Corticosteroid therapy for patients with COVID-19 pneumonia: a before–after study

Firouzé Bani-Sadr, Maxime Hentzien, Madeline Pascard, Yohan N'Guyen,
Amélie Servettaz, Laurent Andreoletti, Lukshe Kanagaratnam, Damien Jolly

HAL Id: hal-03425066
https://hal.univ-reims.fr/hal-03425066v1

Submitted on 22 Aug 2022

1   **Corticosteroid therapy for patients with CoVID-19 pneumonia: a before-after study**

2   Firouzé BANI-SADR[1], Maxime HENTZIEN[1], Madeline PASCARD[2], Yohan N'GUYEN[1], Amélie

3   SERVETTAZ[1], Laurent ANDREOLETTI[3], Lukshe KANAGARATNAM[2], Damien JOLLY[2]

4

5   1- Department of Internal Medicine, Clinical Immunology and Infectious Diseases, Reims

6   University Hospital, Reims, France

7   2- Department of Research and Public Health, Reims University Hospital, Reims, France

8   3- Department of Virology, Reims University Hospital, Reims, France

9

10

11   **Corresponding author:**

12   Prof. Firouzé BANI-SADR
13   Department of Internal Medicine, Infectious Diseases, and Clinical Immunology
14   CHU Robert Debré
15   rue du Général Koenig
16   51092 Reims, France
17   Telephone number: (+33) 3 26 78 71 89
18   Fax number: (+33) 3 26 78 40 90
19   E-mail address: fbanisadr@chu-reims.fr
20

21   **Keywords:** COVID-19; SARS CoV2; COVID-19 pneumonia; corticosteroid;

22   **Total number of words: 1368**

23

24

25   **Abstract**

26   **Background**: Anti-inflammatory drugs such as corticosteroids may beneficially modulate the

27   host inflammatory response to CoVID-19 pneumonia.

28   **Aims:** To evaluate the impact of addition of corticosteroids to the hospital protocol for

29   treatment of suspected or confirmed CoVID-19 pneumonia on rates of death or intensive

30   care unit (ICU) admission.

31   Methods: A before-after study was performed to evaluate the effect of addition of corticosteroids

32   to our institution's COVID-19 treatment protocol on hospital mortality.

33   **Results**: Between March 3rd and April 14th 2020, 257 patients with CoVID-19 diagnosis were

34   included. As corticosteroids were wide used since 27 March 2020, two periods were

35   considered for the purposes of our study: the before period from March 3rd to 20th (n= 85)

36   and the "after period" (n=172) from March 26th to April 14th 2020.

37   The "after" period was associated with a lower risk of death (HR 0.47; 95% CI, 0.23 - 0.97;

38   p=0.04), and a lower risk of intensive care admission or death before ICU admission (HR 0.37

39   95% CI 0.21 - 0.64; p=0.0005) by multivariate analysis adjusted for age, National Early

40   Warning score and institutionalization status.

41   **Conclusions**: In the "after period", the addition of corticosteroids to our institution's CoVID-19

42   treatment protocol was associated with a significant reduction in hospital mortality.

43

Introduction

There is evidence that severe CoVID-19 patients present overwhelming inflammatory reactions with high levels of cytokines and inflammatory biomarkers, leading to lung injury [1,2]. Anti-inflammatory drugs such as corticosteroids may beneficially modulate the host immune response to CoVID-19 pneumonia. With an average of 2-3 days between the occurrence of dyspnea and intensive care unit (ICU) admission, we postulate that corticosteroid treatment initiated as soon as the patient has shortness of breath or needs oxygen therapy, might be effective in preventing acute respiratory distress syndrome and death [3]. Therefore, since 27 March 2020, we have systematically included corticosteroids in the treatment of patients with CoVID-19 pneumonia. Prednisone or methylprednisolone at a dose of 1 mg/kg equivalent per day (0.5 mg/kg for patients also receiving antiviral therapy with ritonavir as coadministration of corticosteroid and ritonavir lead to an increase corticosteroid plasma concentrations and their half-life) for 3 to 4 weeks, according to the severity of pneumonia, with dose tapering over the last week, was added to our initial therapeutic protocol for hospitalized CoVID-19 patients [4]. This protocol included antiviral therapy (lopinavir plus ritonavir or darunavir plus ritonavir) and/or hydroxychloroquine, empiric broad-spectrum antibiotic treatment for 14 days and preventive anticoagulation for 14 to 21 days. The long duration of corticosteroid treatment was chosen by analogy with that recommended for severe pneumocystis pneumonia in order to additionally prevent pulmonary fibrosis [5]. As lopinavir-ritonavir treatment was not available after mid-March due to a drug shortage in our hospital, most of our patients received another HIV protease inhibitor (darunavir-ritonavir) after this date.

