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LETTER TO THE EDITOR

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Silent RSV in infants with SARS-CoV-2 infection: A case series

To the Editor,

We deeply commend Rotulo et al.[1] in a recent issue of *Pediatric Pulmonology* on their hypothesis regarding the possible role of an undiagnosed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in determining a peak of severe cases of bronchiolitis during early 2020, just before the pandemic outbreak in Italy.

Given the limited prevalence of severe SARS-CoV-2 infection in children compared to adults, the role of coexistent infection by other pathogens is of particular interest, as its potential to worsen the clinical expression of the disease is yet to be determined. During the SARS-CoV-2 pandemic, the number of accesses to emergency departments because of viral infections other than SARS-CoV-2 has been significantly lower in comparison to nonpandemic years.[2] On the other hand, respiratory syncytial virus (RSV), the main responsible of bronchiolitis, represents a traditionally important cause of hospitalization in children under 12 months of age.[1] To date, the clinical course of SARS-CoV-2 and RSV coinfection has been poorly described and its impact on patients' outcomes has not been clarified. We described the clinical features and outcome of six infants from the coronavirus disease 2019 (COVID-19) unit of a tertiary care pediatric hospital who were coinfected with both SARS-CoV-2 and RSV.

A total of 97 infants under 1 year of age with SARS-CoV-2 infection were hospitalized at our pediatric COVID-19 unit between December 1, 2020 and March 30, 2021. Among them, six had SARS-CoV-2 and RSV coinfection at admission. SARS-CoV-2 was searched by real-time polymerase chain reaction (RT-PCR) on nasopharyngeal swab. RSV was searched by direct detection of viral antigens on the nasopharyngeal swab (RSV card, RV-7020; Beta Diagnostici; sensitivity > 95%, specificity 100%, accuracy 92%).

Patients' characteristics are reported in Table 1. Patient 1 was admitted because of a 2-day-history of cough. Physical examination was unremarkable, as well as hospital course. Patient 2 was admitted for fever and cough that occurred in the previous 24 h. She had a previously diagnosed compensated interatrial defect. Parents were already positive to SARS-CoV-2 before hospital admission. During the hospital stay, she presented no significant dyspnea or other symptoms. Patient 3 was admitted for dyspnea that occurred a few hours ago. Mother was positive for SARS-CoV-2. During her hospital stay, she presented mild diarrhea with no dehydration. Patient 4 was admitted for fever, whooping cough, and vomiting that occurred in the previous few hours. Both parents were already positive for SARS-CoV-2. The clinical course was unremarkable and no dyspnea or other symptoms occurred. Patient 5 was admitted for a fever that occurred 1 day before. Parents resulted positive for SARS-CoV-2 infection. The clinical course was unremarkable. Patient 6 was admitted for respiratory distress the day before. She had a history of perinatal pneumothorax and neonatal sepsis. She had an unremarkable hospital stay. No patient required oxygen supplementation or other treatments during the hospital observation.

Patients with SARS-CoV-2 infection can be coinfected with other respiratory viruses or bacterial pathogens.[3] In adults, no significant difference in patient outcomes was observed between the simple SARS-CoV-2 and the coinfected group.[3] However, data on RSV-SARS-CoV-2 coinfected patients were not analyzed separately.[3] Whether the combined RSV-SARS-CoV-2 infection in infants results in worse clinical expression compared to the infection by the single viruses is still unclear. Jiang et al.[4] reported a child infected with SARS-COV-2, RSV, and human metapneumovirus who developed severe respiratory symptoms requiring intensive care, with ground glass opacities at chest computed tomography. This finding, typical of COVID-19, suggested that the main responsible of the severe clinical course in this patient was SARS-CoV-2 rather than the other two detected viruses. Similarly, Rotulo et al.[1] hypothesized a role of SARS-CoV-2 in the more severe course of cases of bronchiolitis that occurred during the first 3 months of 2020. They reported that, in comparison to previous years, during early 2020 a higher proportion of infants with bronchiolitis required oxygen supplementation.[1] Nevertheless, their reasonable speculations mostly relied on the assumption that SARS-CoV-2 was likely to circulate in Italy already since the end of 2019, but are not supported by viral detection, as at the time RT-PCR for this pathogen was not available yet.

