

Original Article



Clinical Presentation and Prognosis of SARS-CoV-2 Infection in Infants Aged ≤90 Days: Insights for Management During Outbreaks

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ABSTRACT

Purpose: Infants aged ≤90 days with fever are susceptible to severe infections. This study aimed to analyze the clinical features of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in this particular age group.

Methods: Infants aged ≤90 days who were diagnosed with coronavirus disease 2019 (COVID-19) and hospitalized between March 1, 2020, and May 1, 2022 were included. Medical records of patients were retrospectively reviewed.

Results: A total of 105 infants with COVID-19 were included; 27 (25.7%) neonates aged <28 days, and 48 (45.7%) and 30 (28.6%) infants aged 28–59 days and 60–90 days, respectively. Five (4.7%) patients remained asymptomatic and 68 (62.8%) were febrile, with a median fever duration of 2 days. The most common symptoms were respiratory including cough (66.6%), nasal stuffiness (51.4%), and rhinorrhea (40.9%). Blood cultures were performed in 10 infants but no organisms were detected. Cultures of bag-collected urine specimens from 8 infants were grown, resulting in positive growth for 2 without pyuria. Nine (8.6%) infants were treated with empirical antibiotics for a median duration of 2.3 days (range, 1–7 days). All 105 infants showed improvement without any complications, and there were no fatal cases.

Conclusions: In this study, most infants aged ≤90 days with COVID-19 presented with mild symptoms and none of those evaluated had documented bacterial co-infection. The favorable prognosis among young infants with SARS-CoV-2 may aid clinicians in tailoring their approach to evaluation and management during outbreaks.

Keywords: COVID-19; SARS-CoV-2; Neonatal sepsis; Co-infection; Bacterial infections

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread globally and coronavirus disease 2019 (COVID-19) has affected all ages, including young children. As of December 1, 2022, a total of 2,885,438 cases of COVID-19 have occurred in children <10 years of age, with only 34 deaths (case fatality rate: 0.001%) in Korea.¹⁾ Most pediatric patients with COVID-19 have mild symptoms such as fever and upper respiratory

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: Moon HJ, Han MS; Data curation: Moon HJ, Kim KM, Oh KJ, Chang JY, Lee SY, Choi JE; Formal analysis: Moon HJ; Investigation: Moon HJ; Methodology: Moon HJ; Resources: Kim KM, Oh KJ, Chang JY, Lee SY, Choi JE; Supervision: Han MS; Writing - original draft: Moon HJ; Writing - review & editing: Han MS.

manifestations. Rarely, some children show severe respiratory failure or multi-organ injury during the acute phase of infection.²⁾

Among children, young febrile infants at or under 90 days of age are at increased risk of bacterial infection.³⁾ Therefore, most febrile young infants, especially those with a toxic appearance, undergo extensive testing to rule out severe bacterial infection unless a definite focus of fever is present. Work-up for sepsis includes a blood count with differential, blood culture, urine analysis, urine culture, analysis and culture of cerebrospinal fluid (CSF) samples, and chest radiograph.⁴⁾ Empirical antibiotics are often administered until culture results are available. However, this screening approach is very low yield in febrile young infants with respiratory syncytial virus or influenza infection during seasonal outbreaks.^{5,6)} It remains unclear whether routine laboratory evaluation is absolutely necessary in SARS-CoV-2 infected young infants during the COVID-19 pandemic.

When infected with SARS-CoV-2, infants at or under 90 days of age are often febrile and may only have fever. This study aimed to analyze the clinical manifestations of SARS-CoV-2 in this particular age group and further discuss whether full evaluation for bacterial sepsis and empirical antibiotic administration are necessary in young infants with confirmed SARS-CoV-2 during COVID-19 outbreaks.

MATERIALS AND METHODS

1. Study population

This study included infants aged ≤ 90 days who were diagnosed with COVID-19 and admitted to Seoul Metropolitan Government-Seoul National University Boramae Medical Center between March 1, 2020 and May 1, 2022. Infants were tested for COVID-19 if they presented with expected symptoms or a history of close contact with a confirmed patient. COVID-19 was diagnosed if real-time reverse transcription-polymerase chain reaction or lateral flow antigen testing performed on a nasopharyngeal swab sample was positive for SARS-CoV-2.

