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Inhaled bronchodilators use and clinical course of adult inpatients with Covid-19 pneumonia in Spain: A retrospective cohort study☆

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ABSTRACT

Background: In the current coronavirus health crisis, inhaled bronchodilators(IB) have been suggested as a possible treatment for patients hospitalized. Patients with evidence of Covid-19 pneumonia worldwide have been prescribed these medications as part of therapy for the disease, an indication for which this medications could be ineffective taken on account the pathophysiology and mechanisms of disease progression.
Objective: The main objective was to evaluate whether there is an association between IB use and length of stay. Primary end points were the number of days that a patient stayed in the hospital and death as a final event in a time to event analysis. Pneumonia severity, oxygen requirement, involved drugs, comorbidity, historical or current respiratory diagnoses and other drugs prescribed to treat coronavirus pneumonia were also evaluated.
Methods: A descriptive, observational, cross-sectional study was performed in this tertiary hospital in Madrid (Spain). Data were obtained regarding patients hospitalized with Covid-19, excluding those who were intubated. The primary and secondary outcomes such as duration of hospitalization and death were compared in patients who received IB with those in patients who did not.
Results: 327 patients were evaluated, mean age was 64.4 ± 15.8 years. Median length of hospitalization stay was 10 days. Of them 292 (89.3%) overcame the disease, the remaining 35 died. Patients who had received IB did not have less mortality rate (odds ratio 0.839; 95% CI: 0.401 to 1.752) and less hospitalization period when compared with patients who did not received IB (odds ratio 1.280; 95% CI: 0.813 to 2.027). There was no significant association between IB use and recovery or death. Hypertension and diabetes were the most common comorbidities. The prevalence of chronic respiratory disease in our cohort was low (21.1%). Anticholinergics were the IB more frequently prescribed for Covid-19 pneumonia. Better response in patients treated with inhaled corticosteroids was not observed.
Conclusion: Off-label indication of inhaled-bronchodilators for Covid-19 patients are common in admitted patients. Taken on account our results, the use of IB for coronavirus pneumonia apparently is not associated with a significantly patient's improvement. Our study confirms the hypothesis that inhaled bronchodilators do not improve clinical outcomes or reduce the risk of Covid-19 mortality. This could be due to the fact that the virus mainly affects the lung parenchyma and the pulmonary vasculature and probably not the airway. More researches are necessary in order to fill the gap in evidence for this new indication.

1. Background

Therapeutic approach for Covid-19 worldwide has been primarily supportive therapy and, to date, there is no specific treatment. The fact that it is a new disease leads to the lack of approved medications for this indication. To date, only remdesivir has been authorized by the FDA via emergency use authorization. [1] As a consequence, a large number of patients around the world have received off-label treatments since there

☆ The data have not been presented in abstract or poster form at conferences.

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is currently no clinical evidence supporting the efficacy and safety of medications used against Covid-19 [2].

Increasing the understanding of the coronavirus disease is essential in order to initiate timely and targeted therapy. It is known that it has three consecutive stages [3]: the early stage characterized by flu-like symptoms and subsequently viral pneumonia, followed by pulmonary inflammation, coagulopathy and increased levels of inflammatory biomarkers associated with the development of acute respiratory distress syndrome. Finally, the third stage of the disease with an increased risk of lung fibrosis.

In this scenario, inhaled bronchodilators (IB) have been suggested as a possible treatment. According to the WHO's Anatomical Therapeutic Chemical (ATC) Classification, IB include inhaled adrenergics, anticholinergics and corticosteroids.[4]

Thousands of hospitalized patients with evidence of Covid-19 pneumonia worldwide have been prescribed these medications as part of treatment for the disease. [5] However, taking into account the pathophysiological mechanism of the disease previously exposed, with development of hyperinflammation hypercoagulability and potential fibrosis, the use of these drugs may be ineffective given the absence of airway pathology.

The use off-label of IB for hospitalized patients is not new. Thus, recent studies have shown that nearly half of them are prescribed for unapproved indications for which there is a very little scientific evidence on its effectiveness [6]. To date there are no robust clinical trials proving their efficacy for most of these indications, including pneumonia caused by coronavirus.

