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BRIEF REPORT

Antibiotic Prescribing in Children Hospitalized With COVID-19 and Multisystem Inflammatory Syndrome in Spain: Prevalence, Trends, and Associated Factors

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The SARS-CoV-2 pandemic has caused an increase in antibiotic use in different settings. We describe the antibiotic prescribing prevalence, associated factors and trends, as well as concomitant bacterial infections in children hospitalized with COVID-19 or multisystemic inflammatory syndrome related to SARS-CoV-2 in Spain.

Key words. antibiotic stewardship; bacterial infections; children; COVID-19; SARS-CoV-2.

The COVID-19 pandemic has had a devastating impact on healthcare systems worldwide. In addition to the high morbidity and mortality associated with SARS-CoV-2 infection, resource prioritization has led to a reduction or interruption in activities related to antimicrobial stewardship programs (ASPs) [1, 2]. This effect has also been described in pediatric settings, with an increase in antibiotic prescribing [3].

While bacterial coinfections or secondary infections have been reported in only 7% to 8% of all patients with COVID-19 [4–6], antibiotic prescribing has been estimated to be 56.6% to 74.6% in different series, but lower in children than in adults (38.5% vs 83.4%) [7, 8]. The substantial difference between antibiotic use and bacterial infections highlights the potential antibiotic overuse in patients with COVID-19.

Specific data on children are scarce [9, 10]. Expanding our knowledge of antibiotic prescribing patterns in the COVID-19 pediatric population could help to develop and implement ASPs, leading to more judicious use of antibiotics. In the present study, the authors sought to analyze the antibiotic prescribing prevalence, risk factors, and trends, as well as bacterial coinfections and secondary infections, in children hospitalized with COVID-19 or multisystem inflammatory syndrome (MIS-C) related to SARS-CoV-2 in Spain.

METHODS

We conducted a multicenter, cohort study of patients < 18 years hospitalized from March 1, 2020, through March 31, 2021, with SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR), rapid antigen test, or fulfilling World Health Organization criteria for MIS-C. The study was conducted nationally across 76 Spanish hospitals included in the Epidemiological Study of Coronavirus in Children in Spain (EPICO-AEP). EPICO-AEP cohort has been previously described [11].

Study Definitions

The prevalence of antibiotic prescribing was considered as the proportion of patients receiving any systemic antibiotic during admission. The length of therapy (LOT) was defined as the number of days that a patient received systemic antibiotics

during admission, using 100 patient days of admission as the denominator. Patients were classified according to 2 diagnoses: (1) acute COVID-19 (symptoms and/or signs of acute SARS-CoV-2 infection) and (2) MIS-C. After central review, bacterial infections were considered based upon microbiological isolation (positive culture or PCR) and clinical relevance.

Statistics

Data are summarized as frequency and percentage for categorical variables and median and interquartile range (IQR) for continuous variables. The monthly percentage change (MPC) was estimated to characterize trends. We used Joinpoint regression modeling of MPC calculations with log-transformed data models to calculate trends in antibiotic prescribing. Categorical variables were compared with χ^2 or Fisher's test, and continuous variables were compared with the Mann-Whitney test. To identify factors associated with the prescribing of systemic antibiotics in patients with COVID-19, all factors with a *P*-value < .05 in bivariate analysis were included in a multivariate logistic regression model. Laboratory blood results were not included in multivariate analysis because of the high number of patients without these tests. All calculated *P*-values were 2-sided and an alpha level of 0.05 was used for assessing significance. Data were analyzed using Joinpoint Regression software v4.9.0.0 (Surveillance Research Program, National Cancer Institute) and Stata v15 (StataCorp, College Station, TX).

Ethics

This study was approved by the ethics committees of Hospital 12 de Octubre (20/101) and the other participating centers.

RESULTS

A total of 640 children were hospitalized with COVID-19 (n = 505, 78.9%) or MIS-C (n = 135, 21.1%). The median age was 4.3 years (IQR: 0.2-11.3 years), and 367 (57.3%) were males. One hundred and twenty-six children (19.7%) were admitted to the pediatric intensive care unit (PICU); 34 (5.3%) required invasive mechanical ventilation and 59 (9.2%) required inotropic support. Eight (1.3%) patients died.