In order to evaluate the impact of addition of corticosteroids to the hospital protocol for treatment of suspected or confirmed CoVID-19 pneumonia, we compared rates of death

68 (primary outcome) or intensive care unit (ICU) admission and/or death before ICU admission

69 (secondary outcome) in a before-and-after study, with the introduction of corticosteroids in

70 our therapeutic protocol as the event defining the start of the "after" period.

71

72 **Patients and Methods**

73 Between March 3rd and April 14th 2020, 319 patients with CoVID-19 diagnosis defined as a

74 positive result on an polymerase-chain reaction testing of a nasopharyngeal sample or

75 presence of characteristic findings on chest CT scan were followed in the University Hospital

76 of Reims, France [6]. Two periods were considered for the purposes of our study: the first,

77 from March 3rd to 20th, corresponded to the "before" period, and the admission of the first

78 cases to our center. During the "before" period, corticosteroid therapy was not

79 recommended. The second period comprised March 26th through April 14th 2020, ("after"),

80 with wide use of corticosteroid therapy in this period following our decision to introduce it

81 systematically due to the biological rationale of its use in the inflammatory phase. Patients

82 with initiation of corticosteroid therapy during the transition period (from March 21st to

83 March 25th 2020) were not included in the before-after analysis. Patients with fewer than 7

84 days between symptom onset and April 14th, 2020 - that was the end point date of follow up

85 - were not included.

86 Individual follow-up was defined as the time from first symptoms to death during

87 hospitalization for the primary outcome and to ICU admission or death before ICU admission

88 for the secondary outcome. ICU admission alone was not considered as an outcome, since

89 we did not exclude patients aged over 80 years and/or with comorbidities, who were less

90 likely to have access to ICU care. Data are expressed as mean ± standard deviation, or

91 number (percentage), as appropriate. Quantitative variables were compared between the

92   two periods using the Student t test and qualitative variables using the Chi square test or

93   Fisher's exact test, as appropriate. For the impact of the period on death and on ICU

94   admission and/or death, we constructed Kaplan Meier curves and compared them using the

95   log rank test. For multivariate analysis, we used Cox proportional hazard models

96   systematically adjusted for age, National Early Warning score and institutionalization status

97   at hospital admission [7].

98

99   **Results**

100   At the time of data extraction, a total of 319 patients were included in the cohort, namely 85

101   patients in the "before" period (until March 20th, 2020), 62 patients in the transition period

102   (March 21st – 25th), and 172 patients in the "after" period (March 26th through April 14th).

103   Eleven patients (12.9%) received corticosteroid therapy in the "before period", 20 (32.3%) in

104   the transition period and 119 (69.2%) in the "after" period. The main characteristics of the

105   257 patients in the "before" and "after" periods are summarized in Table 1. Patients in the

106   "after" period were significantly more frequently nursing home residents, had higher

107   prevalence of dementia, a longer time from symptom onset to hospitalization, less

108   frequently received lopinavir and/or hydroxychloroquine, and more often required oxygen

109   therapy than in the "before" period. Patients in the "after" period also had higher serum

110   creatinine. The mean duration of follow-up was 16.0 ± 7.0 days, and was similar between

111   periods (16.0 ± 8.7 versus 16.1 ± 6.2; p=0.92). Of note, deceased patients hospitalized in

112   medical ward were older than those who were transferred to ICU (mean age 83.9 (±11.3)

113   versus 69.6 (±7.2) years).

114   The "after period" was not associated with a lower risk of death (hazard ratio (HR) =0.86;

115   95% confidence interval (CI), 0.47-1.56; p=0.62) by bivariate analyses but was associated by

116   multivariate analysis adjusted for age, National Early Warning score and institutionalization

117   status (HR = 0.47; 95% CI 0.23 - 0.97; p=0.04).

118   The "after period" was associated with a lower risk of ICU admission and/or death before

119   ICU admission by bivariate analyses (HR=0.25; 95% CI = 0.11-0.55) and by multivariate

120   analysis adjusted for age, National Early Warning score and institutionalization status (HR

121   =0.37 95% CI 0.21 - 0.64; p=0.0005).