In this unexpected context, there is no way of knowing if Covid-19 patients treated with IB had been benefited or were injured as they were not compared with a concurrent control group. Thus, it is impossible to differentiate drug related adverse effects from disease manifestations in the absence of a control group.

In addition, among IB, those containing corticosteroids are frequently prescribed. Regarding these drugs, in Covid-19 patients published studies have yielded conflicting results concerning anti-inflammatory effects of systemic corticosteroids; both beneficial [3,7,8,9] and harmful [10,11] effects have been reported. A preliminary analysis from a large, multicentre, randomized, open-label trial for hospitalized patients in the United Kingdom showed that patients with severe Covid-19 randomized to receive systemic dexamethasone had a reduced rate of mortality compared to those who received standard of care. [12] Nevertheless, to date, there is no information on whether IC for Covid-19 patients with pneumonia constitutes a protective or harmful factor. Although scarcely, some researchers are already carrying out studies of this type. [13,14].

Given this situation, the following study was undertaken. We hypothesised that the use of IB for Covid-19 patients could be useless taken on account the pathophysiology and mechanisms of disease progression.

2. Material and methods

We conducted this study in Madrid, the epicentre of the pandemic in Spain, in one of the hospitals with the largest number of patients admitted with Covid-19. A descriptive, observational, cross-sectional study was performed in this tertiary hospital (1300 beds) on March 24, 2020. Physicians prescribed therapies to Covid-19 inpatients using a computerised physician order entry (CPOE) programme where they also record the diagnosis and severity. A community-based clinical information programme available in Spain (Horus®) linked to these CPOE programmes are used for hospitalized patients. This programme allows physicians and pharmacists in hospitals to access patients' information of comorbidity and drug indications, including IB, prior to admission, creating a longitudinal electronic health record of clinical and pharmacologic data.

Treatments of all admitted adults who tested positive were reviewed. Test result for Covid-19 virus from analysis of nasopharyngeal or oropharyngeal swab samples were obtained during hospitalization. These tests were carried out by hospital health personnel and results were registered by physicians in the Electronic Medical Record (EMR).

Although a treatment protocol was established at the centre for these patients, the decision to prescribe, including IB, was left to the discretion of the treatment team for each individual patient.

2.1. Study population

Adult patients diagnosed of Covid-19 at admission were included in the study. As exclusion criteria we considered Covid-19 patients admitted to critical care units.

The institutional review board of our center approved this analysis under an expedited review.

2.2. Aim of the study

The main objective was to evaluate whether there is an association between IB use and length of stay. Pneumonia severity, oxygen requirement, involved drugs, comorbidity, historical and current respiratory diagnoses, other drugs prescribed to treat coronavirus and whether IB had been initiated at admission or before admission were also evaluated.

2.3. Data source

From the clinical data warehouse, we obtained data from all prescription events of hospitalized patients with Covid-19 under IB treatment (according to the WHO's ATC classification [4]) who presented respiratory illness, which was defined as a resting oxygen saturation of less than 94% being treated with IB. The data obtained included patients' demographic details, medication administration data, historical and current medication lists, historical diagnoses, oxygen requirements.

2.4. Statistical analysis

2.4.1. Data management

A database was designed to reflect the case report content form, in which a data entry matrix with possible ranges or values was established, along with the various consistency rules between variables. The quality of information received through exploratory analysis was aimed at detecting discrepancies in the values, out-of-range or missing values. An exploratory analysis also provided information on the distribution of the main variables to be studied and provided guidance on possible transformations.

2.4.2. General considerations

The mean, SD, median, maximum, minimum, and 25% and 75% quartiles were included. For the categorical data, the frequency distributions (absolute and relative) were presented. In addition, 95% CIs were calculated when appropriate. The statistical analysis was performed using SAS9.3 (SAS Institute, Cary, North Carolina, USA).

The median length of hospitalization was 10 days, that's the reason why we chose this value when dichotomizing the variable.

