opiates—both the cumulative dose and the dose administered at the beginning of treatment—and on the integrity of intestinal absorption, hepatic metabolism, and the possibility of interactions at P450 level. To minimize the appearance of complications a moderate approach is to avoid exceeding daily doses of 100 mg and also its use in patients treated with drugs that can extend the QT interval or predispose to serotoninergic clinical signs.

In conclusion, after the study findings, we believe that methadone is a drug that should be taken into consideration to treat the clinical signs of DS following the administration of high and prolonged doses of SED-OPI drugs during MV in patients with ARDS.

Conflicts of interest

Dr. Chamorro-Jambrina, Dr. Alcántara-Carmona, and Dr. Romera-Ortega received speaking fees from Orion-Pharma on behalf of their scientific lectures. The remaining authors declared no conflicts of interest whatsoever.

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Impact of the COVID-19 pandemic on admissions for respiratory infections in the Pediatric Intensive Care Unit☆

Impacto de la pandemia COVID-19 sobre la tasa de ingresos por infecciones respiratorias en Unidad de Cuidados Intensivos Pediátricos

Dear Editor,

Lower respiratory tract infections (LRTI) are a common cause of acute respiratory failure (ARF) in children and a common reason for admission into Pediatric Intensive Care Units (PICU). Syncytial respiratory virus (SRV)—the main causative agent behind acute bronchiolitis and pneumonia in children under two years of age—has a very particular seasonal epidemiological pattern, with maximum incidence peaks in the months of November and February.[1] Although LRTI often have a benign evolution, there are times when they can occur more severely, requiring PICU admission in 10%–20% of children hospitalized due to LRTI.[2]

The disease caused by SARS-CoV-2 (COVID-19), declared a worldwide pandemic back in March 2020, is the cause of severe ARF in adults; however, it affects children in a smaller proportion, usually causing milder manifestations. The COVID-19 pandemic has put tremendous pressure on the healthcare system and changed the epidemiology of other causes of hospitalization in both children and adults.[3,4]

This is an observational, retrospective study, where we analyze the epidemiology of ARF admissions due to LRTI in a PICU during the COVID-19 pandemic (from March 1st, 2020 through February 15th, 2021) compared to 4 previous epidemic seasons (from September 1st, 2016 through February 29th, 2020), the pre-pandemic period. This is a mixed PICU—pediatric and neonatal—that provides healthcare to 105,320 children between the ages of 0 and 14 years with a median of 400 admission/year (20% neonatal disease, 20% critical pediatric patients, 28% postoperative patients, and 32% admissions to perform techniques and procedures).