Bacterial coinfections or secondary infections were detected in 7.0% (45/640) of cases and were more frequent in patients with COVID-19 (8.2%, 42/505) than with MIS-C (2.2%, 3/135) (*P* = .020). Urinary tract infections were the most frequent bacterial infections (40.0%, 18/45), mostly by *Escherichia coli*, followed by bloodstream infections (31.1%, 14/45). Coagulase-negative staphylococci were the most prevalent cause of bacteremia (42.9%, 6/14), followed by *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Streptococcus mitis*, with 2 cases each. Bacterial infections and isolations are included in Supplementary Table S1. Clinical presentation of patients with COVID-19 and bacterial infection are summarized in Supplementary Table S2.

During admission, 347/640 (54.2%) patients received one or more systemic antibiotic, with a LOT of 38.7 days/100 patient days and a median duration of 4.5 days (IQR: 2.5-7.5). Antibiotic prescribing was more common (*P* < .001) in patients with MIS-C (88.9%, 120/135) than with COVID-19 (45.0%, 227/505). Likewise, the LOT was longer for patients with MIS-C (43.4 days/100 patient days) than those with COVID-19 (36.4 days/100 patient-days) (*P* < .001), as was median antibiotic duration (8.5 days [IQR: 6.5-11.5] for MIS-C vs 3.5 days [IQR: 2.5-6.5] for COVID-19; *P* = .004). The most frequently prescribed antibiotic was cefotaxime/ceftriaxone (53.9%, 187/347), followed by azithromycin (26.5%, 92/347), and amoxicillin-clavulanate (18.4%, 64/347). The list of prescribed antibiotics according to diagnosis is included in Supplementary Figures S1-S3.

Changes in the prevalence of antibiotic prescribing among children hospitalized with COVID-19 are shown in Figure 1. There was a significant decline in the prescription of antibiotics in patients with COVID-19 along the study period (MPC: −5.5% [95% confidence interval (CI): −9.7, −1.0]; *P* = .021), and a similar trend was seen for antibiotics prescribed during the first 48 hours of admission (MPC: −5.1% [95% CI: −9.6, −0.4]; *P* = .004). Individual evaluation of antibiotics in patients with COVID-19 revealed a trend for a decline in azithromycin prescription (MPC: −10.8% [95% CI: −21.9, 1.7]; *P* = .081). The LOT in patients with COVID-19 showed a trend for a decrease (MPC: −6.1% [95% CI: −13.9, 2.4]; *P* = .139). There was also a slight but significant decline in the prescription of antibiotics in patients with MIS-C along the study period (MPC: −1.6% [95% CI: −3.1, −0.1]; *P* = .044), but the LOT remained stable (MPC: +4.0% [95% CI: −4.5, 13.3]; *P* = .330).

Factors associated with antibiotic prescribing in patients with COVID-19 in multivariate analysis (Figure 2) were: fever (adjusted odds ratio [aOR]: 3.66 [95% CI: 2.12, 6.31]; *P* < .001), lung infiltrates (aOR: 3.52 [95% CI: 2.08, 5.97]; *P* < .001), sepsis (aOR: 12.95 [95% CI: 1.20, 140.00]; *P* = .035), malignant neoplasm (aOR: 2.86 [95% CI: 1.18, 6.93]; *P* = .020), and hematologic disease (aOR: 3.22 [95% CI: 1.09, 9.51]; *P* = .034). Additionally, every additional year of age increased the odds of receiving antibiotics (aOR: 1.04 [95% CI: 1.00, 1.08]; *P* = .035).

DISCUSSION

To the best of our knowledge, this is the largest study analyzing antibiotic prescribing and concomitant bacterial infection in hospitalized children with COVID-19 or MIS-C. About half (54.2%) of all patients in our cohort received systemic antibiotics during admission, which is higher than that reported by Yock-Corrales et al [10] (24.5%; 243/990 children) in a Latin American cohort including both outpatients and inpatients. Our reported rate is lower than the 69% (415/601) described by

