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REGULAR ARTICLE

Benign course and clinical features of COVID-19 in hospitalised febrile infants up to 60 days old

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Abstract

Aim: Minimal data exist regarding the severity of COVID-19 in febrile infants under 60 days old. This multicentre prospective study explored the clinical course and outcomes of this hospitalised patient population, as, to date, the best approach has not been specifically addressed.

Methods: This study focused on the clinical features, laboratory parameters and outcomes of febrile infants up to 60 days old who tested positive for the virus and were hospitalised in Israel from March 2020 to January 2021. The data were extracted from a real-time prospective surveillance network for COVID-19 that includes 20 of the country's 26 hospitals.

Results: We identified 75 febrile young infants (60% female) with COVID-19 at a median age of 28 days (range 8–56 days). Of these, 84% had an unremarkable medical history, 29% had respiratory symptoms, and 96% had a mild illness. The Rochester criteria showed that 44% were considered at high-risk for serious bacterial infections, and we found that eight infants actually had concomitant bacterial infections. Outcomes were excellent, and no complications or fatalities were reported.

Abbreviations: CRP, C-reactive protein; CSF, Cerebral spinal fluid; ICU, Intensive care unit; LP, Lumbar puncture; PCR, Polymerase chain reaction; SBI, Serious bacterial infection.

Conclusion: The excellent outcomes of young febrile infants with COVID-19 closely resembled other respiratory viral aetiologies of fever in this age group, and there were no fatalities.

KEYWORDS
COVID-19, infants, neonatal fever, Rochester criteria, serious bacterial infection

1 | INTRODUCTION

Millions of people have been infected, hospitalised and died during the COVID-19 pandemic.[1] However, children have mostly had mild symptoms and respiratory disease and have fully recovered within one to two weeks requiring minimal supportive care.[2] There have also been rare cases of multi-system inflammatory disease during convalescence, but this phenomenon has primarily been observed in children, not infants.

Febrile infants up to 60 days old are a unique subclass of the paediatric population. Managing fever in this age group is challenging due to the relatively high rates of serious bacterial infections (SBIs), compounded by a lack of specific signs and symptoms that enable us to discriminate SBIs from simple viral infections.[3] Therefore, these infants traditionally require more comprehensive evaluation, usually performed with risk stratification criteria, such as the Rochester or Boston criteria.[4–7] COVID-19 data in these infants have been lacking, and the appropriate approach to febrile infants infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has not been specifically addressed.

Our aim was to describe the clinical and laboratory characteristics of febrile infants up to 60 days old with COVID-19 and to assess the risk of concomitant bacterial infections in accordance with high-risk and low-risk criteria for SBIs.

Key notes

- Minimal data exist regarding COVID-19 in very young infants and this multicentre prospective Israeli study focused on 75 infants up to 60 days old.
- We found that 84% had an unremarkable medical history, 29% had respiratory symptoms, 96% had a mild illness, and 44% had a high-risk for serious bacterial infections.
- The outcomes closely resembled other respiratory viral aetiologies of fever at this age, with excellent results and no fatalities.

2 | METHODS

2.1 | Setting

This study included all febrile infants aged two to 60 days old hospitalised from 10 March 2020 to 10 January 2021 with a fever of at least 38°C and a positive polymerase chain reaction (PCR) result for SARS-CoV-2. They were identified from Israel's Paediatric Surveillance Network for COVID-19, which is a real-time prospective surveillance network that comprises 20 of the country's 26 hospitals and covers all regions.

2.2 | Case definition

Cases were included if febrile infants up to 60 days old had positive PCR samples which were obtained from the oral cavity and/or nasopharynx. Disease severities were based on Dong et al.[8] Mild disease only involved acute upper respiratory traction infections. Moderate disease included pneumonia without hypoxemia. Severe illness included desaturations below 92%. Critical illness involved acute respiratory distress syndrome or respiratory failure.[8]

The Israeli national evaluation guidelines for young febrile infants are based on the Rochester criteria, which help clinicians identify patients with a low risk for SBIs, who do not necessarily require empiric antibiotic treatment nor hospitalisation.[9] A prospective multicentre study by the American Academy of Pediatrics reported that these criteria had high discriminative power.[10] The criteria used to define low risk include unremarkable medical history, appearing to be well, with no focal signs of infection, a while blood cell count of 5000–15,000/micL, with an absolute band count of less than 1500/micL, normal urinalysis and no mucoid or bloody diarrhoea. However, some modifications are made in many paediatric settings, including most Israeli hospitals. These include C-reactive protein (CRP) levels, when available, and exclude absolute band counts, which are no longer reported in most Israeli hospitals. Lumbar punctures are performed at the physicians' discretion. SBIs were defined as the presence of bacterial meningitis, bacteraemia, a urinary tract infection (UTI), musculoskeletal infection, pneumonia or bacterial enteritis.