3. Results

3.1. Characteristics of the cohort

The pharmacotherapy of 327 hospitalized patients with Covid-19 who were admitted to the hospital the day we carried out the cross section was analyzed. Of them 292/327 (89.3%) overcame the disease, the remaining 35 died. At the time of data cut-off on March 24, 2020, a total of 124 patients were exposed to IB of which 44 contained IC (35.5%) (Fig. 1).

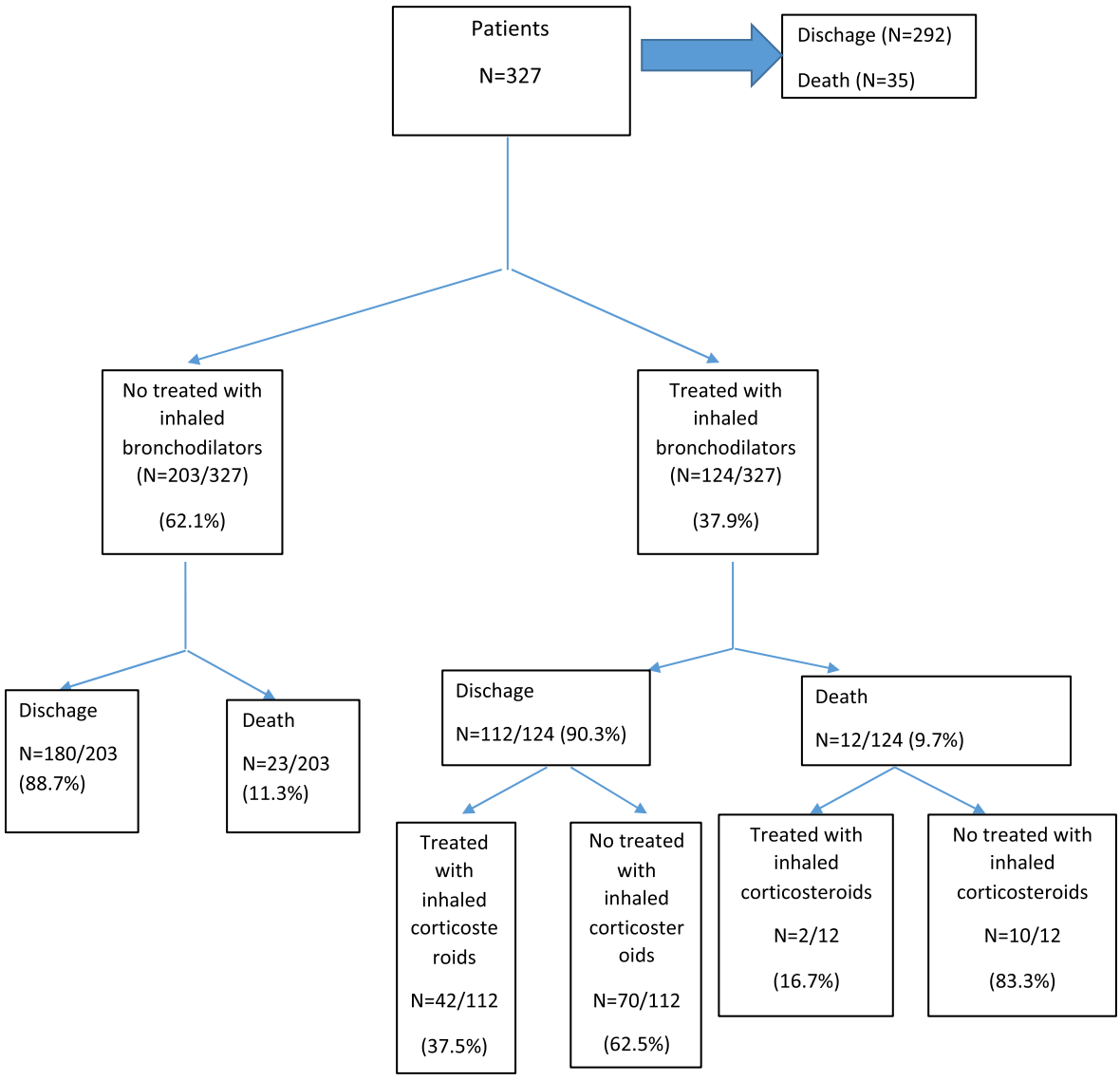

Fig. 1. Study cohort.

