40-60)	0.075	1.104
Fio_2, %	NA	66 (48-91)	70 (50-97)	0.206	0.056
Spo_2, %	94 (92-96)	95 (93-97)	94 (92-97)	0.322	0.060
COVID-19–specific treatment					
Any	74 (67.9)	55 (50.5)	72 (62.6)	0.360	0.111
Remdesivir	18 (16.5)	31 (28.4)	15 (13.0)	0.289	0.098
Lopinavir/ritonavir	1 (1.0)	2 (2.0)	0	0.079	0.136
Hydroxychloroquine	0	0	0	NA	NA
Tocilizumab	0	0	0	NA	NA
Hydrocortisone HS	0	0	0	NA	NA
Prednisone/prednisolone[c]	1 (1.0)	0	2 (1.9)	0.079	0.136
Clinical status					
Time since symptoms onset, median (IQR), d	8 (7-11)	8 (6-11)	9 (7-11)	0.159	0.100
Time since ICU admission, median (IQR), d	0 (0-1)	0 (0-1)	0 (0-1)	0.081	0.083
Vasopressor use	0	3	0	0.238	NA
SOFA, median (IQR)	2 (2-4)	2 (2-3)	2 (2-4)	0.142	0.013
Positive result on first PCR test[d]	98 (96.1)	100 (96.2)	103 (94.5)	0.004	0.075
Biochemistry data, median (IQR)[e]					
White blood cells, /µL	7300 (5700-10 500)	8200 (5700-11 200)	7700 (5800-10 000)	0.106	0.124
Lymphocytes, /µL	800 (600-1100)	700 (400-900)	600 (400-900)	0.168	0.171
Platelets, $\times 10^3$/µL	240 000 (185 000-292 000)	246 000 (178 000-332 000)	219 000 (169 000-265 000)	0.153	0.253
Creatinine, mg/dL)	0.85 (0.70-115)	0.80 (0.64-1.05)	0.90 (0.75-1.10)	0.001	0.034
C-reactive protein, mg/dL	12.9 (7.0-18.9)	13.4 (8.1-19.4)	13.8 (8.2-19.0)	0.066	0.049
D-Dimers, µg/mL	798 (483-1252)	1022 (547-2576)	900 (490-1596)	0.308	0.043
Troponin, ng/mL	10 (10-60)	10 (10-70)	10 (10-90)	0.037	0.137
Ferritin, ng/mL	1280 (739-2618)	891 (494-1846)	1234 (755-1801)	0.218	0.117
Dexamethasone group				0.018	0.054
Standard of care	56 (51.4)	57 (52.3)	56 (48.7)	NA	NA
High-dose	53 (48.6)	52 (47.7)	59 (51.3)	NA	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CPAP, continuous positive airway pressure; Fio_2, fraction of inspired oxygen; HS, hemisuccinate; $HFNo_2$, high-flow nasal oxygen; ICU, intensive care unit; NA, not applicable; PCR, polymerase chain reaction; SMD, standardized mean difference; SOFA, sequential organ failure assessment; Spo_2, oxygen saturation as measured by pulse oximetry.

SI conversion factors: To convert white blood cells and lymphocytes to $\times 10^9$/L, multiply by 0.001; platelets to $\times 10^9$/L, multiply by 1; creatinine to micromoles per liter, multiply by 88.4; C-reactive protein to milligrams per deciliter, multiply by 10; D-dimer to nanomoles per L, multiply by 5.476; troponin to micrograms per liter, multiply by 1; and ferritin to nanograms per liter, multiply by 1.

[a] Missing data for 10 patients.