2.3 | Data collection

The data collected included the test date, recent contact with COVID-19 patients and age, sex and ethnicity. The medical history

covered the perinatal course, prematurity, previous hospitalisation, congenital malformations and background illnesses, including heart disease, chronic lung disease, immune deficiency or malignancy. Signs and symptoms included fever, cough, rhinorrhoea, respiratory distress weakness, diarrhoea, vomiting, conjunctivitis, nausea, rashes and irritability. Laboratory data comprised complete blood count parameters, CRP, blood, urine and cerebrospinal cultures. Disease outcome data included severity, length of hospitalisation, complications, intensive care unit admission and mortality.

2.4 | Statistical analysis

The data are presented as means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous variables, and frequencies and proportions for categorical variables. The study was approved by the local institutional ethics review board, the Helsinki Committee at Rabin Medical Centre. Caregiver consent was not required.

3 | RESULTS

There were 75 febrile infants up to 60 days old who tested positive for the virus and Table 1 summarises their demographic, clinical and laboratory characteristics. Their median age was 28 (range 8–56) days, and 41 (54%) were 28 days or less. Virus test results were available for the caregivers of 36 patients, and they were all positive. Most infants (84%) had an unremarkable medical history, but 8% had congenital malformations or underlying conditions. Of these six infants, four had congenital heart defects, one had a renal malformation, and one had a chromosomal abnormality. Two patients had previously been hospitalised for UTIs, one for early postnatal dyspnoea and one for cyanotic heart disease, namely, Tetralogy of Fallot.

The duration of fever was reported for 93% infants, and the mean was 1.3 days. Mild respiratory symptoms, mainly cough and rhinorrhoea, were observed in 29%. Leukocyte counts of <5000/micL or >15,000/micL were noted in 13% and 14% of infants, respectively. Absolute lymphocyte counts of <1500/micL were documented in 7%, while absolute neutrophil counts of <1500micL or >10,000micL were documented in 17% and 4%, respectively. CRP was measured in 72 infants: 97% were below 5mg/dL, and 96% were below 2mg/dL. It was notable that all three neonates with a CRP of >2mg/dL had a concomitant SBI.

The median hospitalisation duration was 2.0 (range 1–13) days. It is important to note that some neonates were not discharged when medically fit, due to quarantine or administrative issues related to COVID-19 regulations. No complications were documented, and there were no intensive care admissions or fatalities.

COVID-19 disease severity was mild in 96%. One had moderate disease due to shortness of breath without hypoxemia. The other two had severe disease and were treated with supplemental oxygen for a short period: one was otherwise healthy, and one had Tetralogy of Fallot.

When the Rochester criteria were applied, 44% infants were considered at high-risk for SBI and 77% were empirically treated with antibiotics until negative culture results. Concomitant bacterial infections were found in 11% of the infants: seven had UTIs and the other one had *Salmonella* gastroenteritis. Of these eight, seven were under 28 days old and five had a high risk for SBIs. No bacteraemia or meningitis were reported.

4 | DISCUSSION

We believe that this was the first nationwide study on the clinical course and outcomes of young febrile infants up to 60 days old with COVID-19. The 75 infants had short, uneventful disease courses with favourable outcomes. Very young infants with fever are vulnerable to infectious diseases and deserved particular attention and a carefully designed clinical approach.[4–6]

Almost all (96%) of the infants in our cohort had mild disease. The two infants with severe disease, one with cyanotic heart disease and one who was otherwise healthy, had short, uneventful disease courses that only required supplemental oxygen. Studies have shown that COVID-19 is generally a mild disease in paediatric patients, but there is no consensus regarding the clinical course and appropriate approach to infants under 60 days old. Our findings agree with other studies of COVID-19 characteristics in young infants. Ouldali et al. described the clinical course and outcomes of 145 hospitalised children under 90 days old with COVID-19 and only 3% had severe disease.[11] Fever was the most common symptom (92%), and most infants were hospitalised due to the increased risk of SBIs in infants of this age. No fatalities were reported. The authors did not report the rate of SBIs. Lu et al described neonates aged five, 17 and 30 days old with mild COVID-19, with mainly respiratory tract symptoms.[12] A review concluded that COVID-19 left young children and neonates with minimal or no symptoms.[13] Nathan et al. studied five neonates under three months of age with confirmed COVID-19 and reported that two under 60 days old only required acetaminophen.[14] The clinical course was rapidly favourable, they were discharged within one to two days of admission and none had concomitant SBI. An early Chinese report found that only one of nine infants with COVID-19 hospitalised under one year of age was under 60 days old. None required mechanical ventilation or intensive care, and there were no complications.[15]

However, our findings contradict other studies. An early pandemic study by Dong et al. described the epidemiology of 2135 Chinese children with COVID-19, including 85 under one year of age. They reported that 1.9% were critically ill, with acute respiratory distress syndrome or respiratory failure, shock or organ dysfunction. The authors suggested that this indicated that infants under the age of one were more vulnerable than older children. However, the exact number of neonates was not available.[8]

[1]WBC—white blood cells; ANC—absolute neutrophil count; ALC—absolute lymphocyte count

TABLE 1 Demographic, clinical and outcome characteristics of paediatric COVID-19 in infants under 60 days of age[1]

