

Delayed adoption of corticosteroids as standard of care for hypoxic patients with COVID-19 in the UK

Fiina Närhi, Thomas Drake, Ewen Harrison, Jonathan Nguyen-Van-Tam, Peter Openshaw, Kenneth Baillie, Annemarie Docherty, Calum Semple, on behalf of the ISARIC4C / CO-CIN investigators

Introduction

Reducing the morbidity and mortality of coronavirus disease 2019 (COVID-19) requires robust evidence and prompt implementation of effective therapies. At a press conference on 16th June 2020, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial reported a reduction in all-cause mortality in adult patients requiring supplemental oxygen who received moderate doses of dexamethasone, compared to standard care. The study was rapidly published ¹.

On the 2nd September 2020, the Rapid Evidence Appraisal for COVID-19 (REACT) meta-analysis corroborated these results, highlighting corticosteroids as the only current mortality-reducing therapy in COVID-19². These findings have been rapidly translated into clinical guidance recommending corticosteroids – dexamethasone, hydrocortisone, prednisolone or methylprednisolone – for patients with severe or critical COVID-19^{3,4}. The benefit of corticosteroids appears to be a robust class effect. We now report an evaluation of the use of corticosteroids for COVID-19 in the UK since the announcement of the UK trial findings using data from the International Severe Acute Respiratory and emerging infections Consortium (ISARIC) World Health Organisation (WHO) Clinical Characterisation Protocol UK (CCP-UK)⁵.

Methods

ISARIC WHO CCP-UK is an ongoing prospective cohort study recruiting UK hospitalised patients in 260 healthcare facilities with proven or high likelihood of infection with SARS-CoV-2⁶.

For this analysis we included adult patients (age \geq 18 years) enrolled between 16th June and 30th September 2020. Patients were stratified by steroids administered and characterised by demographics, comorbidities, severity of illness and level of care during hospital admission. Data collection is

described elsewhere⁵. An algorithm was used to interpret the free-text medication entries which were then checked manually. All analyses were performed in R version 3.6.3 (R Foundation for Statistical Computing, Vienna, AUT).

Results

Between 16th June and 30th September, 7273 adult patients were enrolled in the study (Table 1). 2440 (33.5%) patients received any of: dexamethasone (2104/7273, 28.9%), hydrocortisone (151/7273, 2.1%), methylprednisolone (36/7273, 0.5%) and prednisolone (407/7273, 5.6%). 3503 patients (47.9%) received no steroid (missing data 1330 (18.3%)).

Patients receiving steroids were younger (median age 67.7 years, IQR 25.7) than those not receiving steroids (72.8 years, IQR 30.4). Notably, 42% of patients receiving prednisolone (n=170/407) and hydrocortisone (n=63/151) had chronic pulmonary disease. Pre-admission immunosuppressants, including corticosteroids, were more common among patients receiving steroids (n=429/2440, 17.6% vs n=192/3505, 5.5%).

The proportion of patients receiving steroids was higher for patients on oxygen (n=2130/3906, 54.5%) versus no oxygen (n=308/2816, 10.9%) and increased with increasing respiratory support: critical care n=583/909 (64.1%), invasive mechanical ventilation n= 182/275 (66.2%).

The proportion of patients receiving corticosteroids increased over time (Figure 1). However, 563/2258 (24.9%) hospitalised patients on oxygen therapy admitted in August and September did not receive any corticosteroid therapy.

Discussion

One quarter of eligible patients are not receiving a readily available inexpensive evidence-based treatment for COVID-19. The higher percentage of patients receiving pre-admission immunosuppressants and higher prevalence of chronic pulmonary disease among patients receiving steroids suggest if anything that our findings overestimate use of steroids specifically to treat COVID-19. Extrapolating the mortality benefit of low dose dexamethasone among patients requiring oxygen –

one life saved for every 25 treated¹ – our observations suggest that of the 1360 patients receiving oxygen but no steroid since 16th June 2020, 55 deaths could have been prevented.

In this study, the robust method to standardise corticosteroid entries minimises misclassification.

Despite missing data, the large proportion of patients with recorded “no” corticosteroids strongly reinforces our main finding: implementation of steroids therapy for COVID-19 in the UK has been slow and incomplete.

Efforts to support the administration of these cheap, well-tolerated, readily available compounds to the right patients should be urgently undertaken, and the reasons for slow uptake evaluated.