122

123   **Discussion**

124   In this before-and-after study of 319 hospitalized CoVID-19 patients, after adjustment for age,

125   National Early Warning score and institutionalization status, the "after" period (n=172) -during which

126   corticosteroids were routinely recommended for patients presenting with CoVID-19 pneumonia

127   at our institution- was associated with a lower risk of death (HR =0.47; 95% CI 0.23 - 0.97; p=0.04),

128   and a lower risk of ICU admission and/or death before ICU admission (HR =0.37 95% CI 0.21 - 0.64;

129   p=0.0005).

130   To this day, corticosteroids are not recommended by the World Health Organization for the

131   treatment of CoVID-19 pneumonia due to their potential adverse effects, such as secondary

132   infections and prolonged virus shedding [8]. However, with our improving knowledge of the

133   role played by overwhelming inflammation in severe CoVID-19 patients, immunomodulatory

134   drugs such as Interleukin-6 or -1 blockade or anti-tumor necrosis factor therapy are being

135   evaluated and all are in favor of a beneficial effect of immunomodulatory drugs during the

136   inflammatory phase of CoVid-19 infection [1,9]. Corticosteroids are old medicines that are

137   inexpensive and accessible to the whole world. In our study, they were associated with a

138   decrease of over 50% in mortality, and in the rate of death and/or ICU admission, even

139   though patients were more dependent and more often required oxygen in the "after" period

140   at the censoring date (although follow-up duration was similar between the two groups).

141   We acknowledge that a before-and-after study yields a low level of evidence, the difference

142   may be the result of overall better patient care with improvements in thrombosis

143   prophylaxis and some of these patients remained hospitalized at end of follow-up and were

144   thus censored for outcomes. Furthermore, the favorable outcome observed with

145   corticosteroids may be partly due to the use of concurrent antiviral drugs in our patients.

146   Another limitation of our study is that CoVID-19 pneumonia diagnosis was more often

147   performed by chest CT scan in patients who received corticosteroids group than in patients

148   who did not. Positive reverse transcriptase polymerase-chain reaction is the gold standard

149   for confirming diagnosis of COVID-19 but its performance presents variable sensitivities,

150   ranging from 37% to 71% [10]. Although chest CT scan is highly sensitive for detecting

151   COVID-19 pneumonia, overlapping CT image features with others viral pneumonia and other

152   respiratory diseases make an exclusion diagnosis difficult and could be therefore a source of

153   bias in our study [10]. Finally, the unavailability of safety data should be acknowledged as a

154   limitation.

155   Nevertheless, these preliminary data support the initiation of clinical trials testing

156   corticosteroids during the inflammatory phase of CoVID-19, and may potentially lead to a

157   change in treatment recommendations.

158

159

160 **Reims COVID Study Group**

161 Ailsa ROBBINS, Kévin DIDIER, Pauline ORQUEVAUX, Violaine NOEL, Paola MARIANETTI,

162 Juliette ROMARU, Dorothée LAMBERT, Jean Luc BERGER, Sandra DURY, Maxime DEWOLF,

163 Jean Hugues SALMON, Jérôme COSTA, Julia SIMON, Natacha NOEL, Sara BARRAUD, Marion

164 BARROIS, Hédia BRIXI, Quentin LAURENT-BADR, Manuelle VIGUIER, Clélia VANHAECKE,

165 Laurence GUSDORF, Isabelle QUATRESOUS, Aline CARSIN-VU, Véronique BRODARD, Antoine

166 HUGUENIN, Morgane BONNET, Aurore THIERRY

167

168 **DECLARATIONS**

169 **Funding :** No

170 **Competing Interests** : None

171 **Ethical Approval** : Not required

172

173 **Author contributions***:*

174 All authors participated in the design of the study protocol and data collection. MH, LK, MP,

175 DJ performed the data management and statistical analyses. FBS, MH and DJ wrote the first

176 manuscript draft. All authors participated in interpretation of the data and writing of the

177 final manuscript and all authors approved the final manuscript. FBS was responsible for the

178 overall supervision of the study.

