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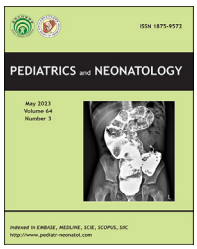

Original Article

# Critically ill infants with SARS-COV-2 delta variant infection

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acute respiratory distress syndrome;
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*Background:* SARS-CoV-2 is described to cause mild to moderate symptoms in children. To date, clinical data and symptoms of the Delta variant in pediatric patients are lacking.
*Aim:* To describe clinical characteristics and outcomes of infants admitted in the pediatric intensive care unit (PICU) during the period of Delta variant predominance.
*Methods:* We performed a retrospective study, between June 23, 2021 and August 16, 2021. We included children aged under 15 years, admitted to PICU with severe and critical form of SARS-CoV-2 infection as confirmed by RT-PCR. We reviewed medical records for all patients.
*Results:* During the study period, 20 infants were included. The median age was 47 days (IQR: 26.5—77). The sex ratio was 0.8 (9 males). No underlying medical conditions were noted. Parents were not vaccinated. Respiratory involvement was the main feature to be observed in our cohort. Eleven patients had pediatric acute respiratory distress (PARDS) with a median oxygen saturation index (OSI) of 9 (IQR: 7—11). PARDS was mild in 4 cases, moderate in 5 cases and severe in 2 cases. Hemodynamic instability was observed in 4 cases. The main radiological finding was ground glass opacities in 11 cases. Seventeen patients were mechanically ventilated and 3 of them were escalated to high-frequency oscillatory ventilation. The median duration of mechanical ventilation was 6 days (IQR 2.5—12.5). The remaining patients were managed with high flow nasal cannula. Four patients died.
*Conclusion:* We report herein a case series of very young infants, with no comorbidities, and with a life-threatening illness due to SARS-CoV-2 Delta variant.

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## 1. Introduction

Severe acute respiratory syndrome-coronavirus type 2 (SARS-COV-2 or COVID-19) was initially detected in Wuhan, Hubei province, China in December 2019.[1] It spread rapidly throughout the world and was later declared a pandemic by the World Health Organization (WHO).[2] In Tunisia, the first COVID-19 confirmed case was reported on March 2, 2020.[3]

The disease was described to cause acute respiratory illness in adults, while children were known to have milder symptoms.[4,5] The frequency of severe and critical illness was 7%,[5] which was lower than that in adults (25,6%). Nevertheless, little is known about the course of the disease in children because there is insufficiency and inaccessibility of the data with respect to outcome of COVID-19 Delta variant in children.

The first cases of the SARS-COV2 Delta variant, also called B1.617.2, were detected in India in April 2021 and led to a new wave.[6] This variant posed the biggest risk for countries with limited access to vaccination. The Tunisian national observatory of new and emerging diseases (ONMNE) confirmed the first cases of delta variant on June 23, 2021.[7,8] The Delta variant had catalyzed the fourth wave in our country. At the time of writing, Tunisia recorded 1 114 370 confirmed SARS-CoV-2 infection cases with 28 942 deaths.[9] The proportion of pediatric population (under 18 years old) was 4.13% and 119 deaths were recorded.[10] During the study period (June 23, 2021 and August 16, 2021), the incidence rate of SARS-CoV-2 infection among children was 633.21 per 100 000: 322 [0—5 years], 398.35 [5—10 years], 773.47 [10—15 years], and 1697.45[15—18years].[10]

During previous waves, only three older children were admitted to our PICU, which is the main referral center for critically-ill children in Tunisia. Here, we report a cluster of young infants with critical illness due to the SARS-CoV-2 Delta variant, without underlying health conditions, to increase the knowledge of the critical form of SARS-CoV-2 infection in children.

## 2. Methods

### 2.1. Study design and participants

We carried out a retrospective study, between June 23, 2021 and August 16, 2021 in a single-center PICU of a children's hospital of Tunis, Tunisia. Our hospital is the only pediatric hospital in the country.

We included all critically-ill children aged under 15 years with a confirmed case of COVID-19, defined as a real time reverse-transcriptase polymerase chain reaction (RT-PCR) positive result testing of a specimen collected on a nasopharyngeal swab. SARS-CoV-2 detection was performed using the 2019-nCoV Real-Time RT-PCR assay (WANDFO®, China) in the Light Cycler 480II Real-Time PCR System (Roche) or EurobioPlex SARS-CoV-2 Multiplex (Eurobio Scientific®, France) in Rotor Gene Q (Qiagen). Multiplex PCR was also performed for detection of concomitant viral respiratory infection using QIAstat-Dx Respiratory SARS-CoV-2 Panel, Qiagen® and Respifinder 2Smart, Pathofinder®. We used the WHO classification to identify the disease severity degrees.[11] We excluded patients admitted to the COVID-19-PICU for a suspected COVID-19 infection with a moderate illness or a negative RT-PCR or if no RT-PCR was performed.

