


Severe and critical SARS-COV-2 delta variant infection in infants without underlying medical conditions

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Abstract

We report herein a case series of infants, with no comorbidities, who developed a life-threatening illness due to the SARS-CoV-2 Delta variant. We retrospectively reviewed the medical records of children, aged under 15 years, admitted to PICU, during the peak of Delta infection, between June 23 and August 16 2021, with severe and critical forms of SARS-CoV-2 infection, confirmed by RT-PCR. Twenty infants were included, the median age was 47 days (IQR: 26.5–77) and sex ratio was 0.8. No underlying medical conditions were noted. Parents were not vaccinated. Respiratory involvement was the main feature observed. Eleven patients had paediatric acute respiratory distress (PARDS) with a median oxygen saturation index (OSI) of 9 (IQR: 7–11). PARDS was mild in four, moderate in five, and severe in two 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 three 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.

KEYWORDS

acute respiratory distress syndrome, intensive care, mechanical ventilation, SARS-CoV-2

INTRODUCTION

Severe acute respiratory syndrome-coronavirus type 2 (hereby denoted as 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 02, 2020.³

The disease was described as causing acute respiratory illness in adults, while children were known to have milder symptoms.^{4,5} The frequency of severe and critical illness was 7%, which was lower than that in adults (25.6%). Nevertheless, little is known about the course of the disease in

children. In addition, outcome of the COVID-19 Delta variant in paediatric cases suffer from insufficiency and inaccessibility.

The first cases of the SARS-COV2 Delta variant, also called B.1.617.2, were detected in India in April 2021 and caused a ferocious wave.⁶ The biggest risk of a similar issue was for countries that have limited access to vaccination. The Tunisian national observatory of new and emerging diseases (ONMNE), confirmed the first cases of the delta variant on June 23, 2021.^{7,8} The delta variant has catalysed the fourth wave in our country.

In Tunisia, the population of children aged 0–15 years old is approximately 2.6 million, with about 589,671 in Tunis (22.1% of all the paediatric population in Tunisia).⁹

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Bécher Hamza Children's Hospital is the only paediatric hospital in the country with a bed capacity of 347. The paediatric intensive care unit (PICU) has 14 beds and has provided four beds for COVID-19 critically ill children since March 2020 and doubled up to eight beds since July 1, 2021.

During previous waves, only three older children were admitted to our PICU. We report herein a cluster of infants with critical illness due to the SARS-CoV-2 Delta variant and without underlying health conditions, to increase the knowledge of the critical form of COVID-19 infection in children.

METHODS

Study design and participants

We carried out a retrospective study, between June 23 and August 16, 2021, in our PICU. 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 degrees¹⁰: The severe form of COVID-19 infection was defined by the presence of severe respiratory distress and/or desaturation (SpO₂ <92% in ambient air) and/or intermittent cyanosis or apnea and/or systemic symptoms such as lethargy, dehydration, convulsions, or suspected sepsis. The critical form was defined by the presence of acute respiratory distress syndrome (ARDS), multiorgan failure, septic shock, or coma. 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 RT-PCR was not performed.

Data collection

We reviewed the medical records of all patients 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. Respiratory indices including the ratio of oxygen saturation (SpO₂) and fraction of inspired oxygen (S/F: SpO₂/FiO₂), and the oxygen saturation index (OSI) for children mechanically ventilated, calculated by the formulae: $([FiO_2 \times \text{mean airway pressure (Paw)} \times 100]/SpO_2)$, were used to assess hypoxemia. The worst variables (indices of oxygenation) were collected within the first 24 h of PICU

admission. Thoracic Imaging (Chest X-ray or Computed tomography [CT] scan of the chest) were evaluated by the paediatric radiologist of our hospital, for the following: parenchymal lung abnormalities (consolidations, ground glass opacities [GGO]) and pleural abnormalities including pneumothorax and pleural effusion.

Paediatric acute respiratory distress syndrome (PARDS) was diagnosed according to the paediatric lung injury consensus conference (PALICC) definition.¹¹

Organ dysfunction and severity of illness were assessed by paediatric logistic organ dysfunction (PELOD-2) scores.¹² ICU interventions were collected (need for mechanical ventilation or non-invasive ventilation, vasoactive drugs, corticosteroid therapy). Outcomes were recorded (bacterial coinfection, complications, mortality, duration of mechanical ventilation and length of stay).

Data analysis

Descriptive statistics were used for all variables. Continuous data were expressed as median and range values (25–75) and were analysed using the Student's *t*-test or Mann–Whitney *U* test. Categorical data were presented as numbers (*n*) and were analysed using the chi-square test or Fisher's test. *p* < 0.05 was considered statistically significant.