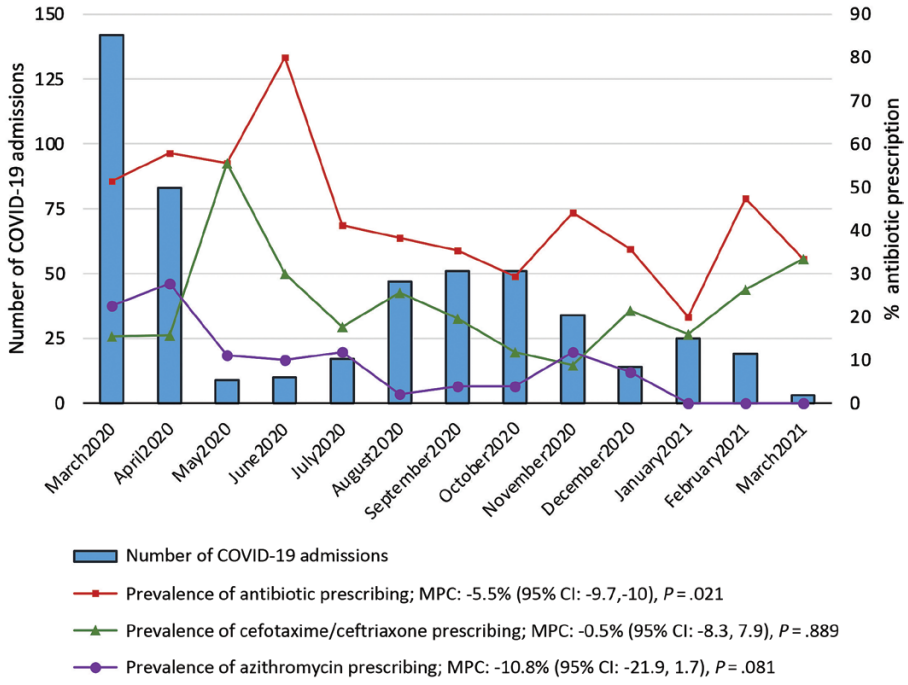

Figure 1. The trend in antibiotic prescribing among children hospitalized with COVID-19. Abbreviation: MPC, monthly percentage change.

Swann et al [9] in hospitalized children in the United Kingdom, perhaps because our study was longer term (until March 2021 vs July 2020), with increasing evidence of low bacterial coinfection in COVID-19. A higher rate has also been described in adults (55%-85%) [7, 8], which is likely explained by the greater severity of SARS-CoV-2 infection in adults than in children.

The severity of acute COVID-19 (eg, fever, lung infiltrates, and PICU admission) and MIS-C was the main reason for antibiotic prescription in our cohort, similar to other adult and pediatric studies [7, 10]. Increasing age has been related to higher antibiotic use in the general population [7] and is confirmed in our study in a pediatric population.

We observed a decline in antibiotic use in COVID-19 cases over time, as reported in adults [7], but not yet described in children [10]. Azithromycin showed the greatest decline in use, likely related to the lack of efficacy in trials [12]. Additionally, a trend toward a reduced LOT was observed in children with COVID-19 but not with MIS-C. Elevated inflammatory markers and the severe clinical presentation in MIS-C overlap with sepsis signs, so empiric antibiotics are usually initiated and later discontinued if MIS-C diagnosis is confirmed.

Notably, we confirm a low rate (7.0%) of bacterial coinfections or secondary infections, especially in MIS-C (2.2%), as described in the aforementioned Latin American cohort (1.3% globally and 0% in MIS-C [10]). Similar to this study, the children in our cohort presented with different bacterial infections when compared with adults, notably urinary tract infections, and all bloodstream infections were due to Gram-positive microorganisms, in contrast to a higher prevalence of Gram-negative bloodstream infections in adults [5, 6].

This considerable difference between the rate of bacterial infections and the prevalence of antibiotic prescribing, especially in MIS-C, underlines the need for a tailored approach to antibiotic use. Antibiotics are likely not needed in the large majority of pediatric admissions for COVID-19. In patients with suspected MIS-C, they can be administered initially after collecting cultures but can be discontinued after 48 to 72 hours of culture incubation if no bacteria are isolated and MIS-C diagnosis is confirmed [13].

Our study has some limitations, including its single-country design. However, a large number of hospitals were included. Also, we focused on hospitalized children, which likely have a higher antibiotic use than outpatients. Because of the nature of our data, we could not distinguish between bacterial coinfections and secondary infections. Further studies are needed to assess this in the pediatric population.

In conclusion, we confirm a high prevalence of antibiotic prescription and low bacterial coinfections or secondary infections in hospitalized children with COVID-19 or MIS-C. A decline in antibiotic use was observed during the first year of the pandemic, but the LOT remained unchanged for MIS-C. Efforts to enhance pediatric ASP actions during the COVID-19 pandemic are needed.

