

BRIEF REPORT

Treatment of a case presenting as critical adenoviral ARDS using Cidofovir with early combinatorial prone ventilation and ECMO

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Abstract

Here, we report a case of adenoviral pneumonia associated with critical ARDS treated with Cidofovir, prone ventilation and extracorporeal membrane oxygenation (ECMO). The patient responded well to therapy and recovered without further complications. Cidofovir, with early prone ventilation and ECMO support, may be a therapeutic option for patients with critical ARDS related to adenoviral pneumonia.

KEYWORDS

adenovirus pneumonia, ARDS, Cidofovir, ECMO, prone ventilation

1 | INTRODUCTION

Pneumonia is a leading cause of death in young children and elderly patients. Many microorganisms, including bacteria, viruses and fungi, are known pathogens causing pneumonia. With the development of molecular diagnostic tools such as NGS (Next-generation sequencing) and polymerase chain reaction (PCR) testing, attention has been focused on viruses as pneumonia pathogens.^{1,2} Infections with some respiratory viruses are associated with a high incidence of lung injury, ARDS and increased mortality. They include influenza A H1N1, avian influenza A viruses H5N1 and H7N9, and the SARS and MERS-Coronaviruses.^{3,4}

Human adenoviruses (HAdV) are a frequent cause of acute upper respiratory tract infection in children and have high respiratory morbidity, in particular, in immune-compromised hosts.^{5,6} Life threatening adenovirus pneumonia rescued by Cidofovir antiviral therapy combined with prone ventilation and ECMO appeared to be rare.

2 | CASE

2.1 | Patient history

A 17-year-old, previously immunocompetent, female student admitted to our emergency department (ED) with the complaint of cough, sputum production for 2 weeks, fever for 1 week. The patient showed no clinical response to therapy with the second-generation cephalosporins combined with azithromycin. Before admission to ED, she had already suffered from bilateral and progressive pneumonia within past 48 hours (Figure 1).

2.2 | Findings on admission

The patient was transferred to RICU for intensified treatment. Under physical examination, she had a high fever (39.7°C) with tachypnea (20/min) and tachycardia (100/min) but normal blood pressure (130/80 mm Hg). Localised coarse crackles were heard in the bilateral lower lobe. The

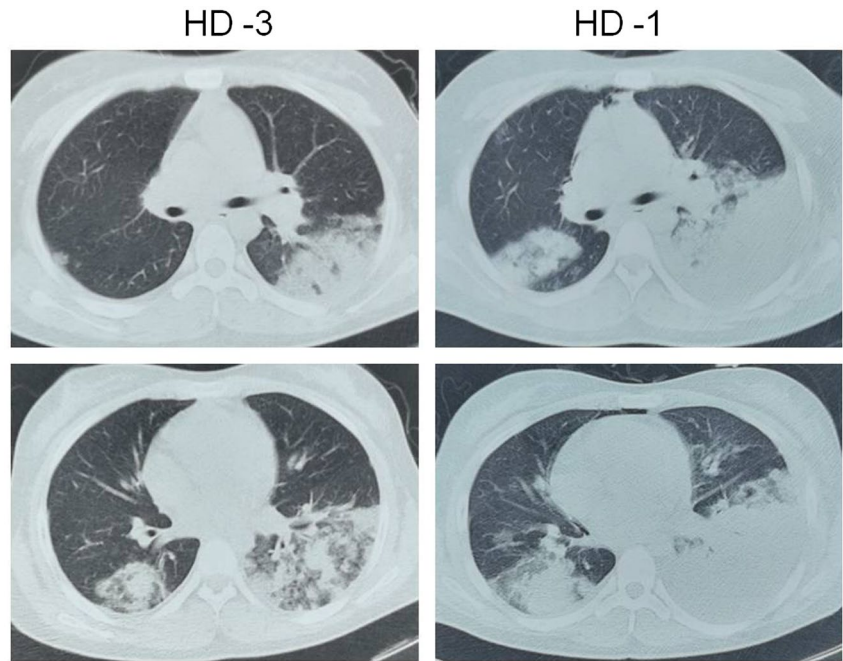


FIGURE 1 Initial chest CT findings in the patient. It was showed that bilateral consolidation and patchy infiltration were aggravated within 48 hours before admission