### 2.2. Data collection

We reviewed the medical records of all patients who were admitted during the study period with the diagnosis of COVID-19 infection confirmed by RT-PCR. Patients' data included demographic and clinical characteristics and laboratory test results. Thoracic Imaging (chest X-ray or computed tomography (CT) scan of the chest) was evaluated by the pediatric radiologist of our hospital for the following: parenchymal lung abnormalities (consolidations, ground glass opacities (GGO)) and pleural abnormalities including pneumothorax and pleural effusion.

Pediatric Acute Respiratory Distress Syndrome (PARDS) was diagnosed according to the pediatric lung injury consensus conference (PALICC) definition.[12]

Organ dysfunction and severity of illness were assessed by pediatric logistic organ dysfunction (PELOD-2) score.[13] ICU interventions were collected (need for mechanical ventilation or noninvasive ventilation, vasoactive drugs, corticosteroid therapy). Outcomes were recorded (bacterial coinfection, complications, mortality, duration of mechanical ventilation, length of stay).

We noted vaccination status of infants' mothers and history of COVID-19 during pregnancy. On admission, RT-PCR was performed for infants' parents for detection of SARS-CoV-2 infection.

### 2.3. Data analysis

Descriptive statistics were used for all variables. Continuous data were expressed as median and range values (25—75), while categorical data were presented as number (n).

### 2.4. Ethical considerations

The Ethical Committee of the Children's Hospital (Approval number13/2021) approved the study. We obtained written consent from children's parents before extracting data.

## 3. Results

From June 23, 2021 to August 16, 2021, 27 patients required intensive care at COVID-19-PICU with a diagnosis of highly suspected COVID-19 infection. We excluded 7 patients: 3 patients due to negative RT-PCR test results, 3 other children because of non-performance of RT-PCR, and one patient who had a moderate form of COVID 19 not requiring supportive therapy. We analyzed the data of twenty patients without underlying medical conditions. The mean cycle threshold value when the patients were admitted to PICU was 27.1 ± 5.2 with extremes between 15 and 35.

None the infants' mothers were vaccinated, and they did not have history of SARS-CoV-2 infection during pregnancy. Parental RT-PCR confirmed COVID-19 in 12 cases, including 9 mothers and 3 fathers.

During the study period, 99 children were admitted in our hospital with positive SARS-CoV-2 PCR test. Among these children, 72% were under five years old, 14% between 5 and 10 years and 7% were older than 10 years old. Most of them (63%) were aged under 12 months of age. Severe and critical forms were observed in 37% of cases. Mild to moderate symptoms were noted in the others. The rate of PICU admission was 20% (20/99).

### 3.1. Demographic data and clinical features (Table 1)

The median age was 47 days (IQR: 26.5–77 days). The sex-ratio was 0.8 (9 male/11 female). The median weight was 4555 g (IQR: 3022–5033) and the median percentile was 32.9 (IQR: 5.3–60.3). Fourteen patients had a critical form of COVID-19 infection, and 6 had a severe form according to the disease severity degrees. Respiratory involvement was the main feature to be observed in our cohort. Eleven patients had PARDS with a median oxygen saturation index (OSI) of 9 (IQR: 7–11). PARDS was mild in 4 cases, moderate in 5 cases and severe in 2 cases. Hemodynamic instability was observed in 4 cases at admission. One patient had a cardiac dysfunction with signs of pulmonary arterial hypertension on the trans-thoracic echocardiography (ETT) findings.

During the first 24 h of hospital stay, the PELOD2 score was calculated for each patient. The estimated risk of mortality is noted in Table 1 (See Table 2).

### 3.2. Paraclinical findings

Laboratory test findings showed an increased level of CRP in 6 cases and lymphopenia in 18 cases. Increased D-dimer levels were noted in 10 cases.

The main radiological finding was GGO in 11 cases. A CT scan was only performed in 3 patients and found GGO in 2 cases and abundant pleural effusion in one case.

