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Case Study

High-level adenovirus-neutralizing antibodies plasma beneficial for adenovirus type 7 (Adv7) induced pediatric severe ARDS

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ABSTRACT

Objective: Respiratory failure and acute respiratory distress syndrome (ARDS) caused by adenovirus pneumonia (AVP) present significant challenges for pediatricians. High-level adenovirus-neutralizing antibody plasma (HL-ANAP), containing elevated levels of neutralizing antibodies (NAbs), might represent a valuable passive immunotherapy option. To assess the therapeutic effects, we investigated three cases diagnosed with adenovirus type 7 (Adv7)-induced severe ARDS, which required combined therapy with extracorporeal membrane oxygenation (ECMO) and HL-ANAP.

Methods: Blood samples from three patients with Adv7-induced ARDS were collected before HL-ANAP administration, and at 6, 12, 24, 48, and 72 hours, and 7, 21, and 28 days after treatment. We measured Adv7 viral load, NAb titers, and cytokine levels in the serum, describing the observed trends.

Results and discussion: All patients survived. Before HL-ANAP transfusion, Adv7 viral loads exceeded 1*10ˆ7. Adv7 viral loads gradually decreased within 72 hours after HL-ANAP transfusion, accompanied by a rising trend in NAb titers. IL-6 and IL-8 levels decreased sharply during the first 24 hours post-HL-ANAP transfusion, followed by a slower decline.

Conclusion: HL-ANAP may be effective in treating ARDS induced by severe type-7 adenoviral pneumonia in children. This approach may reduce adenovirus load, decrease systemic inflammation, and improve clinical outcomes. The neutralizing antibody's activity against the virus may occur within 24–72 hours post-infusion in vivo.

1. Introduction

Adenovirus pneumonia (AVP) is a life-threatening condition in the pediatric intensive care unit (PICU). It can lead to respiratory failure and acute respiratory distress syndrome (ARDS), potentially resulting in fatalities.[1] Additionally, complications such as post infectious bronchitis obstruction (PIBO) can occur in children, particularly in those infected with adenovirus type 7 (Adv7).[2–5] The primary treatment for severe AVP is respiratory support, including oxygen therapy and mechanical ventilation. The antiviral medication Cidofovir may also be a therapeutic option, particularly in early extracorporeal membrane oxygenation (ECMO),[6] but randomized controlled trials (RCTs) confirming its efficacy are still lacking.[7] Children with ARDS induced by severe AVP may require advanced therapies such as continuous renal replacement therapy (CRRT) and ECMO.[8] However, these approaches increase treatment costs and may still result in poor outcomes.[9]

Numerous reports have confirmed that plasma from recovered patients can be successfully used to treat various viral infections,[10–12,24] particularly COVID-19.[13,14] Previous studies demonstrated that plasma from recovered patients, containing high levels of neutralizing antibodies, shortens the course of viral infections and reduces long-term complications. Neutralizing antibodies in the plasma are the most effective antiviral component. The mechanism of these treatments is based on the interaction between antigens and antibodies. Therefore, in this study, we transfused high-level adenovirus-neutralizing antibody plasma (HL-ANAP) to three patients with ARDS induced by severe AVP. We examined the trends in viral loads and antibody titers following HL-ANAP transfusion and observed the effects of this treatment.

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2. Materials and methods

2.1. Study design

The study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center (No. 202054301). Informed consent was obtained from the parents or guardians of pediatric patients receiving high-titer NAbs plasma therapy. The inclusion criteria were: (1) Age below 18 years; (2) Adenovirus infection diagnosed via quantitative real-time polymerase chain reaction (qRT-PCR) using nasopharyngeal swabs, sputum, or bronchoalveolar lavage fluid; (3) Pneumonia confirmed by imaging with significant lung infiltration and respiratory symptoms; (4) Severe adenovirus pneumonia diagnosed, presenting with acute respiratory distress syndrome (ARDS), requiring invasive mechanical ventilation, and a Murray score greater than 2; (5) Receiving ECMO support therapy. The exclusion criteria were: (1) Allergy to immunoglobulins or plasma; (2) Presence of serious underlying conditions, including chronic lung disease, complex congenital heart disease, severe liver or kidney disease, malignancies, severe malnutrition, immunodeficiency, genetic metabolic disorders, or pre-existing brain dysfunction from various causes; (3) Declined participation by pediatric parents or guardians.