Patients were predominantly male (57%). Men and women death rate were 65.7% and 34.3%, respectively. Mean age was 64.4 ± 15.8 years and length of hospitalization stay was 13.2 ± 8.3 days. The distribution of the patient's baseline characteristics according to IB exposure is shown in Table 1.

Regarding patients who had received IB, they did not have less hospitalization period when compared with patients who did not received IB (odds ratio 1.280; 95% CI: 0.813 to 2.027) (Table 2). Also, mean length of stay was not different comparing both groups (Fig. 2). Finally, no differences were observed comparing mortality in patients receiving IB with not receiving IB (9.7% vs. 11.3%, p = 0.639).

At the same time, among patients receiving IB, comparing those treated and not treated with IC, no differences were observed in the length of stay (Table 3). Specific treatment for Covid-19 according to inhalers prescription was also analyzed (Table 4).

We also analyzed the coronavirus pneumonia severity of patients using inhalers compared with those who did not. When using the CURB-65 pneumonia severity score [15] we found that 78/327 (23.8%) suffered severe pneumonia symptoms. Moreover, better results for patients with low and high risk of mortality according to the CURB-65 were observed (Fig. 3).

As for the oxygen needs, we observed that the vast majority of

Table 1
Characteristics of Covid-19 patients receiving or not bronchodilator inhalers.

Characteristic	Total (N = 327)	%	Bronchodilator inhalers (N = 124)	%
Age				
<40 years	28/327	8.5%	6/28	4.8%
40–59 years	87/327	26.5%	27/87	21.6%
60–79 years	157/327	47.9%	71/157	56.8%
≥80 years	56/327	17.1%	21/56	16.8%
Comorbidity	**229/327**	**69.8%**	**92/125**	**73.6%**
Hypertension	90/229	39.3%	59/92	54.3%
Obesity	25/229	10.9%	11/92	11.9%
Cancer	32/229	14%	13/92	14.1%
Cardiovascular	63/229	27.5%	26/92	28.2%
Diabetes	61/229	26.6%	25/92	27.2%
Other	92/229	40.2%	25/92	27.2%
Respiratory illness at baseline	**69/327**	**21.1%**	**43/124**	**21.8%**
COPD	42/69	60.9%	27/43	62.8%
Asthma	13/69	18.8%	12/43	2.8%
OSAS	13/69	18.8%	11/43	2.5%
Other	10/69	14.5%	10/43	2.6%

COPD=Chronic obstructive pulmonary disease. OSAS=Obstructive sleep apnea syndrome.

Table 2
Association between inhaled bronchodilators use and the endpoint of discharge or death and the hospitalization period.

Analysis	Patients receiving Inhaled bronchodilators (N = 124)	Patients not receiving Inhaled bronchodilators (N = 203)	OR (95% CI)
Duration of hospitalization category:			1.284 (0.813–2.027)
<10 days	56/124 (45.2%)	103/203 (50.7%)	
>10 days	68/124 (54.8%)	100/203 (49.3%)	

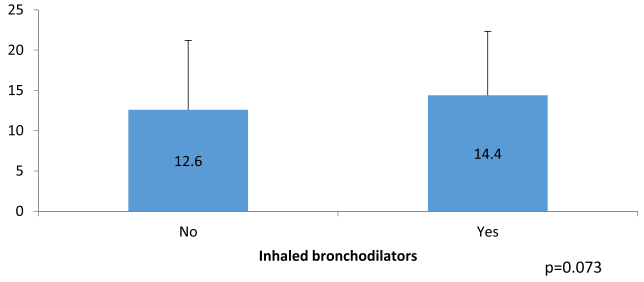

Fig. 2. Length of stay according to the use or not use of inhaled bronchodilators.

analyzed patients needed oxygen supply (286/327; 81.9%).