2. Data collection

The medical records of the study population were retrospectively reviewed and data on clinical features and laboratory tests were obtained. Clinical data reviewed included the following: sex, age, underlying disease, symptoms and signs, clinical diagnosis, laboratory test results, radiological examinations, and treatment. Leukopenia was defined as a total white blood cell count of $< 4,000/\mu\text{L}$. Lymphopenia was defined as an absolute lymphocyte count of $< 1,500/\mu\text{L}$, and neutropenia was defined as an absolute neutrophil count of $< 1,000/\mu\text{L}$. Liver transaminase levels were elevated when aspartate transaminase or alanine transaminase levels were more than 3 times the upper limit of the normal range. Young infants who were not well-appearing or considered at risk for bacterial co-infection were evaluated, by the discretion of physician in charge, with blood culture, urine culture, or CSF culture. This study was approved by the Institutional Review Board (IRB) of the Seoul Metropolitan Government-Seoul National University Boramae Medical Center (IRB No. 20-2022-52) and the requirement for informed consent was waived.

3. Classification of patients

Infants with COVID-19 were classified as having mild, moderate, or severe disease based on their symptoms, signs, and radiological findings. Children with mild COVID-19 are

asymptomatic or have symptoms that do not require oxygen supplementation. Moderate cases were defined as those requiring oxygen supplementation, and severe cases were defined as those in which noninvasive or invasive mechanical ventilation was needed.

4. Statistical analysis

Frequencies and percentages were used to describe patient demographics, symptoms, signs, clinical diagnoses, COVID-19 severity, and treatments. Medians and range were used to describe fever duration, laboratory findings, and duration of antibiotic administration.

RESULTS

1. Clinical features of COVID-19 in young infants aged ≤90 days

A total of 105 infants with COVID-19 aged ≤90 days were admitted during the study period. Twenty-seven (25.7%) cases were neonates aged <28 days, and 48 (45.7%) and 30 (28.6%) infants were aged 28 to 59 days and 60 to 90 days, respectively (**Table 1**). Most young infants included in the study had no underlying medical condition, 10 (9.5%) were born preterm, and 2 (1.9%) had congenital heart disease.

Among the 105 infants with COVID-19, 5 (4.7%) remained asymptomatic throughout the hospital admission period (**Table 2**). Symptomatic patients exhibited a variety of symptoms and signs. Sixty-eight (62.8%) infants were febrile, with a median fever duration of 2 days (range, 1–10 days). The most common symptoms were respiratory manifestations including cough (66.6%), nasal stuffiness (51.4%), and rhinorrhea (40.9%). Ten (9.5%) infants showed gastrointestinal symptoms such as diarrhea (5.7%) and vomiting (3.8%), 4 (3.8%) patients had skin rash, and one (0.9%) had convulsions. When assessed clinically, 2 (1.9%) patients were diagnosed with croup, while pneumonia, febrile seizure, and erythema multiforme were diagnosed in one (1.0%) patient each. All patients but one were classified as having mild COVID-19 (**Table 2**).

There were 3 neonates aged <7 days who were all born to mothers with COVID-19 at delivery. Only one neonate had a fever of 38.6°C, but the fever resolved naturally without antipyretics.

2. Laboratory evaluation of infants with COVID-19 aged ≤90 days

Ninety-three infants underwent examination (**Table 2**). Leukopenia was observed in 4 (4.3%) infants, whereas only one (1.0%) infant had lymphopenia. Neutropenia was observed in 39 (41.9%) infants. The median level of C-reactive protein was 0.04 mg/dL (range, 0.01–0.75

Table 1. Demographic data of 105 young infants with coronavirus disease 2019 aged ≤90 days

Variables	No. (%)
Sex	
Male	55 (52.3)
Female	50 (47.7)
Age, median (range), day	48 (1–90)
<28	27 (25.7)
28–59	48 (45.7)
60–90	30 (28.6)
Underlying medical condition	
None	103 (98.1)
Preterm birth	10 (9.5)
Congenital heart disease	2 (1.9)

Table 2. Clinical manifestations and laboratory findings of young infants aged ≤ 90 days with COVID-19