2.2. Case presentation

2.2.1. Case 1

A 7-month-old (7.5 kg) boy was admitted to the pediatric respiratory ward due to a recurring cough lasting one month. On the fifth day after admission, a throat swab tested positive for adenovirus. Twelve days after admission, the patient became irritable, short of breath, and developed a high fever. The child's blood oxygen saturation was maintained at 88 %–90 % with high-flow oxygen inhalation. Pulmonary moist rales were noted. The chest radiograph revealed blurred lungs. The high-density shadow on both lungs had worsened compared to the baseline (Fig. 1A). Consequently, the patient was transferred to the PICU and quickly intubated for mechanical ventilation (Pressure control: FiO_2: 60 %, PIP: 30 cmH_2O, PEEP: 7 cmH_2O, Ti: 0.6s, f: 35 bpm, VT: 61 mL). The tracheal aspirate nucleic acid test was positive for Adv7. He was then treated with cefoperazone sodium and methylprednisolone, along with therapies to improve microcirculation and maintain optimal fluid balance. On the second day in the PICU, PaO_2 decreased, and the oxygen index (OI) progressively increased to 36. Therefore, we switched to high-frequency oscillatory ventilation (HFOV) (FiO_2: 100 %, Paw: 28.3 cmH_2O, Ti%: 0.33 %, Power: 71 cmH_2O, f: 8 Hz). SpO_2 fluctuated between 80 % and 90 %, and he continued to have recurrent fevers, accompanied by oliguria. CRRT was initiated, followed by the transfusion of 150 mL of HL-ANAP of the same blood and viral type. On the third day in the PICU (day 14 post-admission), under HFOV (FiO_2: 100 %, Paw: 27.6 cm H_2O, Ti%: 0.33 %, Power: 72 cm H_2O, f: 8.5 Hz), the patient's OI remained above 40 for over 12 hours (Fig. 1B), leading to the initiation of ECMO. By the fourth day of ECMO, the patient's pulmonary function had improved. A chest X-ray revealed that the high-density shadow of the bilateral pneumonia had dissipated (Fig. 1C). Consequently, ECMO was terminated after 101 hours. He was discharged without complications on the 40th day post-admission and recovered without any long-term sequelae. His chest X-ray had improved significantly before discharge (Fig. 1D).