179

180

181

182 **Table I: Main characteristics of patients in the periods before and after introduction of**

183 **corticosteroids for CoVID-19 pneumonia in Reims University Hospital**

184

	Before (N=85) n (%) or mean ± SD		After (N=172) n (%) or mean ± SD		p
Received corticosteroids	11	12.9	119	69.2	<0.0001
Age	70.1	±15.1	71.8	±16.4	0.44
Male sex	46	54.1	51.7	41.7	0.72
Charlson comorbidity score	1.8	±2.0	2.05	±1.94	0.42
Dementia	8	9.4	33	19.2	0.04
Nursing home resident	8	9.4	47	27.3	0.001
Time from symptom onset to hospitalization (days)	5.8	±4.2	7.5	±4.9	0.009
Diagnosis by positive PCR	80	94.1	143	83.1	0.01
Diagnosis by chest CT scan	5	5.9	29	16.9	
Risk factor of severity	71	83.5	156	90.7	0.09
- Immunocompromised	11	12.9	22	12.8	0.97
- Cardiovascular disease	41	48.2	94	54.7	0.33
- Complicated diabetes	7	8.2	23	13.4	0.23
- Cirrhosis	1	1.2	3	1.7	0.99
- Chronic respiratory disease	22	25.9	32	18.6	0.18
- Chronic renal disease	4	4.7	16	9.3	0.20
- Cancer	7	8.2	10	5.8	0.46
- BMI>40	2	2.4	13	7.7	0.15
- National Early Warning Score	6.2	3.8	6.9	3.2	0.12
Biological characteristics					
- Lymphocyte count G/L	1.1	±0.56	1.1	±1.0	0.73
- Lymphopenia<1G/L	43	51.2	91	53.9	0.69
- Neutrophil count, G/L	5.0	±3.6	5.6	±4.0	0.26
- C-reactive protein, mg/L	98.0	±90.2	89.9	±77.1	0.46
- Serum creatinine, mol/L	103.5	±106.2	137.7	±174.3	0.05
Treatment use with expected antiviral activity	63	75.0	135	79.4	0.43
- Lopinavir	46	54.8	13	7.9	<0.0001
- Darunavir	27	32.5	133	78.2	<0.0001
- Hydroxychloroquine	11	13.3	10	6.0	0.049
Antibiotic therapy	80	95.2	162	95.9	0.99
Evolution					
- Required oxygen therapy	52	61.9	125	76.7	0.01
- Maximum oxygen flow in medical ward †	5.0	±7.6	5.7	±5.2	0.48
- Death	17	20.0	31	18.0	0.70
- ICU admission and/or Death	29	34.1	40	23.6	0.07

185   †Among those who received oxygen therapy.

186

187 **Fig 1: Kaplan Meier curves for death before ICU admission between patients "before" and "after"**
188 **implementation of corticosteroids for CoVID-19 pneumonia in Reims University Hospital**