Bacterial coinfection was confirmed in 5 patients: Methicillin-sensitive *Staphylococcus aureus* (MSSA) in 3 cases, *Haemophilus influenzae* type b in 1 case and *Streptococcus pneumoniae* in the last one, all of which were isolated on tracheal swab samples. No concomitant respiratory viral infections were reported.

**Table 1** Demographic data and clinical features of patients with severe and critical COVID-19 infection.

| | Total cohort (N = 20) | Severe COVID-19 infection (n = 6) | Critical COVID-19 infection (n = 14) |
|---|---|---|---|
| Median Age (IQR) | 47 (26.5–77) | 71.5 (48.75–349.25) | 36.5 (19.7–59) |
| (Days) < 28 days | 6 | 0 | 6 |
| Female sex (n) | 11 | 3 | 8 |
| Signs and symptoms before PICU admission: (n) | | | |
| Fever | 19 | 6 | 13 |
| Cough | 5 | 2 | 3 |
| Dyspnea | 20 | 6 | 14 |
| Diarrhea and vomiting | 8 | 2 | 6 |
| Poor oral intake | 19 | 5 | 14 |
| Lethargy | 11 | 1 | 10 |
| Median delay between onset symptoms and PICU admission (days) (IQR) | 6 (4.25–7.75) | 6 (3.25–7.25) | 6.5 (4.5–8) |
| Reason for PICU admission: | | | |
| Hypoxia (n) | 17 | 6 | 11 |
| Hemodynamic instability (n) | 3 | – | 3 |
| median PELOD 2 risk of mortality % (IQR) | 1.4 (0.6–2.2) | 0.85 (0.1–1.4) | 1.8 (0.9–3.5) |
| Respiratory failure (n) | 14 | – | 14 |
| Median OSI (IQR) | 7 (3.75–9.7) | 1.5 (0.1–7.2) | 8.5 (6–11.5) |
| Median SF ratio (IQR) | 176.5 (151.5–233.25) | 318 (168.5–407.5) | 162 (143–208) |
| ARDS (n) | 11 | – | 11 |
| Hepatic dysfunction (n) | 6 | 0 | 6 |
| Renal dysfunction (n) | 2 | 0 | 2 |

IQR: interquartile range; PELOD 2: Pediatric Logistic Organ Dysfunction 2 Score; OSI: oxygen saturation index; SF ratio: Spo2/Fio2 ratio; ARDS: acute respiratory distress syndrome.

**Table 2** Biological and radiological findings.

| | Total cohort (N = 20) | Severe COVID-19 infection (n = 6) | Critical COVID-19 infection (n = 14) |
|---|---|---|---|
| Leucocyte count (cells/μL) Median (IQR) **(Ref: 6000–15000 cells/μL)** | 6805 (2875–8582) | 7350 (4445–10745) | 6075 (2630–8147) |
| lymphocyte count (cells/μL) Median (IQR) **(Ref: 3400–6000 cells/μL)** | 1825 (972–2867) | 2445 (1430–3152) | 1585 (867.5–2455) |
| platelet count (103) Median (IQR)] **Ref:50000–450000** | 272 (239–360) | 379.5 (325.5–522.2) | 259 (220–307) |
| C reactive protein (mg/L) Median (IQR) **(Ref: 0.0–0.9 mg/L)** | 12.5 (3.5–54.7) | 29.5 (12.7–156.7) | 7.5 (1.7–34) |
| Procalcitonin (ng/mL) Median (IQR) (Ref:0.0–0.1 ng/mL) | 0.56 (0.12–90) | N/A | 1.28 (0.12–95) |
| D-dimer (ng/mL) Median (IQR) (Ref:0.0–500 ng/mL) | 1006 (850–2500) | N/A | 1006 (880–2655) |
| Fibrinogen (g/L) Median (IQR) (Ref:2–4 g/L) | 3.9 (1.64–3.92) | N/A | 2.7 (1.64–2.78) |
| X-chest ray findings: | | | |
| Unilateral consolidations (n) | 7 | 2 | 5 |
| Bilateral consolidations (n) | 6 | 1 | 5 |
| Unilateral GGO (n) | 7 | 3 | 4 |
| Bilateral GGO (n) | 11 | 2 | 9 |
| Pleural effusion (n) | 3 | 1 | 2 |
| Pneumothorax (n) | 5 | 1 | 4 |

GGO: ground glass opacities, N/A: not available.