2.2.2. Case 2

A 96-month-old (17 kg) girl had experienced a cough and fever for

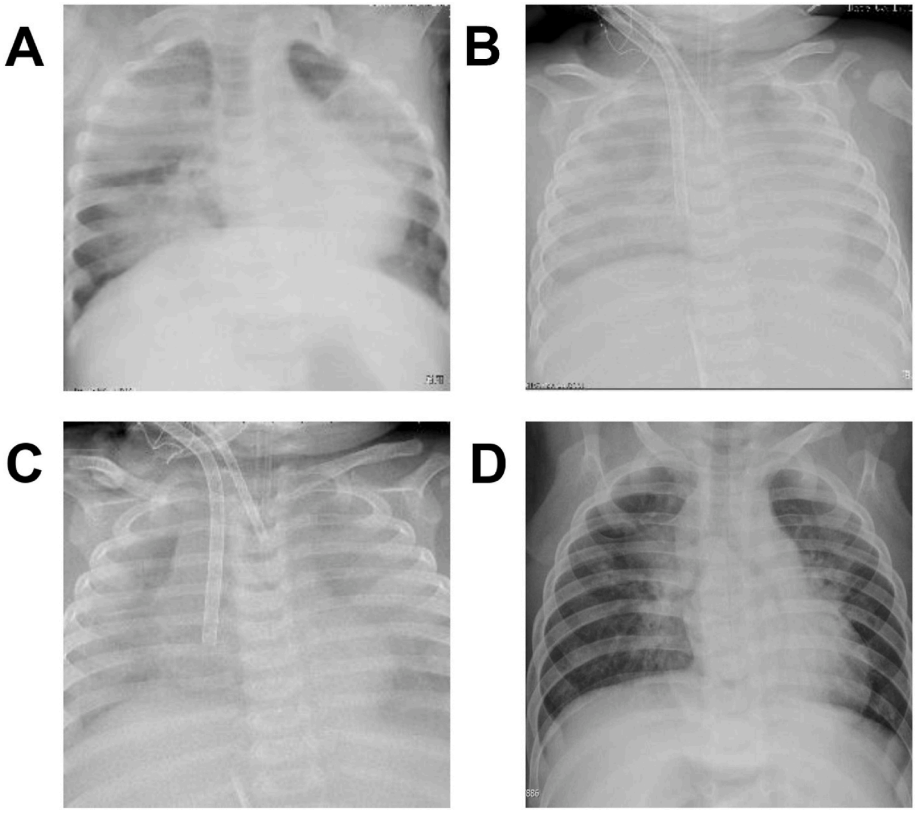

Fig. 1. Patient 1 Chest X-ray
(A) Chest X-ray before admission to PICU, high-density shadow on bilateral lungs;
(B) Chest X-ray after HL-ANAP transfusion and at the beginning of the ECMO, bilateral lung exudates were aggravated;
(C) Chest X-ray before the end of the ECMO, bilateral lung exudation was reduced and tidal volume was increased;
(D) Chest X-ray before discharge, the exudation in both lungs disappeared.

nearly 15 days before being transferred from another hospital. She was admitted to the PICU with CPAP due to respiratory failure caused by Adv. After admission, she exhibited dyspnea, decreased consciousness, nasal flaring, and supraclavicular and subcostal retractions. She was immediately intubated and treated with mechanical ventilation (Pressure control: FiO_2: 60 %, PIP: 22cm H_2O, PEEP: 7 cmH_2O, Ti: 0.75s, f: 30bpm, VT:103mL). Alveolar lavage fluid examination confirmed Adv7 infection. On the third day post-admission, she required higher ventilator settings (Pressure control: FiO2:100 %, PIP: 28cmH_2O, PEEP: 12cmH_2O, Ti: 0.75s, f: 30bpm, VT: 89mL) to maintain oxygenation, and experienced recurrent fevers, prompting a switch to HFOV (FiO_2:100 %, Paw:27.6cm H2O, Ti%: 0.33 %, Power: 72cmH_2O, f: 8.5Hz).

Due to persistent poor microcirculation, indicative of septic shock, she was given a 300 mL infusion of HL-ANAP. On the fourth day after admission, with HFOV, the patient's OI peaked at 50 within 24 hours and remained above 40 for more than 6 hours, leading to the initiation of VA-ECMO treatment. After 14 days, the patient was weaned off ECMO. Her PICU stay lasted 21 days, with a total hospital stay of 28 days. The patient was discharged in stable condition and fully recovered without sequelae.

2.2.3. Case 3

The third case involved a 14-month-old girl (10 kg) who had experienced fever, cough, and shortness of breath for a week. A day before admission, she presented with poor mental status and severe dyspnea accompanied by hypoxemia. She was intubated and transferred to the PICU with mechanical ventilation (Pressure control: FiO_2: 60 %, PIP: 30cm H_2O, PEEP: 7cm H_2O, Ti: 0.6 s, f: 35 bpm, VT: 61 mL). On the third day, her OI continued to increase, leading to a switch to HFOV (FiO_2: 100 %, Paw: 27.6 cm H2O, Ti%: 0.33 %, Power: 72cm H_2O, f: 8.5 Hz). However, her oxygenation did not improve, and the OI remained above 40 for more than 6 hours, reaching a peak of 87.