RESULTS

From June 23 to August 16, 2021, 27 children were admitted to our COVID-19-PICU with a diagnosis of highly suspected COVID-19 infection. We excluded seven patients: three patients due to negative RT-PCR test results, three other children because of non-performed RT-PCR and one patient who had a moderate form of COVID 19 not requiring supportive therapy. We analysed the data of 20 patients without underlying medical conditions. All the infants' mothers were not vaccinated.

Demographic data and clinical features

The median age was 47 days (IQR: 26.5–77 days) with extremes between 15 days and 6 years. The sex-ratio was 0.8 (9/11). The median weight was 4555 g (IQR: 3022–5033). Fourteen patients had a critical form of COVID-19 infection according to the disease severity degree with PARDS in 11 and shock in 3. Six patients had a severe form with severe respiratory distress and oxygen requirements. Respiratory involvement was the main feature observed in our cohort. Eleven patients had a PARDS with a median oxygen saturation index (OSI) of 9 (IQR:7–11). The PARDS was mild in four cases, moderate in five cases, and severe in two cases. Hemodynamic instability was observed in four cases at admission. Three of them had a bacterial coinfection with Methicillin-sensitive *Staphylococcus aureus* (MSSA).

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)	p Value
Median age (IQR) (days)	47 (26.5–77)	71.5 (48.75–349.25)	36.5 (19.7–59)	0.032
<28 days	6	0	6	0.11
Female sex (n)	11	3	8	1
Signs and symptoms before PICU admission: (n)				
Fever	19	6	13	1
Cough	5	2	3	0.6
Dyspnea	20	6	14	-
Diarrhoea	8	2	6	1
Poor oral intake	19	5	14	0.3
Lethargy	11	1	10	0.05
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)	0.53
Reason for PICU admission				
Hypoxia (n)	17	6	11	0.52
Hemodynamic instability (n)	3	-	3	0.5
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)	0.012
Respiratory failure (n)	14	-	14	-
Median OSI (IQR)	7 (3.75–9.7)	1.5 (0.1–7.2)	8.5 (6–11.5)	0.5
Median SF ratio (IQR)	176.5 (151.5–233.25)	318 (168.5–407.5)	162 (143–208)	0.009
ARDS (n)	11	-	11	0.04
Hepatic dysfunction (n)	6	0	6	1
Renal dysfunction (n)	2	0	2	0.1

Abbreviations: IQR, interquartile range; PELOD-2, Paediatric Logistic Organ Dysfunction 2 Score; OSI, oxygen saturation index; SF ratio, SpO₂/FiO₂ ratio; ARDS, acute respiratory distress syndrome.

One patient had a cardiac dysfunction with signs of pulmonary arterial hypertension on the trans-thoracic echocardiography (ETT) findings (Table 1).

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

Critical forms of COVID-19 were significantly associated with younger age (36.5 vs. 71.5 days, $p = 0.03$), higher OSI (58.5 vs. 1.5, $p = 0.009$), lower S/F ratio (162 vs. 318, $p = 0.04$), higher PELOD-2 risk of mortality (1.8% vs. 1.2%, $p = 0.04$) (Table 1).

Paraclinical findings

Laboratory test findings showed an increased level of CRP in 6 cases, lymphopenia in 18 cases and increased D-dimer levels were noted in 10 cases. Only platelet count was statistically significant between severe and critical forms, with a p value of 0.01 (Table 2).

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

Bacterial coinfection was confirmed in five patients: Methicillin-sensitive *Staphylococcus aureus* (MSSA) in three cases, *Haemophilus influenzae* in one case, and *Streptococcus pneumoniae* in the last one, all isolated on tracheal swab samples. No Concomitant respiratory viral infections were reported.

Intensive care management

Seventeen patients were mechanically ventilated, and three 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 FiO₂ 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.

TABLE 2 Biological and radiological findings

	Total cohort (N = 20)	Severe COVID-19 infection (n = 6)	Critical COVID-19 infection (n = 14)	p Value
Leucocyte count (cells/ μ l) Median (IQR) (Ref: 6000–15,000 cells/ μ l)	6805 (2875–8582)	7350 (4445–10,745)	6075 (2630–8147)	0.31
Lymphocyte count (cells/ μ l) Median (IQR) (Ref: 3400–6000 cells/ μ l)	1825 (972–2867)	2445 (1430–3152)	1585 (867.5–2455)	0.24
Platelet count (10^3 / μ l) Median (IQR) (Ref: 50,000–450,000)	272 (239–360)	379.5 (325.5–522.2)	259 (220–307)	0.013
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)	0.57
Procalcitonin (ng/ml) Median (IQR) (Ref: 0.0–0.1 ng/ml)	0.56 (0.12–90)	N/A	1.28 (0.12–95)	0.55
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	1
Bilateral consolidations (n)	6	1	5	0.63
Unilateral GGO (n)	7	3	4	0.61
Bilateral GGO (n)	11	2	9	0.33
Pleural effusion (n)	3	1	2	1
Pneumothorax (n)	5	1	4	1

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

None received renal replacement therapy, extracorporeal membrane oxygenation, or prophylactic anticoagulation.