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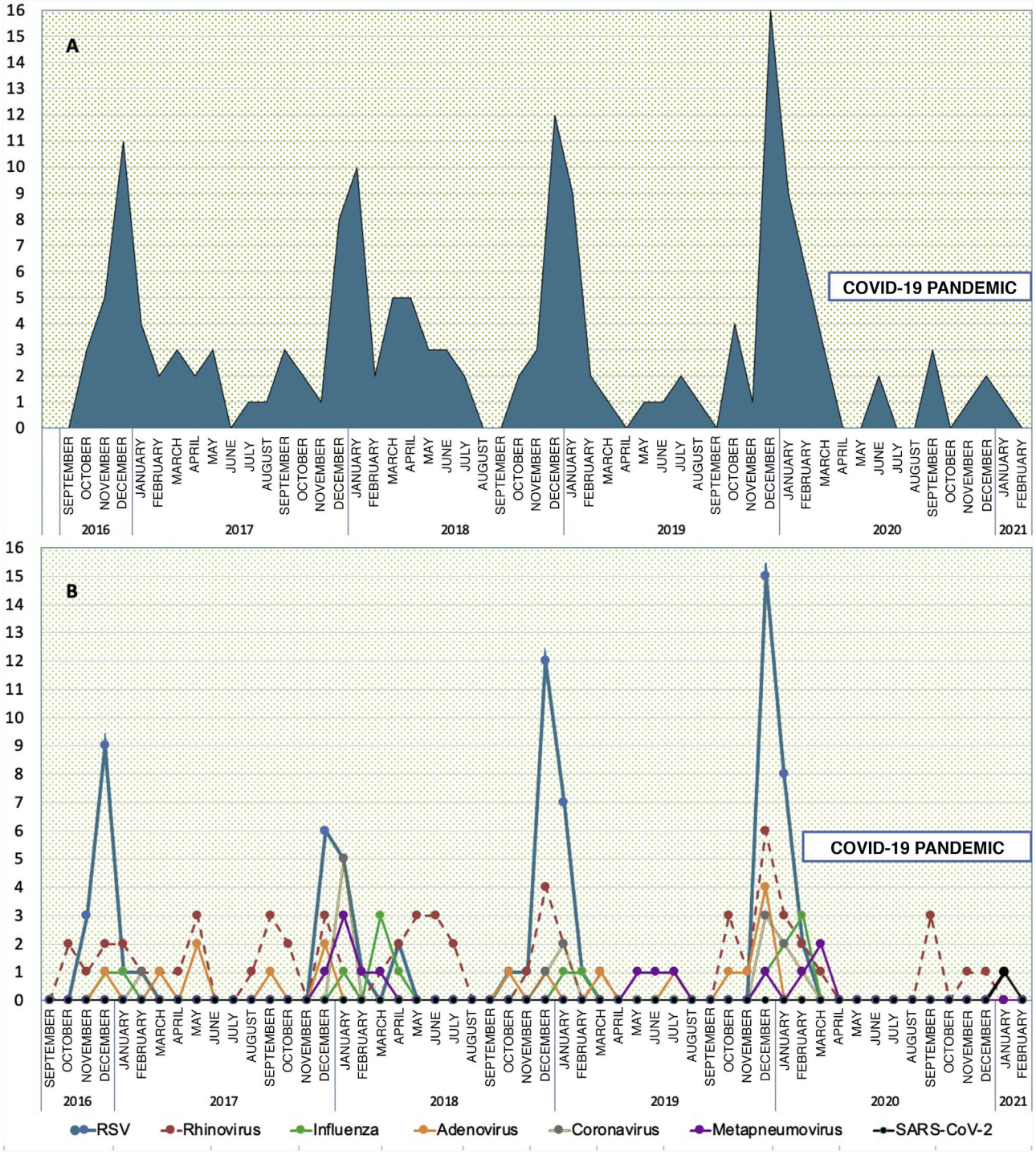

Figure 1 A: number of monthly admissions to the PICU setting due to acute failure insufficiency following LRTI. B: detection frequency of respiratory viruses in nasopharyngeal swaps during the study period.

LRTI was considered when the clinical signs were characterized by cough, tachypnea, and respiratory distress with pathologic lung auscultation preceded by flu-like symptoms with or without fever. We only included patients whose reason for PICU admission was ARF due to LRTI diagnosed with acute bronchiolitis, acute viral bronchitis, status asthmaticus, viral or bacterial pneumonia, and pertussis. Regarding the patients with status asthmaticus, we only included those with bronchial asthma diagnosis who showed signs suggesting LRTI.

The demographic characteristics, clinical data, and etiological agent were all collected. The study was approved by the Drug Research Ethics Committee of our center. During the study period, a total of 1780 patients were admitted to the PICU, 363 (20.4%) due to pediatric critical illness, 182

Table 1 Demographic and clinical characteristics of patients during the 2 study periods.