VA-ECMO treatment was initiated, and Adv7 infection was confirmed by deep sputum analysis on the third day. After obtaining consent, we infused 200 mL of HL-ANAP of the same blood type. Five days later, the oxygenator was replaced due to blockage. ECMO was withdrawn after 15 days. However, three days after ECMO withdrawal, her oxygenation worsened compared to when she was on ECMO. She required higher ventilator settings. Therefore, NO inhalation was provided for 10 days to improve her oxygenation and reduce pulmonary hypertension. She was extubated 48 days after admission, and non-invasive ventilator support was used for six days post-extubation. Ninety-one days post-admission, she was discharged with oxygen support via nasal cannula, which was gradually decreased and finally discontinued after six months. Currently, she experiences wheezing after physical activity and has been diagnosed with PIBO.

2.3. Adv7-HL-ANAP therapy and sample collection

The virus type and viral load were diagnosed by quantitative real-time polymerase chain reaction (qRT-PCR). After confirming Adv7 infection, we transfused 20 mL/kg of HL-ANAP (antibody titer >1:1000) of the same blood type. Blood samples were collected from the patients before plasma administration and at 6, 12, 24, 48, and 72 hours, as well as 7, 21, and 28 days post-transfusion. We measured Adv7 neutralizing antibody (NAb) titers, viral load, and cytokine levels in the collected serum samples.

2.4. Adv7-HL-ANAP preparation and NAb titer test

HL-ANAPs were obtained from healthy blood donors, with plasma collected from the Guangzhou Central Blood Station. The Adv7 NAb titers were determined using neutralization assays based on HAdv7-SEAP,[15] as described previously.[16–18] The same method was used to test the patients' serum Adv7 NAb titers during HL-ANAP therapy.

2.5. Viral load test

qRT-PCR was performed to quantify the serum Adv7 viral load. Nucleic acid was extracted from 140 μL of serum using a nucleic acid extraction and purification instrument (magnetic bead method, Guangzhou Qizi Biotechnology Development Co. Ltd.). Adenoviral nucleic acid kits (Guangzhou Institute of Respiratory Diseases Medical Technology Co. Ltd) were then used to test for Adv7. The baseline start value, stop value, and threshold of the analyzed image were adjusted to optimize the standard curve in the STD curve window. If the amplification curve was S-shaped and the CT value was less than 35, the total Adv7-DNA content in the sample was calculated based on the standard curve.

2.6. Cytokines detection

Six cytokines (IL-2, IL-6, IL-8, IL-10, TNF-α, and IFN-γ) were detected using AimPlex Multifactor Flow cytometry. A volume of 45 μL of two-fold diluted serum samples was mixed with fluorescent beads carrying surface-immobilized antibodies in a 96-well plate. Sample data were acquired by flow cytometry (BD FACSCanto II, Becton, Dickinson and Company, USA) and analyzed using BD FACSDiva Software. Cytokine concentrations were calculated based on calibration standard curves for each cytokine using FCAP Array 3.0 analysis software.

2.7. Statistical analysis

Spot tendency graphs were used to describe trends in NAb titers, type-7 adenovirus load, and cytokine levels. Parental consent was obtained prior to HL-ANAP transfusion.

3. Results

All patients survived following ECMO and HL-ANAP treatment. No transfusion-related complications occurred during or after HL-ANAP transfusion. The information of these patients is presented in Table 1. The Adv7 viral loads before HL-ANAP transfusion were all above 1 × 10^7, reaching up to 5.03 × 10^8 in Case 2. Adv7 viral loads decreased gradually within 72 hours after HL-ANAP transfusion. NAb titers increased significantly within 7 days after HL-ANAP transfusion,

Table 1
Patients' information.

Patient	P1	P2	P3
Gender	Male	Female	Female
Age(month)	6	96	14
Weight(kg)	7.5	17	10
SOFA	6	8	9
Max OI before ECMO	64	50	87
Murray score	4	4	3.67
Immunodeficiency	None	None	None
Sepsis shock	None	Yes	Yes
Days of illness before admission (day)	15	15	9
Fever time before admission (day)	10	14	9
Lenth of stay (day)	39	28	38
PICU length of stay (day)	13	21	38
duration of ECMO (day)	4	12	15
Duration of MV (day)	11	18	38
Volume of Adv7-HL-ANAP (ml)	150	300	200
volume of Adv7-HL-ANAP (ml/kg)	20	17.6	20
Adv7-HL-ANAP neutralizing antibody titer	1:1615	1:1728(150ml)/1:2113 (150ml)	1:1254
CRRT	Yes	None	None
iNO	None	None	Yes
HFOV before ECMO	Yes	Yes	Yes

Murray score: lung injury score; SOFA: Sequential Organ Failure Assessment; MV: mechanical ventilation; iNO: inhaled nitric oxide.

followed by a subsequent decrease (Fig. 2).