Supplementary Data

Supplementary materials are available at the *Journal of The Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org).

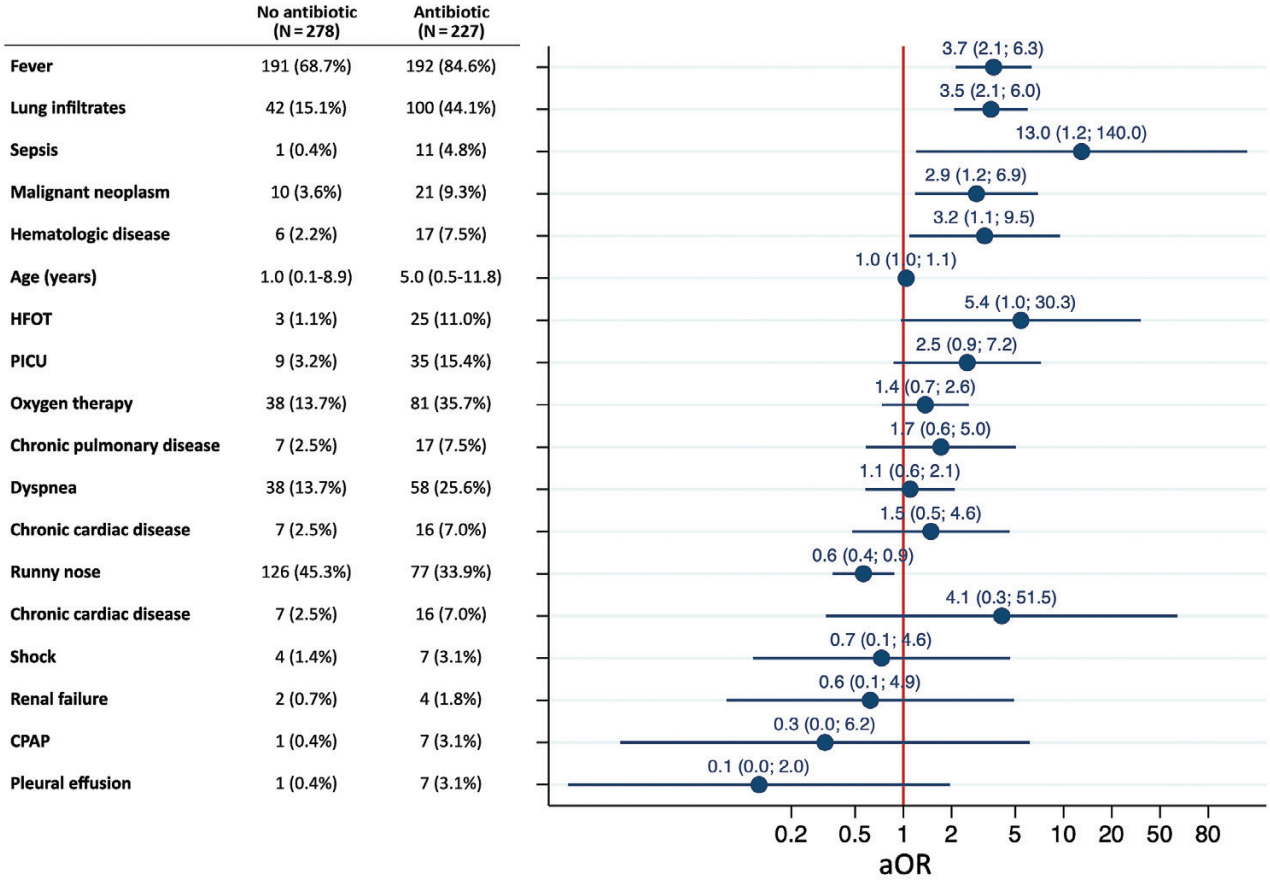

Figure 2. Factors in children hospitalized with COVID-19 associated with antibiotic prescribing in bivariate analysis included in the multivariate analysis. The odds ratio axis is displayed on a logarithmic scale. Abbreviations: aOR, adjusted odds ratio; CPAP, continuous positive airway pressure; HFOT, high-flow oxygen therapy; PICU, pediatric intensive care unit.

Notes

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