189
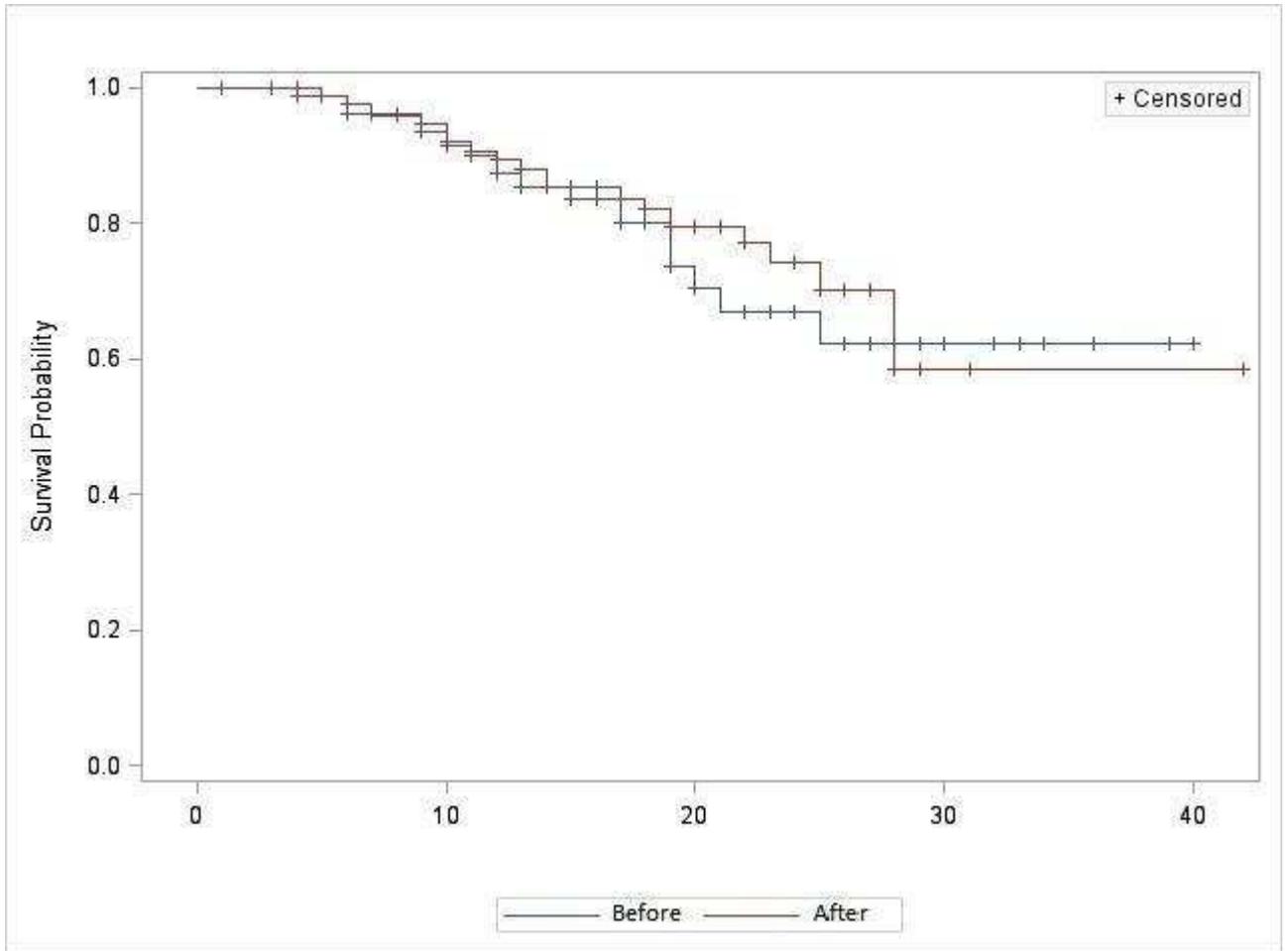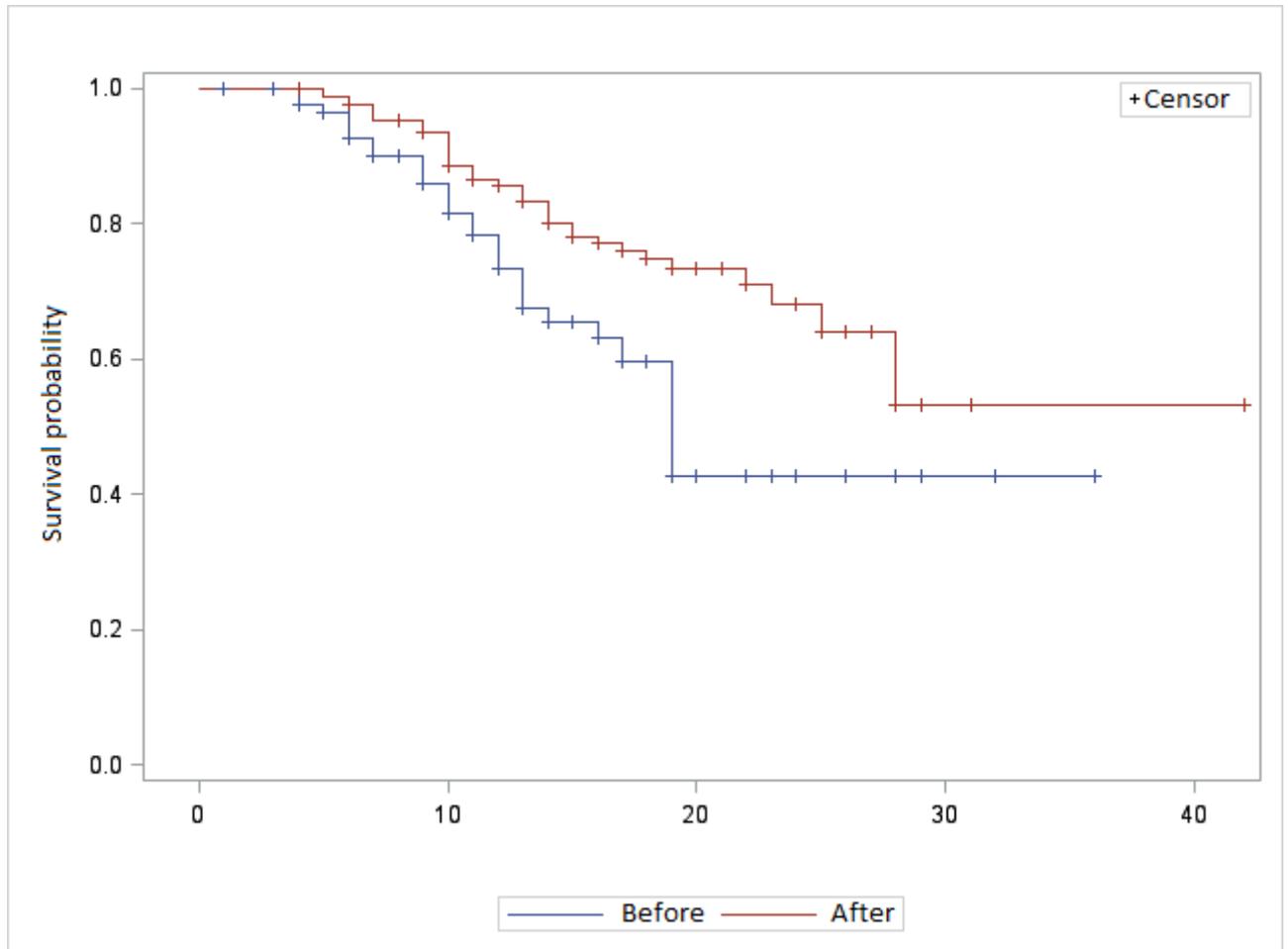