Variables	No./Total No. (%)
Symptoms and signs	
None	5/105 (4.7)
Fever ($\geq 38.0^{\circ}\text{C}$)	68/105 (62.8)
Fever duration, median (range), day	2 (1–10)
Cough	70/150 (66.6)
Sputum	20/105 (19.0)
Rhinorrhea	43/105 (40.9)
Nasal stuffiness	54/105 (51.4)
Diarrhea	6/105 (5.7)
Vomiting	4/105 (3.8)
Skin rash	4/105 (3.8)
Seizure	1/105 (0.9)
Clinical diagnosis	
Croup	2/105 (1.9)
Pneumonia	1/105 (1.0)
Febrile seizure	1/105 (1.0)
Erythema multiforme	1/105 (1.0)
COVID-19 severity	
Mild	104/105 (99.0)
Moderate	1/105 (1.0)
Severe	0/105 (0.0)
Laboratory findings	
WBC count, median (range), $/\mu\text{L}$	8,025 (3,110–19,470)
ALC, median (range), $/\mu\text{L}$	5,412 (1,175–11,074)
ANC, median (range), $/\mu\text{L}$	1,175 (237–9,501)
Leukopenia	4/93 (4.3)
Lymphopenia	1/93 (1.0)
Neutropenia	39/93 (41.9)
Platelet, median (range), $\times 10^3/\mu\text{L}$	394 (118–752)
AST, median (range), IU/L	44.5 (20–376)
ALT, median (range), IU/L	27 (5–467)
Elevated liver transaminases	8/93 (8.6)
CRP, median (range), mg/dL	0.04 (0.01–0.75)
Positive blood culture	0/10 (0.0)
Positive urine culture	2/8 (25.0)
Treatment	
None	96/105 (91.4)
Systemic antibiotics	9/105 (8.6)
Duration of antibiotics, median (range), day	2.3 (1–7)

Abbreviations: COVID-19, coronavirus disease 2019; WBC, white blood cell; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; AST, aspartate transaminase; ALT, alanine aminotransferase; CRP, C-reactive protein.

mg/dL). Blood cultures were performed in 10 infants for the evaluation of possible sepsis, resulting in the growth of no organisms. Cultures of bag-collected urine specimens from 8 infants revealed that 2 had positive growth without pyuria, indicating contamination or asymptomatic bacteriuria. CSF exam was performed in none of the infants.

Among the 105 infants considered, intravenous antibiotics were empirically administered to 9 (8.6%) for a median duration of 2.3 days (range, 1–7 days). The remaining 96 (91.4%) infants did not receive antibiotics, antiviral agents, or corticosteroids. All 105 infants showed improvement without any complications and there were no fatal cases.

DISCUSSION

In this study, most infants aged ≤ 90 days with COVID-19 had mild symptoms and outcomes were favorable. Fever and respiratory symptoms were commonly observed, with only a few patients developing croup, pneumonia, febrile seizure, or erythema multiforme. Previous studies have reported that most young infants with COVID-19 either have mild symptoms or are asymptomatic. A case series examining pediatric COVID-19 cases from the Republic of Korea and a systematic review from Italy showed that almost all neonates with COVID-19 have mild respiratory symptoms typical of acute viral infection.^{7,8)} Most children with COVID-19 present with symptoms such as fever, cough, and rhinorrhea.⁹⁾ Several abnormalities on laboratory examinations were found in this study, as have been seen in previous reports such as leukopenia (4.3%), lymphopenia (1%), neutropenia (41.9%), and elevated liver transaminase levels (8.6%). However, the abnormalities did not seem to indicate clinical severity in patients.¹⁰⁾

All of the young infants with COVID-19 improved without complications, and there was no documented bacterial co-infection in those who were evaluated for invasive bacterial infection in this study. Evaluation of bacterial sepsis is commonly performed in febrile infants aged ≤ 90 days, especially neonates. Laboratory assessment includes cultures of blood, urine, and occasionally CSF samples from high-risk patients. Empirical antibiotics are frequently administered until infants are well and blood cultures are confirmed to be sterile. However, risk of serious bacterial infection is low in febrile infants with concomitant respiratory viral infections and bacteremia is very rare.⁵⁾ A single-center study conducted in the United States reported that febrile infants aged < 90 days with SARS-CoV-2 infection had lower rates of serious bacterial infection than those without (8% vs. 34%, $P=0.001$).¹¹⁾ The most common bacterial infection in SARS-CoV-2-positive infants was urinary tract infection (6%), and none had bacteremia or bacterial meningitis. Other similar studies observed no cases of bacteremia in infants aged ≤ 90 days with COVID-19.^{12,16)} The most recent prospective study performed in Canada also demonstrated no documented bacteremia among infants with SARS-CoV-2.¹⁷⁾ Serious bacterial infections in young infants with COVID-19 was similar to that with other respiratory viruses before the COVID-19 pandemic, and infections were mostly limited to those of the urinary tract.¹⁸⁾