	Total N = 161 (%)	Before the pandemic N = 149 (%)	During the COVID-19 pandemic N = 12 (%)	*p*
Age (months)	13.2 [1.8–40.8]	12.8 [1.8–39]	40.3 [4.2–78.5]	0.14
Weight (kg)	9 [4.6–15.3]	8.7 [4.6–15]	13.8 [4–28.5]	0.06
Male	95 (59)	88 (59.1)	7 (58.3)	0.96
Comorbidity	33 (20.5)	30 (20.4)	3 (25)	0.71
ARF diagnosis due to LRTI				<0.001
Acute bronchiolitis	59 (36.6)	59 (39.6)	0	
Acute viral bronchitis	52 (32.3)	49 (32.9)	3 (25)	
Status asthmaticus	20 (12.4)	15 (10.1)	5 (41.7)	
Viral pneumonia	15 (9.3)	13 (8.7)	2 (16.7)	
Acterial pneumonia	14 (8.7)	13 (8.7)	1 (8.3)	
Pertussis	1 (.6)	0	1 (8.3)	
ARSD	8 (5)	6 (4)	2 (16.7)	0.111
Viral etiology				
SRV	75 (46.6)	75 (50.3)	0	<0.001
Entero/rhinovirus	63 (39.3)	57 (38.3)	6 (50)	0.423
Adenovirus	17 (10.6)	17 (11.4)	0	0.367
Influenza	15 (9.3)	15 (10.1)	0	0.606
Coronavirus NL63, OC43	15 (9.3)	15 (10.1)	0	0.606
Bocavirus	13 (8.1)	13 (8.7)	0	0.606
Metapneumovirus	13 (8.1)	11 (7.4)	2 (16.7)	0.250
Parainfluenza	7 (4.3)	7 (4.7)	0	1
SARS-CoV-2	1 (0.6)	0	1	0.075
Causative agent not found	8 (5)	7 (4.7)	2 (16.7)	0.137
Viral co-infections	55 (34.2)	54 (36.7)	1 (8.3)	0.098
Respiratory support				0.761
LFOT	8 (5)	8 (5.4)	0	
HFOT	17 (10.6)	16 (10.7)	1 (8.3)	
NIV	119 (73.9)	110 (73.8)	9 (75)	
IMV	17 (10.6)	15 (10.1)	2 (16.7)	
Days on ventilation	3 [1.6–5.6]	3 [1.6–5.6]	3 [1.7–5.6]	0.75
PICU stay (days)	3.9 [2.3–6]	3.96 [2.3–6]	3.15 [2–7.9]	0.824

ARDS, acute respiratory distress syndrome; HFOT, high flow oxygen therapy; IMV, invasive mechanical ventilation; LFOT, low flow oxygen therapy; NIV, non-invasive ventilation.
The categorical variables were expressed as absolute values and percentages (%), and the quantitative ones as median and interquartile range [IQR]. The Mann–Whitney–Wilcoxon test was used to compare the continuous variables while Fisher's exact test was used to compare the qualitative variables. Significance level $\leq$0,05.

of whom were admissions due to respiratory causes. A total of 161 ARF admissions were analyzed due to LRTI.

We saw a significant reduction in the rate of ARF admissions at the PICU due to LRTI, from 50% (149/298) in the pre-pandemic period down to 18.5% (12/65) during the pandemic (OR = 0,23; IC95%, 0,12–0,44; p < 0,001). The rate of admissions was estimated on the number of pediatric critical patients, excluding admissions due to neonatal, postoperative illness and those aimed to perform techniques or procedures.

The medians of age and weight were higher in the group of children admitted during the COVID-19 pandemic compared to the pre-pandemic group. The main diagnoses in the pre-pandemic period were bronchiolitis (39.6%), and acute viral bronchitis (32.9%) while during the pandemic no admissions due to bronchiolitis were reported.

Viral agent detection was performed using the molecular diagnosis technique with nasopharyngeal swab specimen collection in all the patients. During the pre-pandemic period, the SRV was the most common causative agent (50.3%) followed by entero/rhinovirus (38.3%). SRV caused 89.8% of all cases of acute bronchiolitis while the entero/rhinovirus was detected more frequently in acute viral bronchitis (43%), and status asthmaticus (53%). In seven patients (4.7%) no causative agent was found (5 with a diagnosis of acute bronchitis, and 2 with a diagnosis of status asthmaticus). Co-infection by 2 or more viruses was reported in 36.7% of the cases.

During the COVID-19 pandemic, the viruses detected were entero/rhinovirus (50%) and human metapneumovirus (16.7%). A total of 5 patients had status asthmaticus, in 4 of them the entero/rhinovirus was isolated compared to 1 patient in whom the human metapneumovirus was seen as the causative agent. A total of 2 cases of viral pneumonia were seen (due to entero/rhinovirus and SARS-CoV-2), and 1 case of acute viral bronchitis with co-infection of 2 differ-

ent viruses (entero/rhinovirus, and metapneumovirus). No causative agent was isolated in 2 patients (16.7%).

Regarding LRTI of bacterial etiology, 13 patients (8.7%) were admitted due to bacterial pneumonia in the pre-pandemic period, and one (8.3%) during the COVID-19 pandemic. Also, a case of pertussis was reported during the pandemic.