We observed the following complications in eight patients: pneumothorax ($n = 4$) due to barotrauma, 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; secondary to bilateral pneumothorax due to late PICU transfer in one patient and barotrauma in the other one and refractory septic shock with late antibiotic administration in one case. The latter survived the acute Covid-19 episode but succumbed later due to tracheal stenosis with failure to intubate. There was no significant difference in clinical and paraclinical findings between survivors and non-survivors.

DISCUSSION

In this study, we describe the clinical manifestations and outcomes of life-threatening forms of SARS-CoV-2 infection in paediatric patients admitted to our PICU in July and August 2021, during the fourth wave catalysed 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 first waves in Tunisia. Only three older children were admitted to our PICU and the MV was needed in a case of a 15-year-old girl

with diabetes. The number of children requiring intensive care increased dramatically in July 2021. That is why we extended our beds capacity from 4 to 8 for patients infected with COVID-19. To our knowledge, our findings have not been reported previously in literature. It might 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.^{13–16} In our study, there were six newborns, and the median age of our patients was shorter than other studies, especially a US cohort with SARS-CoV-2 Delta variant (median age of 8 years).¹⁷

Underlying medical conditions, young age (<1 year) and obesity are known to be risk factors for critical illness in children.^{5,14} A high percentage of the Canadian-American and French cohorts of critically ill children had at least one comorbidity (83% and 70%, respectively).^{14,15} 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 four patients with hemodynamic instability in line with literature.¹⁷ 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 paediatric departments before being transferred for worsening signs. The median delay between onset signs and PICU admission was longer than reports from other cohorts.¹⁸

PARDS was observed in eleven patients among 20, in line with the adults' case series (67%)¹⁹ but less than the children's reports.^{20,21} Chest X-rays showed typical ground glass opacities and consolidations in 15 cases. Chao et al.¹³ and Derespina et al.²⁰ reported, respectively, 10 PARDS among 13 and 21 among 70 patients admitted to the PICUs. However, pleural effusion and pneumothorax at PICU admission were greater in our cohort. Derespina et al.²⁰ reported pneumothorax in one case and pleural effusion in four cases among 70 patients. We think that pneumothorax at PICU admission, observed in five patients, could have been avoided by an early PICU transfer. However, we cannot exclude the hypothetical role of COVID-19 infection as a cause of spontaneous pneumothorax. To the best of our knowledge, there are a few reports of spontaneous pneumothorax and pneumomediastinum in adults and adolescents.^{22,23}

All our patients required respiratory support. In our study, the duration of MV was 6 days (IQR 2.5–12.5), similar to the U.S. cohort.¹⁷ Prone ventilation, which is almost a routine in adults with COVID 19 infection, was used in 14 patients. Prone position decreased high oxygen requirements and the median duration of MV with FiO₂ over 60% was 2 days (IQR: 2–3) in our cohort. There were few reports about the prone position in children.^{13,20}

The mortality rate was high in our cohort despite fewer cases of severe PARDS and a low median PELOD-2. The main explanation was the late transfer to PICU due to the limited availability of ICU beds. There are several limitations to our study. Mainly, it was retrospective and conducted in a single centre with a small sample size. Yet it sheds light by providing additional data about comorbidity-free children, hospitalized in PICU during a ferocious wave of COVID-19 catalysed by the Delta variant. To our knowledge, data from other countries that experienced the Delta variant, with limited access to vaccination, is missing. Future studies from these countries might enable a better understanding of severe and critical forms associated with variants of concern of SARS-CoV-2 in children.

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

AUTHOR CONTRIBUTION

All authors contributed to medical management of the patient presented. Article was drafted by Aida Borgi (corresponding author) and Nejla Benjaballah, then revised,

criticized and corrected by the other authors. All authors approved the final version.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ETHICS STATEMENT

The study was approved by the ethical committee of children's hospital (Approval number13/2021). We obtained written consent from parents 'children, before extracting data.

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