patient's mucous membranes were dry, without any signs of peripheral oedema. There were no signs of bleeding or skin rash. Arterial blood gas analysis (ABGA) showed hypoxia (PaO_2 58 mm Hg) on room air under 5 L/min oxygen via a face mask. The ejection fraction seemed to be maintained to roughly 65% in echocardiography. Her leucocyte cell count was 6.07×10^9 per L, presenting 8.6% of lymphocytes and 89.6% of neutrophils. Platelets were slightly low with 114×10^9 per L. Plasma NT-proBNP was normal (70.28 pg/mL) and albumin concentration was low at 23 g/L (reference 40–55 g/L). Elevated lactate dehydrogenase (LDH, 2274 U/L) and creatine kinase (CK, 2510 U/L) was noted.

2.3 | Bronchoscopy

Bronchoscopy was performed in RICU as soon as possible (Figure 2A–C). Bronchoscopic examination revealed that some formed mucous plug blocked the opening of segmental bronchial of left lower lobe. Convex probe endobronchial ultrasound (CP-EBUS) was used for performing real-time transbronchial needle aspiration (TBNA) of peribronchial lesions, and therefore, was used as a means of tissue culture. Transbronchial lung biopsy (TBLB) and EBUS-TBNA was both reported as inflammatory cell infiltration and necrosis. Pathologic section of intraluminal secretion demonstrated as fibrous exudation (Figure 2D–F). The NGS result from bronchoalveolar lavage fluid (BALF) was positive for human adenovirus 7. Real-time PCR testing of BALF was also performed to screen for adenovirus with a cycle threshold value of 31 (Figure 3). Culture of sputum and BALF did not show any evidence of bacterial or fungal infection. Acid-fast stain

of sputum found no evidence of tuberculosis. Interesting, culture of EBUS-TBNA biopsied tissue showed candida growth.

Bronchoscopy was also used for airway management in further intensive care. Bronchoscopy with BAL in the patient was well tolerated, primarily related to better drainage of secretions and pathogenic investigation (Figure 2G–I).

2.4 | Treatment of ARDS with prone ventilation and V-V ECMO

On admission (HD 1–2, day 1–2), the patient needed 5 L/min oxygen via a face mask, which resulted in an arterial PaO_2 of 45–58 mm Hg and O_2 saturation of 92%–98%. There was no progress of the pericardial effusion and no further decrease of the ejection fraction. The left pleural effusions progressed to 3 and 3.5 cm. Then, diagnostic ultrasound-guided thoracentesis was carried out, which yielded yellow fluid. Analysis of the pleural fluid revealed exudates with 7.47 mmol/L of glucose, 2561.8 U/L of LDH, 34.9 U/L of ADA and 42.4 U/L of amylase. A cell fractionation of pleural effusion revealed 5% of neutrophils and 28% of lymphocytes. On HD 3, her respiratory condition deteriorated. Although we introduced high-flow nasal cannula at FiO_2 60%, the patient had dyspnoea associated with hyperventilation (>30 breaths per min), O_2 saturation fluctuated between 86% and 92%. Chest radiographs on HD 2 and HD 3 showed increasing signs of a pulmonary infiltration.