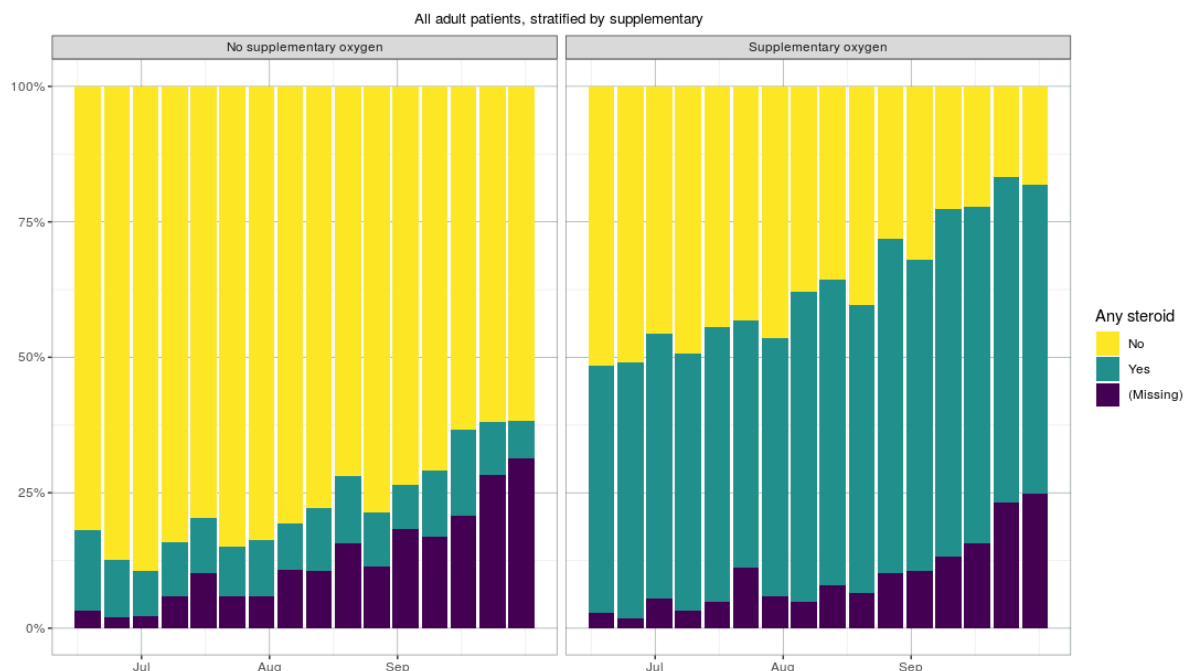


Figure 1. The percentage of COVID-19 patients receiving any or no steroid admitted between 16th June 2020 and 30th September 2020. All patients have at least 21 days follow-up. Different panes represent different levels of care.

Table 1. Characteristics of all adult COVID-19 patients admitted after 16th June and on or before 30th September 2020.

	No steroid (n=3503, 47.9%)	Any steroid (n=2440, 33.5%)	Dexamethasone (n=2104, 28.9%)	Hydrocortisone (n=151, 2.1%)	Methylprednisolone (n=36, 0.5%)	Prednisolone (n=407, 5.6%)	Missing (n=1330, 18.3%)
Age on admission (years), median [IQR]	72.8 (30.4)	67.7 (25.7)	66.9 (25.9)	70.8 (21.2)	65.0 (20.1)	72.2 (22.3)	73.4 (23.6)
Age category, (years), n (%)							
<70	1587 (45.3)	1325 (54.3)	1171 (55.7)	69 (45.7)	23 (63.9)	182 (44.7)	576 (43.3)
70-79	696 (19.9)	534 (21.9)	456 (21.7)	47 (31.1)	9 (25.0)	100 (24.6)	305 (22.9)
≥80	1220 (34.8)	581 (23.8)	477 (22.7)	35 (23.2)	4 (11.1)	125 (30.7)	449 (33.8)
(Missing)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sex, n (%)							
Male	1707 (48.8)	1430 (58.7)	1256 (59.8)	91 (60.3)	23 (63.9)	212 (52.3)	713 (53.6)
Female	1791 (51.2)	1003 (41.2)	844 (40.2)	59 (39.1)	13 (36.1)	193 (47.7)	614 (46.2)
Not specified	2 (0.1)	3 (0.1)	2 (0.1)	1 (0.7)	0 (0.0)	0 (0.0)	2 (0.2)
Ethnicity groups, n (%)							
White	2468 (70.5)	1525 (62.5)	1278 (60.7)	112 (74.2)	15 (41.7)	285 (70.0)	957 (72.0)
South Asian	305 (8.7)	342 (14.0)	313 (14.9)	15 (9.9)	6 (16.7)	45 (11.1)	110 (8.3)
East Asian	11 (0.3)	18 (0.7)	17 (0.8)	0 (0.0)	1 (2.8)	3 (0.7)	4 (0.3)
Black	80 (2.3)	66 (2.7)	61 (2.9)	3 (2.0)	0 (0.0)	7 (1.7)	27 (2.0)
Other ethnic minority	262 (7.5)	242 (9.9)	213 (10.1)	13 (8.6)	7 (19.4)	36 (8.8)	75 (5.6)
(Missing)	377 (10.8)	247 (10.1)	222 (10.6)	8 (5.3)	7 (19.4)	31 (7.6)	157 (11.8)
National early warning score, median [IQR]	2.0 (3.0)	5.0 (4.0)	5.0 (4.0)	6.0 (4.0)	5.0 (4.0)	4.0 (4.0)	3.0 (5.0)
Any comorbidity, n (%)	2719 (77.6)	2000 (82.0)	1686 (80.1)	134 (88.7)	29 (80.6)	382 (93.9)	718 (54.0) ^a
Hypertension	1439 (41.1)	1076 (44.1)	934 (44.4)	62 (41.1)	20 (55.6)	188 (46.2)	397 (29.8)
Chronic cardiac disease	1072 (30.6)	631 (25.9)	524 (24.9)	52 (34.4)	9 (25.0)	140 (34.4)	281 (21.1)
Non-asthmatic chronic	499 (14.2)	471 (19.3)	340 (16.2)	63 (41.7)	5 (13.9)	170 (41.8)	163 (12.3)