Concerning treatments for Covid-19, the most frequent combination was hydroxichloroquine plus azithromycin. When comparing patients treated with inhaled therapy with those who not, we found that systemic corticosteroids were used more often for patients treated with IB (13.7% vs. 5.4%). Moreover, of 17 patients treated with systemic corticosteroids concomitantly with IB, 7 received IC (41.2%) the remaining 10 received inhaled anticholinergics. Regarding antimicrobials, azithromycin and ceftriaxone were more frequently prescribed, both in patients treated and not treated with IB.

With regard to the inhaled drug classes involved, anticholinergics were the IB more frequently used in Covid-19 respiratory illness in our center, but those treated with IC were more likely to overcome the disease and were admitted for fewer days (Fig. 3).

Finally, we evaluated if the IB therapy was initiated at admission or previously. 52 out of 124 (41.9%) patients were prescribed IB therapy prior to hospitalization. Similarly, 56 out of 124 were discharged under IB therapy, including those 52 patients initiating IB prior to admission which means that most IB initiated at admission were withdrew at discharge. We also analyzed the length of stay depending on when IB therapy was initiated, prior or during hospitalization (15.38 (SD 8.9) and 13.58 (SD 7.06) months, respectively), without finding statistically significant differences.

4. Discussion

This study shows that a high percentage (37.8%) of Covid-19 admitted patients received IB during hospitalization. The risk of increased hospitalization period or death was not significantly lower among patients who received IB than among those who did not (odds ratio 0.839; 95% CI: 0.401 to 1.752 and odds ratio 1.280; 95% CI: 0.813 to 2.027 respectively). The lack of efficacy could be explained as Covid-19 predominantly causes inflammation in lung parenchyma and in vascular system over conducting airways, the target of IB.

Our findings do not support the use of these drugs since there are not of randomized clinical trials (RCT) proving their efficacy yet. RCT is the best way to prove whether benefit can be attributed to any new treatment, minimizing confounding bias.

To our knowledge, this study is the first that evaluates the degree of IB prescribed for coronavirus respiratory illness use as there exists no other data available to compare with.

As we noted in the introduction, previous researches have already proven that IB are widely used off-label for respiratory infections with lack of evidence [2,16,17] Moreover, it is known that the use of drugs for unapproved conditions is not always beneficial, in some cases they have been associated with higher rate of ADEs [2,18] and avoidable costs [19,20,21]. Our results suggest a need for more IB monitoring in Covid-19 pneumonia in order to identify their effects not only in terms of clinical efficacy, but safety.

As in other observational cohorts, our study reveals that patients with coronavirus had numerous comorbidities, the most common of which were arterial hypertension and diabetes. [22,23,24,25,26,27] Nevertheless, we did not find differences between patients treated and not treated with IB in terms of comorbidity. Surprisingly, the prevalence of chronic respiratory disease among patients with Covid-19, in agreement with other researchers [2] in our cohort was low (21.1%).

In this analysis, consistently with previous published studies [20]' we detected a high proportion of unapproved use of anticholinergics. In addition, our study could not prove that IC were associated with clinical improvement in Covid-19 patients.

Stratifying by severity and inhaled therapy, we did not find in our observational cohort that patients treated with IB showed a better prognosis for the same stratum of severity.

Table 4
Specific treatments for Covid-19 according to inhalers prescriptions.