Early in the morning of HD 4, sufficient oxygen uptake was no longer possible, resulting in the need for oral intubation and mechanical ventilation (MV). Mechanical respiratory support with smaller tidal volume ventilation (300 mL, ideal body weight = 50 kg) and high positive end-expiratory pressure

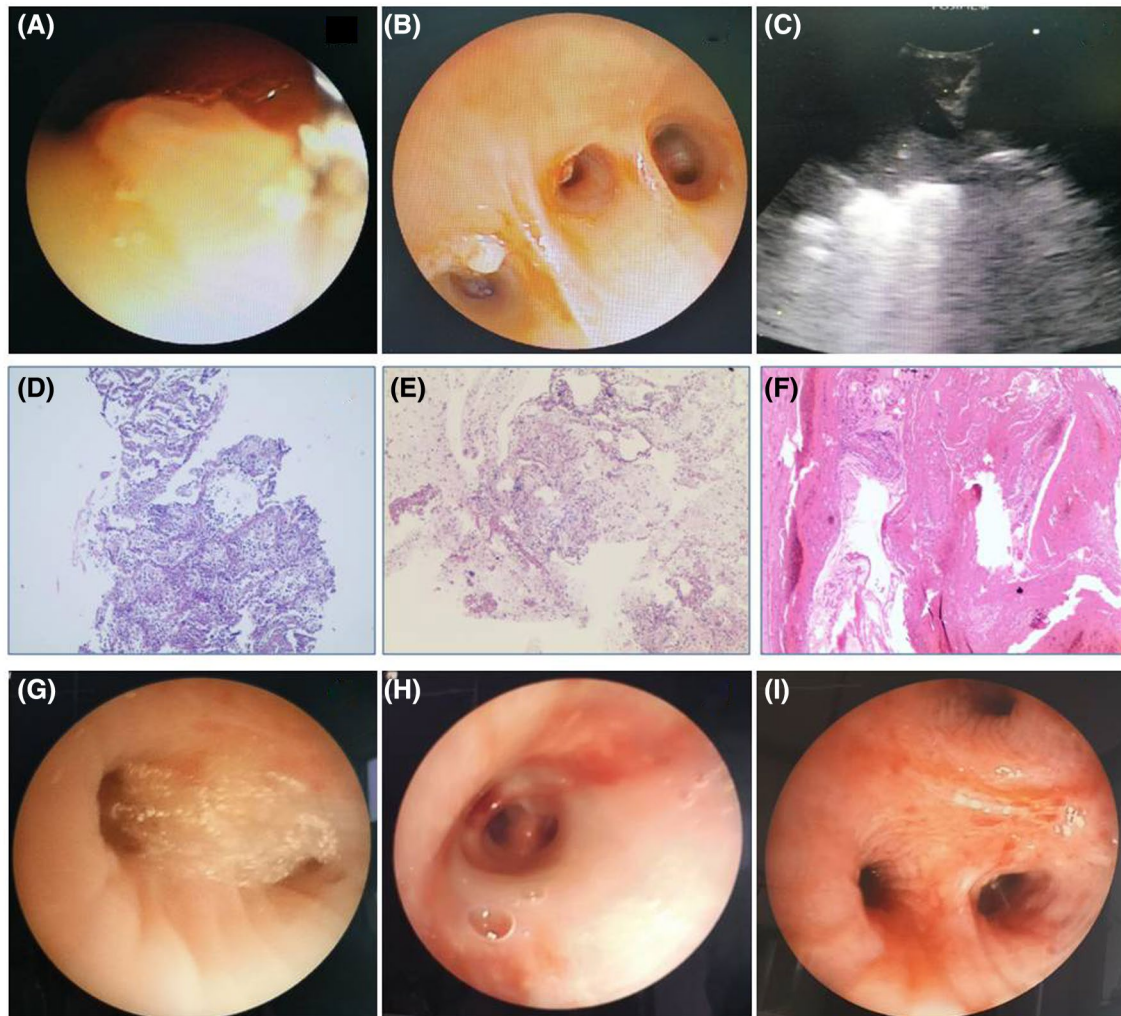


FIGURE 2 Bronchoscopic and pathologic findings in the patient. Initial bronchoscopic examination revealed that most of intraluminal secretion plug blocked the opening of left lower lobe segmental bronchial (A, B). EBUS-TBNA (C) and transbronchial lung biopsy (TBLB) was reported as inflammatory cell infiltration and necrosis (D, E). Pathologic section of Intraluminal secretion demonstrated as fibrous exudation (F). Bronchoscopy was also used for airway management in further intensive care, primarily related to better drainage of secretions (G, H, I)