Findings from a large multicenter study on pediatric SARS-CoV-2 infection seem to support these results, as viral coinfection was reported to be significantly related to a higher risk of intensive care unit (ICU) admission.[5] However, some drawbacks prevent the generalization of these results. First, the presence of coinfections was tested only in one-third of patients, mostly hospitalized, thus a selection bias cannot be excluded. Furthermore, data on specific RSV-SARS-CoV-2 coinfection are not provided, and the authors state that viral coinfections were mostly sustained by rhino/enterovirus. Therefore, of the eight patients who required ICU admission out of 45 with viral coinfection, we do not know how many, if any, had RSV. Finally, unlike viral coinfection, the presence of underlying comorbidities was found to be a risk factor for ICU admission at multivariate analysis, thus suggesting a possible interference of this variable.

Unlike the mentioned studies, our data do not support the hypothesis that the combined RSV-SARS-CoV-2 infection leads to a more severe clinical picture, as our patients only presented mild fever and respiratory symptoms with an uncomplicated evolution.

In addition to the limitations discussed so far, these conflicting data likely derive from the patients included in the available

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TABLE 1 Characteristics of 6 infants with SARS-CoV-2 and RSV coinfection

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	19 days	9 months	18 days	7 months	24 days	2 month
Gender	F	F	F	M	M	F
Gestational age (weeks)	38	39	37	40	39	37
Duration of hospital stay (days)	4	2	7	1	3	3
Peak temperature (°C)	37.1	36.5	37.8	38	39	36.8
Lowest oxygen saturation (%)	99	95	98	95	99	100
Clinical findings						
Systemic	–	–	Fever	–	Fever	–
Respiratory	Cough	Cough, coarse pulmonary crackle, mild subcostal retraction	Dyspnea, mild subcostal retraction	Mild respiratory distress	Unremarkable	Sporadic rales
Gastrointestinal	–	–	Diarrhea	Vomit	–	–
Inflammatory index						
CRP highest value	7.39	1.53	1.57	1.01	1.32	1.27
PCT highest value	0.1	0.06	0.13	0.08	0.22	0.14
Ferritin highest value	338	58.8	1054	39.4	671	36
Blood count ($\times 10^9$cells/L)						
Leukocytes	15.76	13.50	9.49	23.19	11.30	9.58
Neutrophils	1.88	3.73	2.39	7.94	3.16	2.18
Lymphocytes	11.38	7.15	4.20	12.24	5.99	6.06
Monocytes	2.33	2.52	2.54	2.85	2.11	1.23
Chest X-ray	Unremarkable	Not performed	Unremarkable	Not performed	Not performed	Small areas of linear consolidation in the left lower lobe

Note: CRP (n.v. < 5 mg/L); PCT (n.v. < 0.5 ng/ml); ferritin: n.v. < 320 ng/ml.

Abbreviations: CRP, C-reactive protein; F, female; M, male; PCT, procalcitonin; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

studies. Indeed, RSV is known to be of scarce clinical relevance in adults, but it may cause severe respiratory disease in infants. Therefore, one could speculate that no worse clinical expression was found in patients with combined RSV and SARS-CoV-2 infection due to the fact that in adults RSV is generally not responsible for significant symptoms. However, unexpectedly, our results confirm that, also in infants, RSV coexistence does not worsen COVID-19 symptoms. A very recent study showed that pathways for overexpressed genes are highly concordant between patients with SARS-CoV-2 and non-SARS-CoV-2 viral infections.[6] We can speculate that, in coinfected patients, increased SARS-CoV-2 viral replication may occur compared to concomitant other viruses, due to the characteristics of infectivity and replication of SARS-CoV-2. As COVID-19 in children is a mild disease in the majority of cases,[7] it is possible to hypothesize that, in coinfected children, SARS-CoV-2 overbears RSV, inhibiting its replication and thus its clinical expression.

As for the accuracy of the RSV diagnostic test used in our study, no cross-reaction with other respiratory antigens as influenza A and B or adenovirus has been reported.[8] No data on possible SARS-CoV-2 cross-reaction are available. Further studies with different diagnostic techniques (e.g., PCR) and larger samples are mandatory to better define the role of RSV in infants with a concomitant SARS-CoV-2 infection.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

KEYWORDS

infants, outcome, respiratory syncytial virus, SARS-CoV-2

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