Covid-19 therapy	Patients treated with bronchodilator inhalers N = 124	Patients not treated with bronchodilator inhalers N = 203	OR (95% CI)
Hydroxychloroquine	119/124 (95.9%)	190/203 (93.6%)	1.642 (0.571–4.723)
Lopinavir/ritonavir	29/124 (23.4%)	33/203 (16.3%)	1.556 (0.891–2.719)
Costicosteroids IV	17/124 (13.7%)	11/203 (5.4%)	2.747 (1.242–6.079)
Tocilizumab	14/124 (11.3%)	20/203 (9.9%)	1.154 (0.560–2.377)
Remdesivir	6/124 (4.8%)	12/203 (5.9%)	0.803 (0.293–2.195)
Antimicrobials	**118/124 (95.2%)**	**185/203 (91.1%)**	**1.823 (0.699–4.754)**
Azitromicyn	91/124 (73.4%)	110/203 (54.2%)	2.263 (1.399–3.661)
Ceftriaxone	79/124 (63.7%)	135/203 (66.5%)	0.865 (0.543–1.378)
Levofloxacin	8/124 (6.5%)	31/203 (15.3%)	0.379 (0.168–0.864)
Other	16/124 (12.9%)	33/203 (16.2%)	0.811 (0.431–1.527)

Table 3
Inhaled corticosteroids prescription in Covid-19 patients according to length of hospitalization and the final endpoint (discharge or death).

Analysis	Treated with Inhaled corticosteroids N = 44	Not treated with Inhaled corticosteroids N = 80	OR (95% CI)	*p* value
Duration of hospitalization category:			1.111 (0.521–2.371)	0.848
<10 days	18/44 (40.9%)	37/80 (46.3%)		
>10 days	26/44 (59.1%)	43/80 (53.7%)		

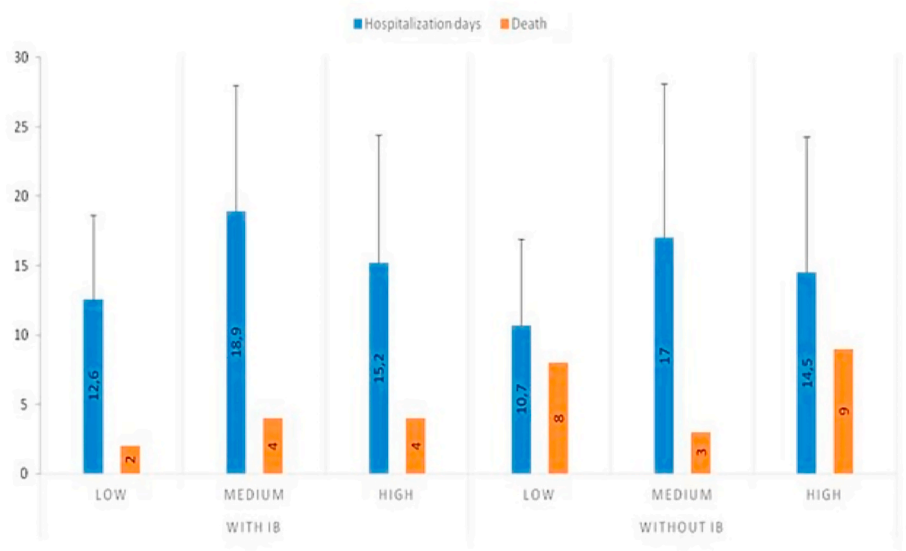

Fig. 3. Association between bronchodilator inhalers use and the composite end point of shortening admission period and death according to clinical conditions
IB: inhaled bronchodilators.

The assessment of IB off-label prescription in a setting not previously described renders clinical relevance and strength to this study. However, it is limited by weaknesses inherent in a cross-sectional and single-centre study. Other limitations may be that there could have been patients who met inclusion criteria but were not assessed because of missing data for some variables and potential for inaccuracies in the electronic health records such as lack of documentation of coexisting illness for some patients. Finally, the response to systemic corticosteroids could interfere with the results, although very few patients were treated and existed in both groups, whether or not they received IB.

5. Conclusion

Off-label indication of inhaled-bronchodilators for Covid-19 patients are common in admitted patients. Taken on account our results, the use of IB for coronavirus pneumonia apparently is not associated with a significantly patient's improvement. Our study confirms the hypothesis that inhaled bronchodilators do not improve clinical outcomes or reduce the risk of Covid-19 mortality. This could be due to the fact that the virus mainly affects the lung parenchyma and the pulmonary vasculature and probably not the airway.