(PEEP, 14 cmH₂O) was started due to the development of ARDS. The patient received strategies of sedative analgesics and neuromuscular blockade with midazolam and vecuronium. The patient did not need norepinephrine immediately after intubation. The hypoxia further worsened (ABGA: pH 7.7448, PaCO₂ 32.8 mm Hg, PaO₂ 40.9 mm Hg, O₂ saturation 75%, with ventilator settings at FiO₂ 100%). After applying with prone ventilation, O₂ saturation fluctuated between 80% and 88%. To overcome intractable hypoxia, venovenous ECMO (V-V ECMO) was started (6 hours after prone ventilation). ECMO device parameters including rotate speed, blood flow and sweep gas are reported in Table 1, where changes over time were shown.

From HD 5 to 11, prone ventilation was done every night for 12-14 hours to reduce in intrapulmonary ventilation perfusion mismatch and ventilator induced lung injury, and to obtain better drainage of secretions.

Until HD 10, the patient began to improve gradually in ventilator parameters (Table 2). Notably, the deterioration

of C dyn peaked on HD 5 with an index value of 7.5 mL/cmH₂O, and improvement of the C dyn was noticed on HD 10. Then, spontaneous breathing with oral intubation was attempted with V-V ECMO with settings at FiO₂ 21% (ECMO circuit). At that time, the patient maintained haemodynamic and oxygen saturation with MV settings at Vt 280 mL, PEEP 10 cmH₂O, RR 20/min, FiO₂ 50%, which resulted in an arterial PaO₂ of 84.6 mm Hg, PaCO₂ of 42.3 mm Hg, and pH 7.471. We noted no signs of disseminated bleeding, and only the nasal cavity bleeding was noticed on HD 9-11. On HD 11, V-V ECMO was weaned. The patient received 6 units of red blood cell concentrates on HD 11 in response to decreasing hemoglobin concentrations after V-V ECMO removal.

After V-V ECMO was weaned, she maintained good saturation in supine position with PEEP 6-10 cmH₂O and FiO₂ between 40% and 50%. The strategies of sedative analgesics and neuromuscular blockade were weaned. Over the next 2 days, the P/F ratio stayed between 220 and 300. On HD 15,