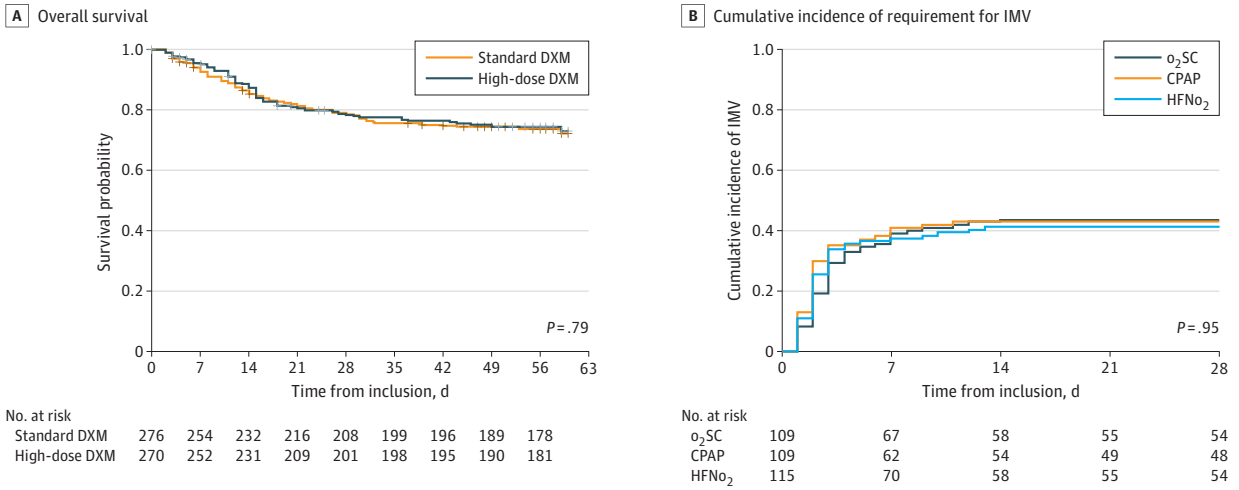
[b] Number of liters of o_2 per minute for the standard o_2 group.

[c] Long-term treatment with prednisone or prednisolone of less than 0.5 mg/kg/d.

[d] Patients with negative PCR at randomization had a positive PCR just before.

[e] Missing data for 14 patients for white blood cell count, 108 patients for lymphocytes, 18 patients for platelets, 13 patients for creatinine, 140 patients for C-reactive protein, 104 patients for D-dimers, 109 patients for troponin, and 147 patients for ferritin.

Figure 2. Primary End Points of Both Interventions



A. Standard dexamethasone (DXM) included 37 patients who received placebo DXM then dexamethasone-phosphate 6 mg/d for days 1 to 10; high-dose DXM was dexamethasone-phosphate 20 mg/d for days 1 to 5, then 10 mg/d for days 6 to 10. CPAP indicates continuous positive airway pressure; $HFNo_2$, high-flow nasal oxygen; and o_2SC, oxygen standard of care.

Table 3. Outcomes of Patients According to the Dexamethasone Group in the Overall Study Sample

Outcome	Standard of care dexamethasone (n = 276)	High-dose dexamethasone (n = 270)	Estimate (95% CI)	
			Difference	Hazard ratio[a]
Overall survival at 60 d, Kaplan-Meier estimate, % (95% CI)	72.2 (66.2 to 82.6)	73.0 (67.8 to 76.5)	0.8 (-6.8 to 8.4)	0.96 (0.69 to 1.33)
Secondary end points				
Viral load evolution, mean slope (SE)	0.31 (0.08)	0.46 (0.06)	0.15 (-0.05 to 0.35)	NC
HAI at 28 d, No. (%)	75 (27.2)	81 (30.0)	2.8 (-4.8 to 10.4)	1.10 (0.85 to 1.44)
Alive free of IMV at 28 d, median (IQR), d	28 (6 to 28)	28 (9 to 28)	1.0 (-2.9 to 0.9)	NC
Alive free of KRT at day 28, median (IQR), d	28 (14 to 28)	28 (16 to 28)	0.8 (-2.4 to 0.8)	NC
LOS, median (IQR), d				
ICU	9 (5 to 15)	8 (5 to 15)	0.1 (-3.0 to 2.7)	NC
Hospital	15 (10 to 24)	16 (11 to 27)	1.3 (-4.4 to 1.8)	NC
SOFA evolution: mean slope (SE)	0.10 (0.01)	0.09 (0.01)	-0.01 (-0.05 to 0.03)	NC
≥1 Adverse event, No. (%)	208 (75.4)	202 (74.8)	-0.6 (-7.8 to 6.7)	0.99 (0.90 to 1.09)