190
191
192
193
194
195
196
197
198
199
200
201
202

203 **Kaplan Meier curves for ICU admission and/or death before ICU admission between patients**
204 **"before" and "after" implementation of corticosteroids for CoVID-19 pneumonia in Reims**
205 **University Hospital**

206

207

208

209 The "before" period was until March 20th, 2020 and the "After" period began on March 26th, 2020.
210 Log -rank: (p=0.006)

211   **References**

212

213   1   Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, *et al.* **The use of anti-inflammatory drugs in**
214   **the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives**
215   **of clinical immunologists from China**. *Clinical Immunology* 2020; **214**:108393.

216   2   Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. **COVID-19: consider**
217   **cytokine storm syndromes and immunosuppression**. *The Lancet* 2020; **395**:1033–1034.

218   3   Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al.* **Clinical features of patients infected with**
219   **2019 novel coronavirus in Wuhan, China**. *The Lancet* 2020; **395**:497–506.

220   4   Busse KH, Formentini E, Alfaro RM, Kovacs JA, Penzak SR. **Influence of Antiretroviral Drugs**
221   **on the Pharmacokinetics of Prednisolone in HIV-Infected Individuals:** *JAIDS Journal of*
222   *Acquired Immune Deficiency Syndromes* 2008; **48**:561–566.

223   5   Bozzette SA, Sattler FR, Chiu J, Wu AW, Gluckstein D, Kemper C, *et al.* **A Controlled Trial of**
224   **Early Adjunctive Treatment with Corticosteroids for** *Pneumocystis carinii* **Pneumonia in the**
225   **Acquired Immunodeficiency Syndrome**. *N Engl J Med* 1990; **323**:1451–1457.

226   6   Xu J, Wu R, Huang H, Zheng W, Ren X, Wu N, *et al.* **Computed Tomographic Imaging of 3**
227   **Patients With Coronavirus Disease 2019 Pneumonia With Negative Virus Real-time Reverse-**
228   **Transcription Polymerase Chain Reaction Test**. *Clinical Infectious Diseases* 2020; :ciaa207.

229   7   B Williams, G Alberti, C Ball, D Ball, R Binks, L Durham. Royal College of Physicians, National
230   Early Warning Score (NEWS), Standardising the assessment of acute-illness severity in the NHS,
231   London.

232   8   Clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus.
233   https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-
234   when-novel-coronavirus-%28ncov%29-infection-is-suspected

235   9   Feldmann M, Maini RN, Woody JN, Holgate ST, Winter G, Rowland M, *et al.* **Trials of anti-**
236   **tumour necrosis factor therapy for COVID-19 are urgently needed**. *The Lancet* 2020;
237   :S0140673620308588.

238   10   Rubin GD, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, *et al.* **The Role of**
239   **Chest Imaging in Patient Management During the COVID-19 Pandemic**. *Chest* 2020;
240   :S0012369220306735.

241

242

243