High levels of IL-6 and IL-8 were observed prior to HL-ANAP transfusion. However, during the first 24 hours after HL-ANAP transfusion, IL-6 and IL-8 levels sharply decreased, followed by a slower reduction. IL-10, IL-2 and TNF-α had low level baselines and decreased after HL-ANAP transfusion. IFN-γ increased slightly within 72 hours after HL-ANAP transfusion and then decreased (Fig. 3).

4. Discussion

Pediatric cases of adenovirus pneumonia are often complex. Increased mortality is observed when adenovirus pneumonia progresses to ARDS.[19] ECMO serves as a salvage treatment for these patients.[8] However, fatalities or severe long-term pulmonary sequelae in children can occur even after ECMO application.[3,4] Yu reported that Adv-7 pneumonia caused higher mortality (28.6 %) than other types of Adv during 2010–2012.[20] It also caused critical clinical situation such as longer duration of fever, higher morbidity of tachypnea/dyspnea, higher rates of pneumonia, and longer mechanical ventilation. Our data indicated that Adv7 infection, with a 30.8 % mortality rate, was the leading cause of severe, fatal human adenoviral pneumonia in children between 2016 and 2021.[21] Severe pediatric ARDS remains a critical issue in the PICU, necessitating more advanced life support therapies and incurring greater costs.[22] Our patients underwent treatment escalation from standard mechanical ventilation to HFOV, HL-ANAP, and ultimately ECMO. Their conditions eventually improved, and they were discharged; only one patient experienced complications. ECMO is a rescue therapy for respiratory failure that can preserve valuable time when the OI rises sharply and plays a key role throughout the entire treatment process.

Plasma from patients recovered from viral infections, used as passive immunotherapy, can be effectively utilized to combat viremia and prevent ongoing organ injury. This treatment has been historically applied against various viruses.[10–13] Although adverse reactions, such as rash and allergic reactions, may occur during all types of plasma transfusion, no adverse reactions were observed in our group or in other studies on high-titer viral plasma therapy, such as coronavirus-inactivating plasma.[23] However, therapy for Adv infections in children, particularly Adv7, has been rarely reported. We defined HL-ANAP as plasma with a neutralizing antibody titer greater than 1:1000. This standard was established with reference to previous investigations.[16,17] In this study, Cases 1 and 2 had adenovirus-neutralizing antibodies before HL-ANAP administration, likely due to the intravenous transfusion of gamma globulin during early-stage treatment. However, we also found high viral loads in patients before HL-ANAP administration, with rapid increases in OI and life-threatening hypoxia. It is possible that the adenovirus-neutralizing antibodies received by our patients were insufficient to neutralize the virus and control the progression of sepsis. After HL-ANAP transfusion, the adenoviral load in plasma decreased significantly within 72 hours, while neutralizing antibody titers increased. However, in Case 1, the adenoviral load increased again 24 hours after HL-ANAP transfusion, possibly due to viral release from apoptotic or dead cells. This may indicate that the interaction between adenovirus and neutralizing antibodies occurred within 72 hours post-HL-ANAP transfusion. As the patients recovered, the adenoviral load was completely eradicated, and neutralizing antibody levels increased, albeit with fluctuations.