Abbreviations: HAI, health care–associated infection; ICU, intensive care unit; IMV, invasive mechanical ventilation; KRT, kidney replacement therapy; LOS, length of stay; NC, not calculated; VAP, ventilator-associated pneumonia.

[a] Hazard ratios were stratified on the IMV strata.

assigned strategy, a well-defined study protocol that included prespecified criteria for intubation, a prolonged follow-up, and a very low rate of protocol violations for dexamethasone administration.

Randomized clinical trials in patients with COVID-19 have shown that dexamethasone 6 mg/d improves 28-day survival[9,19] and dexamethasone 6 mg/d for 10 days became a standard of care for patients with COVID-19 and AHRF. Therefore, we applied it as standard care in this study. The benefits of high-dose dexamethasone in patients with COVID-19 and AHRF remain uncertain. One open-labeled randomized study compared dexamethasone 16 mg/d on days 1 to 5 then 8 mg/d on days 6 to 10 with 6 mg/d for days 1 to 10.[20] The trial was prematurely halted after 98 patients were enrolled without any effects observed on ventilator-free days at day 28 or mortality; however, the successful discontinuation from mechanical ventilation was more frequent in the high-dose group. Another open-label RCT with 200 patients with o_2 support tested the same dexamethasone intervention as our study.[21] High-dose dexamethasone did not impact 28-day mortality or time to recovery. A recent blinded RCT in 1000 patients who were severely hypoxemic with COVID-19 showed no statistically significant difference in days alive without life support at day 28 with dexamethasone 12 mg/d (dexamethasone-

phosphate 14.4 mg/d) vs dexamethasone 6 mg/d (dexamethasone-phosphate 7.2 mg/d), and no significant differences in 28-day and 90-day mortality.[12] In this study, high-dose dexamethasone also did not improve 60-day survival, regardless of a patient's IMV status. The rate of infectious and noninfectious complications was comparable between dexamethasone strategies. The population enrolled in both trials was similar, although the 28-day mortality was 9% higher in the study by Munch et al.[12] We used dexamethasone-phosphate 20 mg/d (equivalent to dexamethasone 16.6 mg/d) compared with 12 mg/d of dexamethasone in the study by Munch et al.[12] The standard of care was similar, except that all our patients were in ICUs and fewer patients received remdesivir. Although the study by Munch et al[12] was blinded, its robustness is weakened by drawbacks, such as the inclusion of 55 patients with decisions to limit life-sustaining treatment at randomization or the lack of administration of the assigned intervention to 75 patients (7.6%).

Before the COVID-19 pandemic, NIRS were associated with decreased rates of endotracheal intubation and death in patients with AHRF, as shown in a recent large meta-analysis.[3] However, the observed association was no longer significant after excluding patients who were hypercapnic and patients with mean Pao_2:Fio_2 ratio of less than 200 mm Hg. Nonrandomized studies have suggested that $HFNo_2$[1-12,14-25] and CPAP[26,27] may improve oxygenation and decrease the likelihood of requiring IMV.[28,29] Only few randomized studies have investigated the benefit of NIRS strategies in patients with COVID-19.[30-32] In a small-size RCT, helmet noninvasive ventilation and $HFNo_2$ yielded similar results in terms of number of days free of respiratory support at day 28, although the rate of endotracheal intubation was significantly decreased with helmet noninvasive ventilation.[30] In a trial that compared 22 patients treated with $HFNo_2$ vs standard o_2, $HNFo_2$ improved the Pao_2:Fio2 ratio and reduced ICU LOS.[32]