Fig. 1 shows the number of ARF admissions to the PICU on a monthly basis due to LRTI and the frequency of detection of respiratory viruses.

The use of ventilation support was similar in the 2 study periods. During the pre-pandemic period, 73% required non-invasive ventilation (NIV) while 10.1% required invasive mechanical ventilation. On the other hand, during the pandemic, NIV was used in 75% of the cases and 2 patients (16.7%) were intubated, 1 with pneumonia due to COVID-19. Table 1 shows the patients' demographic and clinical characteristics during the 2 study periods.

This study shows a significant decrease in the rate of PICU admissions due to ARF following LRTI during the COVID-19 pandemic. The measures implemented to reduce SARS-CoV-2 transmission such as hand sanitation, use of the face mask, and social distancing, have probably contributed to reduce the transmission of other respiratory viruses.

The SRV is associated with approximately 30%–40% of all LRTI episodes and seasonal flu epidemics reported that affect 10%–20% of the population each year (20%–40% are children).[1,5] During the 2020–2021 season in our cohort neither SRV nor influenza were detected. This finding is seen in the rest of Spain and other countries.[3,6,7] The Influenza and other Respiratory Viruses Surveillance System in Spain reported only 6 cases of SRV in the week of 6/2021 from 3732 samples analyzed (0.16%) and 7 cases of influenza since the beginning of the 2020–2021 season. The flu vaccine campaign advanced to October 2020 may have contributed to the decrease in the transmission of the influenza virus. Although detection tests are being performed on an ongoing basis, the rate of respiratory viruses different than SARS-CoV-2 during the 2020–2021 epidemic season remains very low.[5]

The low rate of respiratory viruses, especially SRV, explains the absence of bronchiolitis during the 2020–2021 autumn–winter season in our cohort, which justifies the heavier weight and older age of patients compared to the pre-pandemic period. These findings are consistent with the data published in the Southern hemisphere during their bronchiolitis epidemic months (April–June).[3,8,9] In Australia, the median of hospital admissions due to bronchiolitis in 2020 was 85.9% less than expected, with an 89.1% reduction of PICU admissions.[8] In the study conducted by the Collaborative Pediatric Network of Latin America, a 83% reduction of PICU admissions due to LRTI was reported between January 2020 and August 2020 compared to the years 2018–2019.[3]

During the COVID-19 pandemic, the only viruses detected in our cohort were metapneumovirus (March 2020) and entero/rhinovirus (autumn–winter 2020–2021). It is not clear why—unlike other viruses—the entero/rhinovirus has become so persistent during the pandemic. Britton et al. suggest that in these viruses the absence of a viral envelop makes them less susceptible to inactivation through hand sanitation, therefore making its transmission easier by contact.[8]

Only 1 case of an ARF admission due to SARS-CoV-2 was reported. It is well known that in the pediatric age, the rate of PICU admission due to SARS-CoV-2 is lower compared to that of other infectious agents and other age groups, which is consistent with the low frequency of COVID-19-related pneumonia seen in our study.

This is the first study published in Spain to report on the low rate of ARF admissions to the PICU setting during the COVID-19 pandemic. More multicenter studies need to be conducted to better analyze the epidemiology of respiratory viruses during the pandemic so that action guidelines can be designed to control the epidemic peaks of the main respiratory viruses in the years to come while taking into consideration the impact that the measures implemented during the pandemic have had reducing the rate of LRTI.

Conflicts of interest

None whatsoever.

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2173-5727/

Combined therapy of tocilizumab and corticosteroids in severe SARS-CoV-2 disease☆

Terapia combinada de tocilizumab y corticoides en la enfermedad grave por SARS-CoV-2

Dear Editor,

Diseases due to SARS-CoV-2 is characterized by cytokine storm mediated by the overproduction of proinflammatory cytokines that can be expressed with a higher level of interleukin 6 (IL-6). On the other hand, infection can cause pneumonia, and eventually progress into acute respiratory distress syndrome being one of the leading causes of death in these patients.[1,2]

The basis of treatment of critically ill patients with pneumonia due to SARS-CoV-2 is symptomatic and supportive: only the use of corticoids has proven capable of reducing mortality[3] while the effects of tocilizumab as a recombinant humanized monoclonal antibody antagonizing the IL-6 receptor have been confirmed.[4]

During this pandemic a great number of patients have received a great variety of therapies in all sorts of combinations. Some of these combinations—based on the premises described before—have been the combined use of tocilizumab and corticoids.

