Case Report: severe paediatric COVID-19 pneumonitis treated with remdesivir and nitazoxanide [version 1; peer review: awaiting peer review]

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Abstract
Paediatric severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection rarely results in a critical respiratory presentation. It is not yet known which children are at particular risk of adverse outcomes. We describe a paediatric case of critical SARS-CoV-2 infection requiring Extra Corporeal Membrane Oxygenation (ECMO), who made a full recovery after receiving a dual antiviral therapy of remdesivir and nitazoxanide.

Keywords
SARS-CoV-2, COVID-19, remdesivir, nitazoxanide, combination therapy, whole genome sequencing

This article is included in the Coronavirus (COVID-19) collection.
Case Report
We describe the case of a five-year-old girl who developed severe pneumonitis secondary to SARS-CoV-2 infection in December 2020 in the United Kingdom (UK), requiring maximal intensive care, who was treated with a dual antiviral therapy of remdesivir and nitazoxanide and made a full recovery.

Background
The girl was born at term in the UK to consanguineous parents (first cousins), with no requirement for neonatal care. She first became unwell at the age of five months with influenza A bronchiolitis and atypical haemolytic uraemic syndrome. She was ventilated and haemofiltered for 22 days, including a period of time on high frequency oscillatory ventilation (HFOV). She recovered from this illness but at eight months of age had parainfluenza bronchiolitis requiring ventilation for seven days. She continued to have recurrent severe respiratory illnesses with viral infections which resulted in several admissions to hospital as well as six admissions to the paediatric intensive care unit (PICU).

She was extensively investigated for underlying conditions by respiratory and immunology specialists at our centre. There was no family history of predisposition to severe infections. Immunologically, she was initially found to have absent NK cells, low B-cells, low CD8 cells and was panhypoglobulinaemic. She was commenced on three-weekly intravenous immunoglobulin (IVIg) replacement as well as prophylactic co-trimoxazole and flucanazole at the age of 10 months. Her immunology subsequently normalised and no underlying cause was identified for the repeated infections on whole exome (R15) sequencing. Her IVIg replacement and antibiotic/antifungal prophylaxis were therefore stopped at the age of 18 months. At the age of two and a half years, following another severe respiratory infection requiring intubation a chest computed tomography (CT) was performed which showed evidence of bronchiectasis and bronchiolitis obliterans and after multi-disciplinary discussions, she was re-started on IVIg replacement and azithromycin prophylaxis. She had a lung biopsy at the age of three years following a further life-threatening infection, which confirmed chronic peribronchial inflammation and scattered bronchiolitis obliterans. She received monthly pulsed methylprednisolone for six months at that time, followed by a mild improvement in her clinical condition, which also coincided with her moving out of a mould infested house.

COVID pneumonitis
The episode we describe here occurred in December 2020 when she was five years old, where she presented with cough, wheeze, increased work of breathing and a positive SARS-CoV-2 polymerase chain reaction (PCR) test in respiratory secretions. She initially stabilised with bronchodilators and steroids but developed progressive respiratory failure over three days, leading to intubation and transfer to our PICU. She was difficult to ventilate (conventionally and with HFOV), and rapidly reached thresholds for Extra Corporeal Membrane Oxygenation (ECMO) with a pH of 6.8 and unrecordably high PCO2. On commencement of ECMO, she was started on a course of compassionate use remdesivir (130mg loading dose followed by 65mg once daily) and was pulsed with methylprednisolone. At this time, the cycle threshold (Ct) value for SARS CoV-2 was 20, but this reached a peak of 16 on day two. There was no obvious response of viral load to remdesivir and it was discontinued after four doses, on day four of admission, due to increasingly deranged liver function tests. SARS CoV-2 Ct values improved to 28 on day 9 but on day 15, while still on ECMO, they worsened to 25; a decision was then made to commence a second course of remdesivir (with the same dosing regimen) together with adjunctive nitazoxanide (500mg twice daily), which has been shown to have an antiviral activity against SARS-CoV-2. Dual therapy was continued for ten days with evidence of viral load suppression from Ct 25 to Ct 36 occurring within 36 hours (Figure 1). She also received a second pulse of methylprednisolone on day 13. Her chest x-ray aspect gradually appeared to improve, as well as her SARS CoV-2 viral load (Figure 2). She received at total of 20 days of veno-venous ECMO and was ventilated for a further four days following decannulation. She was stepped down to the ward on day 30 and was off daytime oxygen by day 45. She required significant physiotherapy input in her rehabilitation both from a respiratory and neurological point of view after stepping down from PICU, and was finally discharged almost three months after her initial admission. SARS-CoV-2 has subsequently been intermittently detectable in her respiratory secretions for six months following the start of this episode.

Whole genome sequence analysis
To investigate the response to treatment, we obtained full length SARS-CoV-2 genome sequences from six positive bronchoalveolar lavage samples and four nasopharyngeal aspirate samples (dates of sampling shown in Figure 1) using SureSelect target enrichment and Illumina sequencing. A unique patient reference sequence was generated by mapping the reads of the first sample to the SARS-CoV-2 reference genome (NC_045512) from GenBank using bwa-mem\(^2\). Reads from the subsequent samples were mapped to this patient reference. Consensus sequences were aligned using MAFFT\(^3\). Minority allele variants with a frequency of above 2% were identified using VarScan\(^4\).

All samples were identified as lineage B.1.1.7 using Local Lineage and Monophyly Assessment (LLAMA)\(^5\). In a phylogenetic tree with other global and local SARS-CoV-2 samples, all ten consensus sequences from this patient clustered together, indicating no evidence of multiple haplotypes or mixed infection. No resistance mutations were identified.

We have previously reported heterogeneous responses in three patients who received remdesivir monotherapy treatment, with viral suppression occurring in only one\(^6\). Longitudinally sampled viruses sequenced from these patients suggested the presence of lung compartmentalisation, wherein viral replication occurs in physically separated niches within the lung\(^7\). A similar phenomenon has been observed for other...
persistent inflammatory lung infections, including tuberculosis and influenza, with combination chemotherapy recommended to achieve adequate pathogen clearance. Based on previous experience and the extreme severity of her condition, we added nitazoxanide. The rapid suppression of viral load and clinical improvement raises the possibility that combining...
remdesivir with a second antiviral agent may improve outcomes in SARS-CoV-2 pneumonitis.

**Consent**
The parents/guardians provided informed consent for the publication of this case report.

**Ethics Approval**
This work was approved for publication by the Great Ormond Street Hospital (Clinical Audit Number #2857) and PHE Research Ethics and Governance Group (REGG) (R&D NR0195).

**Data availability**
All data underlying the results are available as part of the article and no additional source data are required.

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**References**