Even though our study do not support this use for IB, it proves that more researches are necessary in order to fill the gap in evidence for this new indication.

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CRediT authorship contribution statement

Elena Villamañán: Conceptualization, Methodology, Software, Data curation, Writing – original draft, Writing – review & editing. **Carmen Sobrino:** Data curation, Writing – original draft, Writing – review & editing. **Carlos Carpio:** Data curation, Writing – original draft, Writing – review & editing, Software, Validation. **Marta Moreno:** Investigation. **Ana Arancón:** Investigation. **Catalina Lara:** Investigation. **Ester Pérez:** Investigation. **Carlos Jiménez:** Investigation. **Ester Zamarrón:** Investigation. **Inmaculada Jiménez-Nácher:** Investigation. **Alicia Herrero:** Supervision. **Rodolfo Álvarez-Sala:** Supervision.

Declaration of competing interest

The authors declare no conflict of interest in this article.

References

[1] Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment.
[2] A.C. Kalil, Treating COVID-19-off-label drug use, compassionate use, and randomized clinical trials during pandemic, J. Am. Med. Assoc. (2020), https://doi.org/10.1001/jama.2020.4742.
[3] C. Wu, X. Chen, Y. Cai, J. Xia, X. Zhou, S. Xu, 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. 180 (7) (2020) 934–943, https://doi.org/10.1001/jamainternmed.2020.0994.
[4] Anatomical Therapeutic Chemical Classification (ATC). Available at: https://www.whocc.no/atc_ddd_index/?code=R&showdescription=no.
[5] D.M.G. Halpin, D. Singh, R.M. Hadfield, Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective, Print 2020 May, Eur. Respir. J. (5) (2020 May 7) 55, https://doi.org/10.1183/13993003.01009-2020, 2001009.
[6] E. Villamañán, C. Sobrino, C. Bilbao, J. Fernández, A. Herrero, M. Calle, D. Alvaro, M. Segura, G. Picazo, J.M. Rodríguez, G. Baldominos, M.T. Ramirez, Y. Larrubia, J. Llorente, A. Martinez, R. Alvarez-Sala, Off-label use of inhaled bronchodilators in hospitalised patients in Spain: a multicentre observational study, Eur. J. Hosp. Pharm. (2020 Apr 24), https://doi.org/10.1136/ejhpharm-2019-002171 pii: ejhpharm-2019-002171.
[7] C. So, S. Ro, M. Murakami, R. Imai, T. Jinta, High-dose, short-term corticosteroids for ARDS caused by COVID-19: a case series, Respirol. Case Rep. 8 (6) (2020), e00596. https://www.ncbi.nlm.nih.gov/pubmed/32514354.
[8] R. Fadel, A.R. Morrison, A. Vahia, Z.R. Smith, Z. Chaudhry, P. Bhargava, et al., Early short course corticosteroids in hospitalized patients with COVID-19, Clin. Infect. Dis. 71 (16) (2020) 2114–2120, https://doi.org/10.1093/cid/ciaa601.
[9] L. Kolilekas, K. Loverdos, S. Giannakaki, L. Vlassi, A. Levounets, E. Zervas, et al., Can steroids reverse the severe COVID-19 induced 'cytokine storm'? J. Med. Virol. 92 (11) (2020) 2866–2869, https://doi.org/10.1002/jmv.26165.
[10] Z. Yang, J. Liu, Y. Zhou, X. Zhao, Q. Zhao, J. Liu, The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis, J. Infect. 81 (1) (2020) e13–e20, https://doi.org/10.1016/j.jinf.2020.03.062.
[11] M.1 Yuan, X. Xu, D. Xia, Z. Tao, W. Yin, W. Tan, et al., Effects of corticosteroid treatment for non-severe COVID-19 pneumonia: a propensity score-based analysis, Shock 54 (5) (2020) 638–643, https://doi.org/10.1097/SHK.0000000000001574.
[12] RECOVERY Collaborative Group, P. Horby, W.S. Lim, J.R. Emberson, M. Mafham, J.L. Bell, L. Linsell, et al., Dexamethasone in hospitalized patients with covid-19 - preliminary report, N. Engl. J. Med. (2020 Jul 17), https://doi.org/10.1056/NEJMoa2021436. NEJMoa2021436.
[13] Protective role of inhaled steroids for covid-19 infection (INHASCO). NCT04331054, Date last updated: 17 April 2020; date last accessed: 15 April, https://clinicaltrials.gov/ct2/show/NCT04331054, 2020.