We wanted to analyze the impact that a combined therapy of tocilizumab and corticoids in this context has on the short-term survival (28 days) of patients admitted to an intensive care unit (ICU) due to SARS-CoV-2. Therefore, we conducted a retrospective study that included cases hospitalized due to SARS-CoV-2 infection admitted from March 10, 2020 through December 5, 2020. Patients were categorized into 4 groups based on the different combinations used: group A: did not receive corticoids or tocilizumab; group B: received combined therapy with corticoids and tocilizumab; group C: received tocilizumab only; group D: received corticoids only.

Tocilizumab was used in patients with disease progression with a PaO_2/FiO_2 ratio <300, and D-dimer levels >1500 ng/mL (or in gradual increase) or IL-6 levels >40 pg/mL or elevated ferritin levels. The dose administered in patients of >75 kg of weight was a single dose of 600 mg, and in patients of <74 kg of weight, the dose administered was 1 single dose of 400 mg. Five patients received a second dose of tocilizumab, 6 patients received 3 doses of tocilizumab, and 2 patients received 4 doses of tocilizumab.

The use of corticoids was registered as a binary variable (Yes or No) if patients received, at least, 40 mg of methylprednisolone or its equivalence for, at least, 3 days to treat inflammation associated with viral pneumonia.

A descriptive analysis of the sample was initially conducted and then followed by Cox regression and a 28-day survival analysis using the Kaplan-Meier method for the variable of time of death. Survival curves were compared using the log-rank test.

In the study period a total of 254 patients were admitted. A total of 46 patients were excluded from the study due to lack of data or no confirmation of the presence of SARS-CoV-2. A total of 208 patients were analyzed. The main characteristics of the 4 groups of patients are shown on Table 1.

Using Cox regression analysis (method: intro; state: dead at ICU; covariates used: age, sex, patients' comorbidities, therapies involved in the management of these patients, the SOFA score, the PaO_2/FiO_2 ratio at admission, and the analytical values and ventilatory support therapies). The PaO_2/FiO_2 ratio at the ICU admission behaved as a protector factor against mortality (HR, 0.98; 95%CI, 0.97—0.99; $P = .01$). Out of all the therapies analyzed, the combined use of corticoids and tocilizumab was associated with a better survival rate at the ICU setting (HR, 9.623; 95%CI, 2.39–38.69; $P = .001$). No significant differences were seen with the remaining variables analyzed.

In the 28-day survival analysis, the group on a combined therapy of tocilizumab and corticoids had more chances of survival after 28 days (OR, 2.83; 95%CI, 1.24–6.44) compared to the nonuse of tocilizumab and corticoids. This significant difference was not observed compared to the other 2 groups analyzed: OR, 1.26; 95%CI, 0.54–2.94 vs therapy with tocilizumab; OR, 1.31; 95%CI, 0.57–3.01 vs corticoid therapy (Fig. 1).

Currently, the most consistent and recent studies that assessed tocilizumab in monotherapy against COVID-19 revealed no beneficial effects whatsoever.[5–7] This data proves that blocking one single cytokine is not enough to have a significant clinical impact in these patients.

Similarly, it could be interpreted that one single fixed dose of steroids regardless of disease severity, the cytokine storm released or the presence of acute respiratory distress syndrome would be insufficient in many of these patients.[8]

Our results are consistent with those reported in the REMAP-CAP study[9] that analyzed the use of tocilizumab in a population of patients admitted to the ICU for organ support. This study confirmed that the addition of tocilizumab to the use of dexamethasone improved the mortality of the sample. Consistent with this, the study conducted by Mikulska et al. confirmed that the negative impact of the immune response to COVID-19 might mitigate through the early administration of corticoids plus tocilizumab.[10]

On the other hand, we wish to mention that the group that only received tocilizumab had worse oxygen levels at admission, required more vasopressor drugs and renal replacement therapies during the ICU admission. Also, they developed more nosocomial over-infections, among them, ventilator-associated tracheobronchitis and pneumonia (VAT/VAP). In this sense,

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