		Results
Demographics	Age in weeks, median (range)	4.0 (0. 5–8.0)
	Male sex, *n* (%)	38 (40)
Caregiver COVID−19 status, *n* (%)	Positive	36 (48)
	Not available	39 (52)
Past medical history, *n* (%)	Unremarkable postnatal course	63 (84)
	Prematurity	2 (3)
	Chronic disease/congenital anomaly	8 (11)
	Prior hospitalisation	4 (5)
	Prior antibiotic treatment	3 (4)
Clinical presentation		
n (%) Symptoms	cough	12 (16)
	Rhinorrhoea	18 (24)
	Shortness of breath	1 (1)
	Somnolence/Irritability	8 (11)
	Decreased intake	6 (8)
	Diarrhoea	6 (8)
	Rash	3 (4)
n (%)	Well appearing	72 (96)
General appearance	Ill-appearing	3 (4)
n (%)	None	73 (97)
Respiratory support	Non-invasive oxygen supplementation	2 (3)
	Mechanical ventilation	0 (0)
	Hypoxemia	1 (1)
Fever	Length of fever days (mean, SD)	1.3, 0.6
	Maximal fever, Celsius (mean, SD)	38.4, 0.6
Laboratory findings		Median (Range)
	WBC (K/micL)	8.4 (3–20.6)
	ANC (K/micL)	2.7 (0.2–10.7)
	ALC (K/micL)	3.5 (1.06–12.0)
	CRP (mg/dL)	0.3 (0.01–10.5)
Antibiotic or antiviral treatment, *n* (%)	Received antibiotics	58 (77)
	Received Acyclovir	1 (1)
SBI, *n* (%)	UTI	7 (10)
	Pneumonia	0 (0)
	Meningitis	0 (0)
	Bacteraemia	0 (0)
	Enterocolitis	1 (1.3)
Other	ICU admission	0 (0)
	Length of admission, days, median (range)	2.0 (1–13)

Kanburoglu et al. studied 37 neonates of less than 28 days old with COVID-19 admitted to a Turkish neonatal intensive care unit and reported a high rate of respiratory support requirements: supplemental oxygen (41%), non-invasive ventilation (16%) and mechanical ventilation (3%).[16] Hospitalisation was prolonged at a median of 11 days. The majority had severe or critical disease (43%) and only 27% had mild disease.[16] It was notable that none of our infants required invasive respiratory support or intensive care and only one received antiviral therapy until negative results were obtained. The differences between various studies may stem from several factors: prematurity, concomitant SBIs or the setting. For example, the Kanburoglu et al study was conducted in a neonatal intensive care unit and only included neonates aged ≤28 days with respiratory distress or feeding difficulties, admitted to rule out bacterial sepsis.[16] Other population characteristics and genetic factors may also play a role. In addition, many reports were case series where complication rates could not be determined due to selection bias.[17]

During the last few decades, several risk stratification protocols have been published to identify young febrile infants at high risk for SBIs. The Rochester criteria were introduced to help clinicians decide whether neonates up to 90 days old were low or high risk for SBIs. These have been adopted in many countries, including Israel. The criteria are very sensitive, but not specific, and the goal is to discharge low-risk patients without antibiotic treatment. In our study, 44% of infants had a high risk for SBIs according to the Rochester criteria. Yet the actual rate for SBIs in our cohort (11%) was in accordance with rates in the literature, and no cases of bacteraemia or meningitis were reported.[19] It is notable that CRP is not part of the Rochester criteria, but studies indicate that this valuable laboratory test can assess hospitalised febrile infants aged ≤3 months. Furthermore, a CRP of ≥2 mg/dl had better sensitivity and specificity for SBIs than the classic predictor of leukocyte count <5000/micL or >15,000/micL.[18] Indeed, all our infants with a CRP of ≥2 mg/dl had concomitant SBI. These findings indicate that COVID-19 does not predispose young infants to bacterial co-infection, similar to older children.[10,20,21]

4.1 | Strengths and limitations

The main strength of this study was its multicentred and prospective approach. The national guidelines for evaluating fever in neonates and infants under 90 days old in Israel are well defined and allow limited variability. They recommend a comprehensive investigation, including referral to the emergency department for clinical assessment, laboratory evaluation and very often hospitalisation. Thus, we believe that this study permitted good estimations of the characteristic course of COVID-19 infections in young infants in Israel, even though it was carried out in inpatient settings.

Our study had several limitations. Our sample size meant that specific clinical recommendations could not be made. However, the prospective multicentre nature of this study, and the well-defined guidelines for evaluating fever, allow important insights into the natural course and outcome of COVID-19 in young infants under 60 days old. Another limitation was that the study population only included COVID-19 patients who were febrile.

5 | CONCLUSION

Our data suggest that the clinical course and outcomes of infants under 60 days of age with COVID-19 closely resembled other respiratory viral aetiologies for neonatal fever. Furthermore, this age group was not associated with an increased risk of secondary SBIs. Large, prospective studies are needed to develop clinical management recommendations for COVID-19 in this age group.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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