[14] A trial of ciclesonide in adults with mild COVID-19. NCT04330586, Date last updated: 1 April 2020; date last accessed: 15 April, https://clinicaltrials.gov/ct2/show/NCT04330586, 2020.
[15] Y. Nguyen, F. Corre, V. Honsel, S. Curac, V. Zarrouk, B. Fantin, et al., Applicability of the CURB-65 pneumonia severity score for outpatient treatment of COVID-19, J. Infect. (2020 May 29), https://doi.org/10.1016/j.jinf.2020.05.049.
[16] L. Poulos, R. Ampon, G. Marks, H. Reddel, Inappropriate prescribing of inhaled corticosteroids: are they being prescribed for respiratory tract infections? A retrospective cohort study, Prim. Care Respir. J. 22 (2013) 201–208.
[17] M. Teichert, T. Schermer, L. Van den Nieuwenhof, P.A. De Smet, M. Wensing, Prevalence of inappropriate prescribing of inhaled corticosteroids for respiratory tract infections in The Netherlands: a retrospective cohort study, NPJ Prim. Care Respir. Med. 24 (2014 Oct 16) 14086, https://doi.org/10.1038/npjpcrm.2014.86.
[18] T. Eguale, D.L. Buckeridge, A. Verma, N.E. Winslade, A. Benedetti, J.A. Hanley, et al., Association of off-label drug use and adverse drug events in an adult population, JAMA Intern. Med. 176 (2016) 55–63.
[19] G.W. Hoo, Off label, on target? Chest 126 (2004) 1022–1025.
[20] S.L. Nightingale, Off-label use of prescription drugs, Am. Fam. Physician 68 (2003) 425–427.
[21] J.M. Pomerantz, S.N. Finkelstein, E.R. Berndt, A.V. Pore, L.E. Walker, R.C. Alber, et al., Prescriber intent, off-label usage, and early discontinuation of antidepressants: a retrospective physician survey and data analysis, J. Clin. Psychiatr. 65 (2004) 395–404.
[22] P. Goyal, J.J. Choi, L.C. Pinheiro, E.J. Schenck, R. Chen, A. Jabri, et al., Clinical characteristics of covid-19 in New York city, N. Engl. J. Med. 382 (24) (2020 Jun 11) 2372–2374, https://doi.org/10.1056/NEJMc2010419. Epub 2020 Apr 17.
[23] S. Richardson, J.S. Hirsch, M. Narasimhan, J.M. Crawford, T. McGinn, K. W. Davidson, et al., Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area, J. Am. Med. Assoc. (2020 Apr 22), https://doi.org/10.1001/jama.2020.6775 [Epub ahead of print].
[24] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet 395 (10229) (2020 Mar 28) 1054–1062, https://doi.org/10.1016/S0140-6736(20)30566-3. Epub 2020 Mar 11.
[25] W.J. Guan, Z.Y. Ni, Y. Hu, W.H. Liang, C.Q. Ou, J.X. He, et al., Clinical characteristics of coronavirus disease 2019 in China, N. Engl. J. Med. 382 (18) (2020 Apr 30) 1708–1720, https://doi.org/10.1056/NEJMoa2002032. Epub 2020 Feb 28.
[26] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (2020) 497–506.
[27] A.M. Borobia, A.J. Carcas, F. Arnalich, R. Álvarez-Sala, J. Monserrat-Villatoro, M. A. Quintana, et al., Cohort of patients with COVID-19 in a major teaching hospital in Europe, J. Clin. Med. 9 (6) (2020 Jun 4) E1733, https://doi.org/10.3390/jcm9061733.