pulmonary disease								
Asthma		375 (10.7)	405 (16.6)	325 (15.4)	45 (29.8)	4 (11.1)	108 (26.5)	109 (8.2)
Diabetes		638 (18.2)	486 (19.9)	425 (20.2)	32 (21.2)	6 (16.7)	81 (19.9)	164 (12.3)
Obesity		302 (8.6)	359 (14.7)	329 (15.6)	20 (13.2)	7 (19.4)	41 (10.1)	92 (6.9)
Chronic neurological disease		358 (10.2)	229 (9.4)	195 (9.3)	16 (10.6)	3 (8.3)	35 (8.6)	91 (6.8)
Dementia		457 (13.0)	178 (7.3)	143 (6.8)	14 (9.3)	2 (5.6)	31 (7.6)	99 (7.4)
Chronic kidney disease		558 (15.9)	339 (13.9)	273 (13.0)	23 (15.2)	2 (5.6)	84 (20.6)	147 (11.1)
Liver disease		159 (4.5)	85 (3.5)	72 (3.4)	6 (4.0)	0 (0.0)	16 (3.9)	24 (1.8)
Malignant neoplasm		363 (10.4)	205 (8.4)	171 (8.1)	14 (9.3)	1 (2.8)	38 (9.3)	91 (6.8)
Rheumatic disease		380 (10.8)	279 (11.4)	205 (9.7)	18 (11.9)	6 (16.7)	83 (20.4)	93 (7.0)
Pre-admission immune-suppressants		192 (5.5)	429 (17.6)	274 (13.0)	60 (39.7)	6 (16.7)	191 (46.9)	65 (4.9)
AIDS/HIV		20 (0.6)	15 (0.6)	11 (0.5)	0 (0.0)	0 (0.0)	6 (1.5)	5 (0.4)
Supplementary oxygen	No, n (%)	2143 (61.2)	308 (12.6)	189 (9.0)	26 (17.2)	1 (2.8)	111 (27.3)	365 (27.4) ^a
	Any, n (%)	1360 (38.8)	2130 (87.3)	1914 (91.0)	125 (82.8)	35 (97.2)	295 (72.5)	416 (31.3) ^a
Level of care	Ward, n (%)	3325 (94.9)	1856 (76.1)	1576 (74.9)	107 (70.9)	8 (22.2)	332 (81.6)	681 (51.2) ^a
	ICU, n (%)	178 (5.1)	583 (23.9)	527 (25.0)	44 (29.1)	28 (77.8)	75 (18.4)	148 (11.1) ^a
Invasive ventilation	No, n (%)	3455 (98.6)	2255 (92.4)	1940 (92.2)	125 (82.8)	17 (47.2)	387 (95.1)	721 (54.2) ^a
	Yes, n (%)	46 (1.3)	182 (7.5)	162 (7.7)	26 (17.2)	19 (52.8)	19 (4.7)	47 (3.5) ^a

^aPercentages in this column may not add up to 100% due to missing data.

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