Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Scientific letter

Prescription profile of medication in patients with SARS-CoV-2 infection hospitalized in Aragón, Spain☆

Perfil de prescripción de los pacientes con infección por SARS-CoV-2 hospitalizados en Aragón

To the Editor:

On 14th March 2020, a state of alarm was declared in Spain due to the SARS-CoV-2 virus pandemic. After 12 weeks since the beginning of the pandemic, confirmed cases in Aragon reached 5,781, 46% requiring hospitalisation, 5% admission to ICU and 15% died.

The rapid progression of the pandemic and the absence of effective treatment and clinical trials prompted the initiation of multiple therapeutic combinations. Most of the prescription proposals were based on Chinese publications, after their experience in patients with COVID-19.

Although there is currently no effective treatment for COVID-19 infection, different therapeutic approaches have been proposed since the beginning of the pandemic: antivirals that inhibit enzyme systems with the aim of reducing viral replication, those that inhibit SARS-CoV-2 entry in the cell, and immunomodulators that try to reduce the cytokine storm and associated lung damage.[1]

With the "evidence generated" in clinical practice and with data from ongoing studies, the Ministry of Health issues, and updates recommendations for the treatment of patients with the infection.[2] Likewise, in Aragon, a regional protocol for pharmacological management has been established incorporating these recommendations for use.

In order to have a clear picture of the treatments used during the pandemic, the most common combinations and whether they were in line with the recommendations based on the available evidence, a retrospective descriptive study in the consumption and dispensing of in-hospital drugs was carried out in a sample of patients admitted for COVID- 19 (PCR positive), covering all of Aragon's Health Service hospitals, between 1st March to 8th May 2020 (phases 0–1). Data from 1,482 patients admitted with confirmed infection (60% of hospitalized COVID-19 patients) were analysed: 813 (54.9%) men and 669 (45.1%) women, with a median age of 75 years IQR (62–85). No statistically significant differences were observed in sex according to province, except in Huesca (39% women and 61% men, p = 0.04). 12% required ICU admission.

The behaviour of the analysed sample is similar to the reports from other national hospitals during the study period.[3] 46% of patients required hospitalization (45% Spain), predominantly males (54% Aragon, 57% Spain), and a median age above the national level (75 years IQR 62–85, compared to 70 IQR 55–81 in Spain).

A total of 456 different drug substances were prescribed, with a median of 13 drug substances per patient (IQR 9–19). 73% (1,093) of patients received hydroxychloroquine, lopinavir/ritonavir, or azithromycin. 81% in combination (Table 1).

Hydroxychloroquine and lopinavir/ritonavir were among the options recommended in the protocol, alone or in combination, while the lack of results of the hydroxychloroquine and azithromycin combination, and the risk of QT prolongation of both drugs, were reported.[4] The recommendation to use combination therapies is based on the possible synergistic action of their different mechanisms of action. However, there is no evidence about their benefit, and they present a risk of cardiac complications, as the three drugs increase the QT interval.[1]

The prescription profiles against the virus used in clinical practice are unknown. In a recent systematic review,[5] the drug most frequently administered was lopinavir/ritonavir (21.9%), with hydroxychloroquine (1.2%) and azithromycin (1.4%) with a much lower frequency. These data contrast with those observed in the study sample.

Table 1
Profile of the most common antibiotic, antiviral and immunomodulatory treatments prescribed (combined or alone) during the study period.

Drug combination administered	Number of patients (n°)	Percentage of patients (%)	N (%) Men	N (%) Women	Median age (IQR) (years)
Hydroxychloroquine + Lopinavir + Ritonavir	307	28.09%	191 (62%)	116 (38%)	68 (57–77)
Hydroxychloroquine + Lopinavir/Ritonavir + Azithromycin	302	27.63%	181 (60%)	121 (43%)	69 (57–77)
Hydroxychloroquine + Azithromycin	266	24.34%	130 (49%)	136 (51%)	75 (61–84)
Azithromycin + Lopinavir/Ritonavir	7	0.64%	3 (43%)	4 (57%)	87 (76–91)
Azithromycin	104	9.52%	52 (50%)	52 (50%)	87 (78–93)
Hydroxychloroquine	88	8.05%	47 (53%)	41 (47%)	79 (64–83)
Lopinavir/Ritonavir	19	1.74%	12 (63%)	7 (37%)	75 (59–85)
Total	1093	100%	616 (56%)	477 (44%)	75 (59–80)