Cytokine test results showed that IL-6 and IL-8 concentrations were high before HL-ANAP transfusion but sharply decreased afterward. This outcome suggests that HL-ANAP has the potential to significantly reduce the inflammatory response. IL-6 and IL-8 levels increase during the acute phases of pneumonia, particularly in patients with severe Adv7 infection.[24,25] High levels of these cytokines were also observed in an in vivo Adv7 infection experiment with alveolar epithelial cells.[26] IL-8 concentrations followed the same trend and were independent of time and viral load. These results suggest that specific HL-ANAP is effectively involved in treating Adv7 viremia; it can delay the progression of viremia, providing more time and opportunities for treatment and improving the inflammatory response. However, it may take at least 24 hours for HL-ANAP to act against the virus. Based on the trends of NAb titers and viral loads, the interaction between antibodies and the virus may last up to 72 hours. Therefore, sufficient life support should be provided during and after HL-ANAP transfusion.

5. Conclusions

HL-ANAP, as a passive immunotherapy, could be used to treat ARDS induced by severe type-7 adenoviral pneumonia in children. Its application can reduce the Adv7 viral load, decrease systemic inflammation, provide more time for treatment, and improve patient outcomes. The

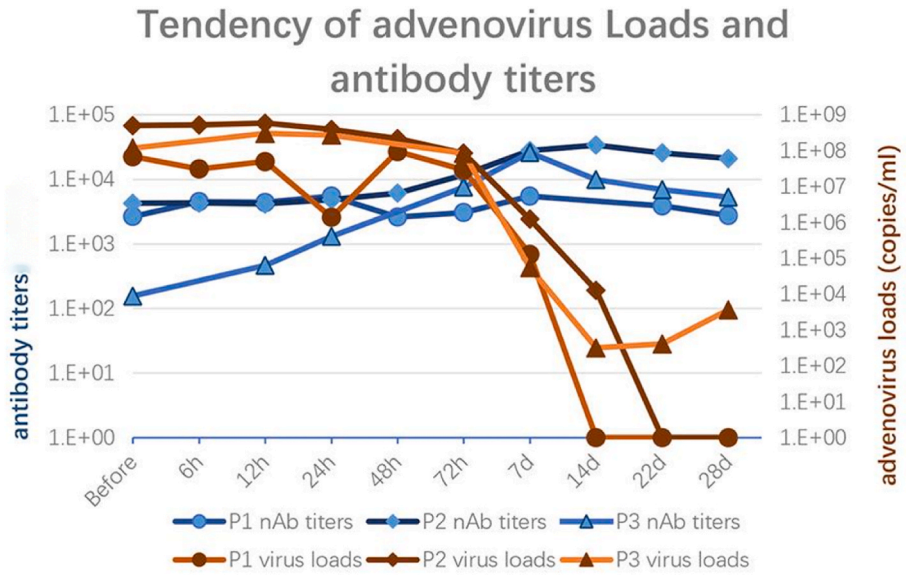

Fig. 2. Tendency of nAb titer and virus load in blood
Patient 1, Patient 2, and Patient 3's Adv7 viral loads decreased within 72 hours after HL-ANAP transfusion; After HL-ANAP transfusion, Patient 1, Patient 2 and Patient 3's NAb titers increased significantly within 7 days. Antibody titers are determined by reciprocal dilutions.