### 3.3. Intensive care management

Seventeen patients were mechanically ventilated, and 3 of them were escalated to high-frequency oscillatory ventilation due to refractory hypoxemia on conventional mechanical ventilation. All these patients needed neuromuscular blocking agents. Prone positioning (18/24 h) was used in 14 of them. The $FiO_2$ was higher than 60% in 11 patients for a median duration of 2 days (IQR: 2–3). Four patients required inhaled nitric oxide because of pulmonary arterial hypertension. The median duration of mechanical ventilation was 6 days (IQR 2.5–12.5 days).

The three remaining patients were exclusively managed with high flow oxygen therapy.

All patients received dexamethasone (0.15 mg/kg/day for 10 days). Viral therapy was not used in any patient. No patient received renal replacement therapy, extracorporeal membrane oxygenation, or prophylactic anticoagulation.

We observed the following complications in eight patients: pneumothorax (n = 4), acquired hospital infection (n = 6) and post intubation stridor (n = 3). Sixteen patients were discharged from PICU after a median length of stay of 10 days (IQR: 5–19). Four deaths occurred in our cohort. The causes were refractory hypoxemia in two cases, a refractory shock in one case and tracheal stenosis in the last case.

In the first year following discharge, none had developed multisystem inflammatory syndrome in children (MIS-C) or long COVID.

## 4. Discussion

In this study, we describe the clinical manifestations and outcomes of life-threatening forms of SARS-CoV-2 infection in pediatric patients admitted to our PICU, in July and August 2021, during the fourth wave catalyzed by the Delta variant. Severe and critical forms in young infants with a median age of 47 days were observed. Such forms occurring in young infants were not observed during the earlier waves in Tunisia. To our knowledge, these findings have not been reported previously in literature. It may be possible that non-vaccinated mothers transmit the virus to their young infants. Emerging variants of concern, such as the Delta variant, were responsible of serious illness in infants, more often occurring in countries with limited access to vaccination like Tunisia. In the first waves, we observed a critical disease in older children. In fact, among PICU admissions reported in literature, the majority of children were more than 11 years old.[14–17] In our study, there were 6 newborns, and the median age of our patients was lower than other studies, especially a US cohort with SARS-CoV-2 Delta variant (median age of 8 years).[18]

Underlying medical conditions, young age (<1 year) and obesity are known to be risk factors for critical illness in children.[5,15] A high percentage of the Canadian-American and French cohorts (83% and 70%, respectively) of critically-ill children had at least one comorbidity.[15,16] All our patients were previously healthy infants.

Fever, respiratory and gastrointestinal signs dominated symptoms prior to PICU admission in all cohorts.[5] In our patients, hypoxia was the main feature on admission. Seventeen patients presented with hypoxia and 4 patients with hemodynamic instability, which was in line with literature.[18] The life-threatening clinical presentation in our cohort could be explained by younger age, a long median delay between first symptoms and PICU admission (6 days), and the fact that most of the children had already started respiratory support by High Flow Nasal Cannula in pediatric departments before being transferred for worsening signs. The median delay between onset signs and PICU admission was longer than reports from other cohorts.[18,19]

PARDS was observed in eleven of 20 patients, in line with the adult case series (67%)[20] but less than that of the children reports.[21,22] Chest X-rays showed typical ground glass opacities and consolidations in 15 cases. Chao et al.[14] and Derespina et al.[21] reported 10 PARDS among 13 and 21 among 70 patients admitted to the PICUs, respectively. However, pleural effusion and pneumothorax at PICU admission were greater in our cohort. Derespina et al.[21] reported pneumothorax in one case and pleural effusion in 4 cases among 70 patients.

All our patients required respiratory support. In our study, the duration of MV was 6 days (IQR 2.5—12.5), which was similar to the US cohort.[18] Prone ventilation, which is routine in adults with COVID 19 infection, was used in 14 patients. There were reports about the prone position in children.[14,21]

There are several limitations to our study. It was retrospective study which was conducted in a single center with a small sample size. However, the study provides additional data about comorbidity-free children, hospitalized in PICU during a COVID-19 wave catalyzed by the Delta variant. To our knowledge, data from other countries that experienced the Delta variant with limited access to vaccination are missing. Future studies from other countries might enable a better understanding of severe and critical forms associated with variants of concern of SARS-CoV-2 in children.

## 5. Conclusion

To date, the characteristics of pediatric patients with the critical form of SARS-CoV-2 Delta variant in July and August 2021 are not well-described in countries with limited access to vaccination. Our study highlights the severity of illness compared to that documented in children admitted over first wave. In fact, the Delta variant seems to be more pathogenic for young infants.

## Declaration of competing interest

No conflict of interest.

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