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The immunosuppressive treatments recommended to act on the progression of the disease[1] were prescribed in 48% of the patients, with corticosteroids being the most widely used: 84% methylprednisolone (with a more powerful immunosuppression profile), 8.7% dexamethasone, 3.8% associated both corticosteroids, and 3.5% associated with tocilizumab (methylprednisolone 84%), in line with the recommendations of some studies.[5]

There is currently insufficient quality evidence to recommend any treatment, and safety alerts are issued regarding the use of combinations that put patients at risk without obtaining any benefit. More randomised and controlled clinical studies are needed to clarify the optimal treatment for SARS-CoV-2 infection.

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Conflict of interests

The authors declare no conflict of interest.

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CD64, CD11a and CD18 leukocytes expression in children with SARS-CoV-2 multisystem inflammatory syndrome versus children with Kawasaki disease: Similar but not the same

Comparación de la expresión de CD64, CD11a y CD18 en leucocitos de niños con síndrome inflamatorio multisistémico relacionado con SARS-CoV-2 y enfermedad de Kawasaki: semejantes pero distintos

Dear Editor,

The immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appears to be a critical factor in the prognosis of coronavirus disease 2019 (COVID-19).[1] Generally, children are less affected and developed asymptomatic or mild forms. Despite this, pediatricians across Europe have describe severe cases of the disease. Firstly recognized as "*Kawasaki like*" processes and later named as pediatric multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS).[2–4] We have seen similar cases in our center adding to its clinical and analytical study the application of immunophenotyping by flow cytometry (FC).[4]

In this report, we describe CD64, CD18, and CD11a expression in three children with PIMS-TS and compare it with three cases of Kawasaki Disease (KD, years 2018 and 2019). The CD64 is a type I high-affinity receptor for the Fc fraction of the immunoglobulin G, located on the surface of monocytes, macrophages, dendritic cells, and neutrophils. Increased CD64 on the cell surface is related to the intensity of stimulation received by inflammatory cytokines. Additionally, CD18, also known as integrin β2, participates in leukocyte adhesion and signaling. CD11a associates with CD18 to form the lymphocyte function-associated antigen 1, or LFA-1. Expressed on leukocytes, this T cell integrin plays a central role in leukocyte cell-cell interactions and lymphocyte stimulation.

The cases clinical trajectories are described in Table 1. The children were studied after informed consent obtained from their parents or legal guardians. The samples were collected in sterile EDTA at room temperature, refrigerated at 4 °C and analyzed by FC within 24 h. Cell surface expression of CD64, CD18, and CD11a were measured by BD FACS Canto II flow cytometer (Becton Dickinson, New York, USA). CD64 (clone 10.1), CD18 (clone CBR LFA-1/2), and CD11a (clone HI111) monoclonal antibodies were obtained from Biolegend® (San Diego, CA, USA). Expressions were measured in monocytes, neutrophils and lymphocytes were identified on a dot-plot and gated. Cell viability was confirmed by 7-AAD staining. At least 10,000 events were recorded for each sample. Flow-cytometry settings and samples were prepared according to manufacturer instructions. The intensity of CD64, CD18, and CD11a surface expression were measured as mean fluorescence intensity in arbitrary units (MFI).

The expression of CD64, CD11a, and CD18 are in Table 1. All PIMS-TS cases received methylprednisolone prior to FC, the KD cases were studied before received immunoglobulin. As main finding, we observe higher upregulation of the three proteins studied in SARS-CoV-2 patients. This response appears to be similar but higher than in KD.

Recent papers have described that a dysregulated immune response may result in inflammation and clinical worsening in COVID-19 cases. Our cases show high levels of CD64 expression. This expression is also higher than the described in some