Favorable Outcome in Infants Hospitalized With COVID-19: Single Center Experience from Athens, Greece

This study aims to describe the clinical characteristics and outcome of 92 infants (aged <12 months) with community-acquired coronavirus disease 2019 (COVID-19) between March, 2020 and June, 2021 at a single center in Athens. Infants with COVID-19 developed mild disease (89, 96.7%), and were infected mostly by their household contacts (74, 80.4%). Disease complications were rare, indicating that hospitalization is the result of low threshold for admission rather than disease severity.

Keywords: *Community-acquired, Outcome, Hospitalization, Management, Severity.*

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Children infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), typically have a milder and often asymptomatic course of illness [1]. Severe disease is rare and mortality is associated with existing comorbidities or disease complications such as the multisystem inflammatory syndrome (MIS-C) [2]. Coronavirus disease 2019 (COVID-19) in infants was a major concern when the disease was first described, in view of their immunological immaturity and close contact with household members infected with SARS-CoV-2 [2]. Reports indicate that 62% of children hospitalized with COVID-19 are <1 year of age, although it is not clear if this is related to disease severity or to a lower threshold for admission [3,4].

There are limited data on disease severity in infants with community-acquired COVID-19 and these largely come from case reports and small case series. The primary aim of this study was to describe disease characteristics, transmission and outcome of COVID-19 in infants. The secondary aim was to identify clinical or laboratory markers linked to disease severity.

This single-center medical record review was conducted for the period between March, 2020 and June, 2021 in infants (aged <12 months) admitted to a COVID-19 referral pediatric hospital in Athens, Greece, following a positive reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2. After clearance from the Institutional ethics committee, medical records of infants included in the study were reviewed for demographic, clinical and laboratory characteristics, and disease outcomes. Amplification cycle threshold (Ct) values were recorded, with lower values indicating a higher viral load. Ct cutoff for negativity was 35-40 cycles [5]. Contact tracing was performed by standard interview of parents for suspected COVID-19 symptoms, and reason and timing of PCR testing in any family member. The severity of COVID-19 was defined as asymptomatic, mild, moderate, severe and critical, according to the National Institutes of Health (NIH) classification [6].

Statistical analysis was performed using SPSS, version 25.0. Associations between infants' characteristics were evaluated with spearman's Rho correlation coefficient. *P*-value <0.05 was considered as statistical significant.

Overall, 92 previously healthy infants (56.5% boys) with mean (SD) age of 3.3 (3.1) months were admitted during the study period. Demographic and clinical characteristics of these infants are shown in **Table I**. The majority of the infants (89, 96.7%) had a mild illness. Three patients required supplemental oxygen administration, while only one developed moderate respiratory distress and required pediatric intensive care unit (PICU) admission for short course non-invasive ventilation.

Table I Characteristics of Infants With COVID-19 in Athens, Greece (2020-21) (*N*=92)

Characteristics	
Age at admission (mo)	3.3 (3.1)
Girls	40 (43.5)
History of COVID-19 exposure	74 (80.4)
Household COVID-19 case	74 (100)
Ct value	16.7 (5.3)
Symptoms and clinical findings	
Fever (>38ºC)	62 (67.4)
Low-grade fever (<38ºC)	33 (35.9)
Cough	20 (21.7)
Rhinitis	43 (46.7
Poor feeding	38 (41.3)
Gastrointestinal (vomiting, diarrhea)	25 (27.2)
Respiratory distress	3 (3.3)
Febrile seizures	1 (1.1)
Laboratory findings[a]	
White blood cells ($x10^3$/µL)	9429 (4139)
Neutrophil count ($x10^3$/µL)[b]	3088 (2280)
Lymphocyte count ($x10^3$/µL)	4862 (2527)
Neutrophil/Lymphocyte count	0.9 (0.9)
C-reactive protein (CRP) (mg/L)	7.9 (32.4)
Platelet count ($x10^3$µL)	373196 (127003)
Creatinine (mg/dL)	0.3 (0.1)
Alanine aminotransferase (ALT) (U/L)	30.8 (27.6)
Aspartate aminotransferase (AST) (U/L)	47.9 (26.9)
Abnormal chest radiograph	3 (3.3)
Disease severity[c]	
Mild	89 (96.7)
Severe	3 (3.3)
Treatment	
Antimicrobials	22 (24.2)
Corticosteroids	3 (3.3)
Remdesivir	2 (2.2)
Supplemental oxygen[d]	3 (3.3)
Non-invasive ventilation	1 (1.1)
No respiratory support	89 (96.7)
Outcome[e]	
Co-infection	2 (2.2)
Hospital stay (d)[a]	4.1 (1.9)
Pediatric intensive care unit (PICU) admission	1 (1.1)

Values in no. (%) or [a]mean (SD); [b]24 (26.1%) had neutropenia; [c]None had moderate or clinical disease; [d]No infant required invasive ventilation; [e]No infant developed any complications or died.

Mean (SD) Ct value was 16.7 (5.3), indicating high viral load. Two infants were diagnosed with concominant bacterial infection on admission (one with urinary tract infection and one with gastroenteritis caused by *Campylobacter* spp). Antimicrobials were administered in 22 (24.2%) of the infants and the majority of them (18, 81.2%) were infants <3 months old that were initially admitted with fever with no focus. Antibotics were given in these, pending culture results, with a median treatment duration of 3 days. Mean (SD) duration of hospitalization was 4.1 (1.9) days, and all infants had a favorable clinical outcome without complications. No infant to adult transmission was reported during hospitalization or during follow-up.

Results from a multivariate analysis identifying risk factors related to disease severity showed that higher Ct values (hence lower viral loads) were seen in older infants (P=0.01), and were associated with higher white blood cell (WBC) (P=0.04) and neutrophil count (P=0.3), as well as increased C-reactive protein (CRP) (P=0.005). There was no significant association between patient's age and days of hospitalization, and between Ct values and laboratory results with the duration of hospitalization.

There is now growing evidence that children, especially infants and toddlers, develop mostly asymptomatic or mild COVID-19 [1]. This may be due to the immunological characteristics of this age group, the physiology of their respiratory tract where ACE2 receptors are not abundant, and the interaction with seasonal coronaviruses in older children [7]. Also, despite recent evidence that children have comparable viral loads with adults [8] and that infants and toddlers may spread SARS-CoV-2 [9], the current study findings support the notion that infants can rarely be a primary case and possibly not a source case for other members of their households either.

This study has some limitations. Firstly, this is a retrospective, single-centre study. However, it represents the general population, as the hospital is one of the two COVID-19 referral pediatric hospitals in Athens. Secondly, in this cohort, there were only three infants with severe COVID-19 disease and all infants were previously healthy with no co-morbidities. Finally, the study period reflects the hospitalizations during the first and second COVID-19 wave, but not the period when the delta and omicron variant were dominant.

We can safely suggest that infants with COVID-19 can be treated at their home environment since hospitalization can lead to unecessary laboratory testing, parent-infant separation and increased risk for SARS-CoV-2 in-hospital transmission. It is of prime importance to deteremine the expected benefit of young child vaccination, and the number of adult cases prevented, especially when the vaccination coverage in other age groups is high. Studies on antibody kinetics and risk of reinfection from SARS-CoV-2 in this age group are under way and will further support decision-making.

Ethics clearance: Institutional ethics committee, 'P. and A. Kyriakou' Children's Hospital, Athens, Greece; No.4336, dated 9 March, 2021.
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