Meanwhile, neonates, especially those aged < 7 days, are still at risk for early-onset sepsis, and young infants with certain underlying medical conditions may be prone to bacterial sepsis. Case reports have reported bacteremia in preterm infants with COVID-19.^{19,20)} One infant with Shwachman-Diamond syndrome developed *Streptococcus mitis* bacteremia.²¹⁾ In this study, there was one febrile neonate aged 2 days with SARS-CoV-2 infection. The neonate suffered from stuffy nose and experienced a fever once, which subsided naturally. As a result, evaluation for bacterial infection was withheld. However, a work-up for bacterial sepsis may be still warranted in risk groups when febrile, even with a positive SARS-CoV-2 result, hence evaluation and management decisions need to be individualized. Larger prospective studies are necessary to ascertain risk factors for bacterial co-infection in young infants with SARS-CoV-2 and to evaluate the utility and necessity of obtaining cultures from various specimens alongside the administration of empirical antibiotics.

Our study had several limitations. First, the study sample was small and from a single institution, which limits the generalizability of our findings. Second, only ten infants were evaluated for sepsis via blood culture. However, the fact that all infants whose blood was not

cultured also improved well without the administration of antibiotics may imply that bacterial sepsis is in fact very rare in infants infected with SARS-CoV-2.

In conclusion, most young infants aged ≤ 90 days with SARS-CoV-2 infection presented with mild symptoms and none of those evaluated had documented bacterial co-infection. The favorable prognosis and the very low risk of invasive bacterial infections among young infants with SARS-CoV-2 may aid clinicians in tailoring their approach to evaluation and management during outbreaks, especially when tests for SARS-CoV-2 are readily available.

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요약

목적: 발열이 있는 생후 90일 이하의 영아에게는 심각한 감염의 위험이 높다. 본 연구는 코로나바이러스감염증-19 감염증(코로나19)이 발생한 90일 미만의 영아의 임상적 특징을 분석하기 위해 진행되었다.

방법: 2020년 3월 1일부터 2022년 5월 1일까지 코로나19로 진단받고 입원한 생후 90일 이하 영아의 의무기록을 후향적 연구로 검토하였다.

결과: 총 105명의 영아가 포함되었으며, 이 중 27명(25.7%)은 생후 28일 미만 신생아, 48명(45.7%) 및 30명(28.6%)는 각각 생후 28-59일과 60-90일 사이의 영아였다. 이 중 5명(4.7%)은 무증상이었고, 68명(62.8%)은 발열이 있었으며, 평균 발열 기간은 2일이었다. 가장 흔한 증상은 기침(66.6%), 코 막힘(51.4%), 콧물(40.9%) 등 호흡기 증상으로 확인되었다. 총 10명의 영아에서 혈액배양검사가 시행되었으나 균은 동정되지 않았다. 8명의 영아에서 채노백을 이용하여 소변 검사를 시행하였고 2명에게서 농뇨는 없었으나 세균이 배양되었다. 9명(8.6%)의 영아가 경험적 항생제를 투약 받았으며, 투약 기간의 중간값은 2.3일(범위, 1-7일)이었다. 모든 105명의 영아들은 합병증 없이 증상이 호전되었으며, 사망 사례 또한 없었다.

결론: 본 연구에서 코로나19로 진단된 90일 이하의 영아들 대부분이 경미한 증상을 보였으며, 배양 검사가 시행된 환자들에게서 세균 동시감염은 없었다. 이러한 결과는 임상 의들이 코로나19 유행기 동안 코로나바이러스 감염이 있는 어린 영아들에게 적절한 검사를 시행하고 치료하는 데에 도움이 될 수 있을 것이다.