The RECOVERY-RS[33] RCT included 1272 inpatients among 3 o_2 support strategies: 29.9% received CPAP, 32.8% received $HFNo_2$, and 37.3% received standard o_2 therapy. Compared with standard o_2 therapy, CPAP, but not $HFNo_2$, reduced the composite outcome of intubation or death at day 30, without significant impact on mortality. Safety events occurred more frequently in the CPAP group (130 events among 380 patients [34.2%]) than in the $HFNo_2$ group (86 events among 417 patients [20.6%]) or the standard o_2 therapy group (66 events among 475 patients [13.9%]; $P < .001$). Of note, findings of the RECOVER-RS study[33] cannot be extrapolated to the treatment of patients who have been systematically admitted to the ICU. Ultimately, the investigators in the RECOVERY-RS study[33] could choose to enroll in 1 of the 2 tested strategies, and the decision to intubate was left to physician's discretion instead of adhering to predefined criteria.

Limitations

Our study has some limitations, such as the lack of adherence to the allocated o_2 strategy for 57 patients (17%). However, the as-treated analysis provided similar results. We also used as primary end point the fulfillment of criteria for starting IMV, as previously defined,[5] but 58 patients that reached the primary end point and fulfilled criteria but they were not intubated. However, neither time-to-IMV criteria fulfillment nor time-to-actual intubation differed among groups.

In addition, CPAP treatment with a face mask is more burdensome than $HFNo_2$, and centers were less experienced with CPAP than with $HFNo_2$; this was illustrated by range of nonadherence in oxygenation supply, from 0.3% up to 27%, across centers. Therefore, signs of failure might have been identified earlier among patients with CPAP vs $HFNo_2$. Nevertheless, results were not modified by analyses assessing center effect or in the as-treated population. The use of awake prone positioning was neither standardized nor recorded; it might have been more frequently used in patients in the o_2SC or $HFNo_2$ groups. Additionally, our study was powered to detect large benefits of the experimental arms across the controls and, notably, not to detect the reported effect observed in the RECOVERY-RS trial (ie, an 8% difference in the intubation rate at day 28 with CPAP). Such an analysis would have required enrollment of 585 patients per group for 80% power; nevertheless, no retrospective observed power calculations were performed, given their reported misleading results.[34]

Overall, we lack strong evidence on the efficiency of 1 NIRS strategy over the others in ICU patients with severe AHRF. The use of $HFNo_2$ or CPAP is only suggested, with low-grade recommendations. Our study supports the use of standard o_2 treatment over CPAP or $HFNo_2$ for hospitals managing the COVID-19 crisis. Our findings also support refraining from broadly deploying CPAP or $HFNo_2$ oxygen strategies outside ICUs. To our knowledge, this was the first RCT that investigated fully randomly assigned oxygenation strategies in patients admitted and carefully surveyed in ICUs. The impact of NIRS implementation upstream of ICU admission during COVID-19–related AHRF, compared with later use that starts in the ICU, requires further research.

Other more general limitations should be acknowledged. First, all participating centers were in France, which raises questions about the general applicability of these findings. Second, this study spanned from April 2020 to January 2021, ie, a time period during which the treatment of patients with severe COVID-19 changed greatly, especially for concomitant treatments and supportive care.[35] This was highlighted by the need for the change in the control group, owing to reported benefit of low doses of dexamethasone; of note, no evidence of any interaction between the type of control was detected. Additionally, an interaction between both types of interventions cannot be excluded, given the limited power of interaction tests.

Conclusions

In this RCT among ICU patients with COVID-19–related severe AHRF, no significant difference in 60-day survival was observed in patients treated with high-dose dexamethasone compared with standard of care. Standard o_2, CPAP via face mask, or $HFNo_2$ as primary oxygenation mode had no significant impact on the 28-day risk of IMV requirement.

ARTICLE INFORMATION

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Supervision: Bouadma, Burdet, Cohen, Visseaux, Beldjoudi, Timsit.

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