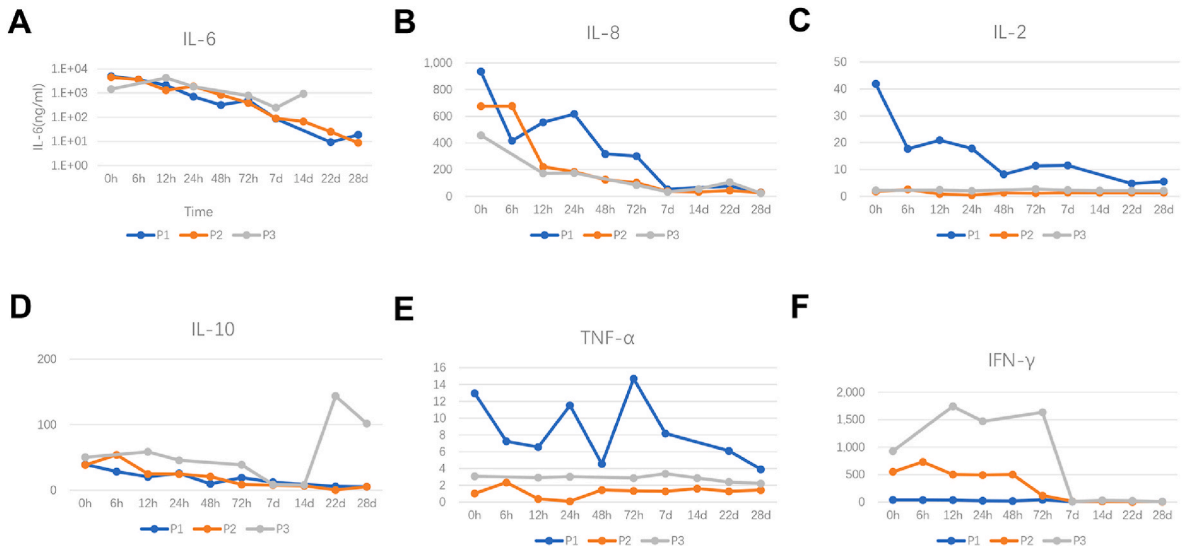

Fig. 3. Cytokines level of patients' plasma
(A) IL-6 tendency: Gradually decreased after HL-ANAP transfusion;
(B) IL-8 tendency: Decreased after HL-ANAP transfusion;
(C) IL-2 tendency: Decreased after HL-ANAP transfusion in patient1;
(D) IL-10 tendency: Decreased after 7 days of HL-ANAP transfusion;
(E) TNF-α tendency: The absolute value is low, with light changes in patient 1;
(F) IFN-γ tendency: Increased slightly within 72h after HL-ANAP transfusion and then decreased.

action time of neutralizing antibodies may occur within 24–72 hours after in vivo infusion. Continued organ support, such as ECMO, may be required before or after the infusion.

CRediT authorship contribution statement

Feiyan Chen: Writing – review & editing, Writing – original draft, Software, Formal analysis. **Run Dang:** Data curation. **Mingqi Zhao:** Resources. **Yi Chen:** Resources. **Jinda Huang:** Writing – review & editing. **Yunlong Zuo:** Investigation. **Yiyu Yang:** Project administration.

Limitations

There are several limitations in our study. First, we report only three cases because such severe cases requiring ECMO treatment are rare. Additionally, the HL-ANAP bank was still under development during the study, and we did not have sufficient paired plasma for our patients. Therefore, further observations are needed to evaluate the effectiveness of this treatment in future clinical trials. Second, we did not have data on viral load and NAb titers for control patients who did not receive HL-ANAP. Third, we lacked sufficient evidence to confirm whether Adv7 was alive or not. The specific mechanism of action of neutralizing antibodies in HL-ANAP remains unclear. It may reduce the number of viable viruses or inhibit their replication. Fourth, this study focused on children with severe ARDS induced by Adv7, where the treatment process is highly complex. Therefore, the effects of these therapies remain difficult to fully explain.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement

This research was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center (202054301). Parental consent was obtained before HL-ANAP transfusion.

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Abbreviations

Adv7	adenovirus type 7
ARDS	acute respiratory distress syndrome
AVP	adenovirus pneumonia
HL-ANAP	high-level adenovirus-neutralizing antibody plasma
NAbs	neutralizing antibodies
ECMO	extracorporeal membrane oxygenation
PICU	pediatric intensive care unit
PIBO	post infectious bronchitis obstruction
RCTs	randomized controlled trials
CRRT	continuous renal replacement therapy
qRT-PCR	quantitative real-time polymerase chain reaction
OI	oxygen index
HFOV	high-frequency oscillatory ventilation
SOFA	Sequential Organ Failure Assessment
MV	mechanical ventilation
iNO	inhaled nitric oxide

Declaration of competing interest

As the corresponding author of this manuscript, I declare that there are no conflicts of interest associated with this publication. I have no financial or personal relationships with other people or organizations that could inappropriately influence or bias the content of this manuscript.

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All authors have contributed significantly to the research and have approved the final manuscript. We confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere.

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Data availability

Data will be made available on request.

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