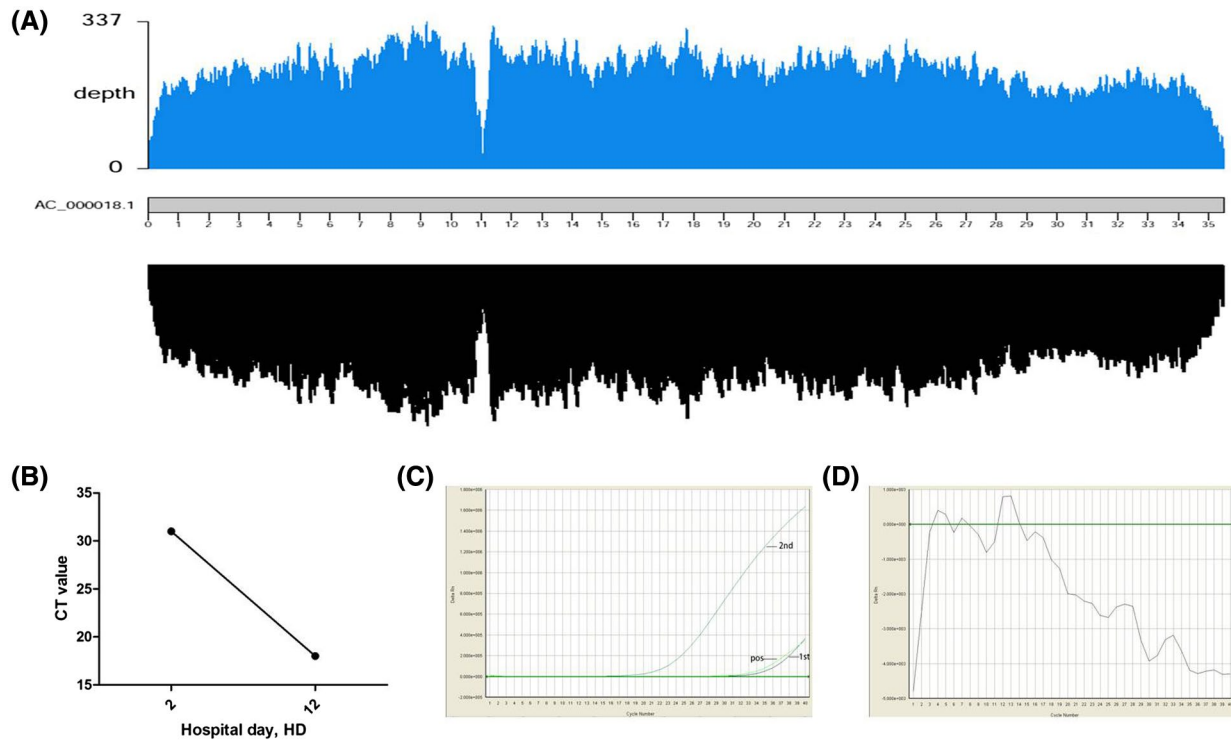


FIGURE 3 NGS and real-time PCR testing of BALF were performed to screen for adenovirus. Nucleotide position along human adenovirus 7 Genome was analysed by NGS (A). A total of 34 484 sequence reads derived from the patient's BALF sample were mapped to the closest matched HAdV B genome (Tax id:108098) in the reference database, human adenovirus 7 (Tax id:10519). Based on real-time PCR, although concentrations of virus DNA (second, HD 12) in BALF had not dropped after the first dose of Cidofovir on HD 7 (B, C), it became undetectable in oropharyngeal swabs samples after the second dose of Cidofovir on HD 14 (HD 23, D)

TABLE 1 ECMO parameters at window of combined MV and ECMO

Time	Rotate speed (R/min)	Blood flow volume (L/min)	Oxygen concentration (%)	Sweep gas flow rate (L/min)
HD4	3040	3.65	100%	3.5
HD5	3760	4.43	100	4.4
HD6	3080	3.56	100	3.42
HD7	3000	3.48	90	3.2
HD8	2980	3.47	90	3.3
HD9 ^a	3000	3.44	90	3.35
	3000	3.44	45	3.35
HD10 ^b	2980	3.38	50	3
HD11	2980	3.41	50	3

^aWe reduced oxygen concentration slowly during the day.

^bThe patient passed the weaning test that day.

the oral intubation was removed and sequenced with high-flow nasal cannula at FiO₂ 40%.

2.5 | Diagnostic thoracic ultrasound

The point of care ultrasound of chest was used to assess cardiac function, lung B lines, fluid responsiveness and

inferior vena cava diameter (IVCD), suggested evidence of fluid overload (Figure 4). The patient did not need norepinephrine after intubation and ECMO. The anteroposterior IVCD was kept at 1.5 cm below the diaphragm in the hepatic segment in supine position during normal inspiration and expiration. It also presented the extravascular lung water by lung ultrasonography. Comparison of the chest ultrasound from HD 7, HD 8, and HD 10 showed improvement

TABLE 2 Ventilator parameters at window of combined MV and ECMO

Time	Mode	TV set (mL)	PEEP (cmH ₂ O)	P _{peak} (cmH ₂ O)	C dyn (mL/cmH ₂ O)
HD4	PRVC	380	10	33	–
HD5	PRVC	200	11	32	7.5
HD6	PRVC	200	11	33	12.3
HD7	VCV	200	11	30	–
HD8	VCV	200	10	29	12.6
HD9	VCV	200	10	29	13.0
HD10	VCV	200	12	29	15.9
HD11	VCV	200	12	26	–

Abbreviations: HD, hospital day; PEEP, positive end expiratory pressure; P_{peak}, peak pressure; TV, tidal volume; VCV, volume control ventilation.

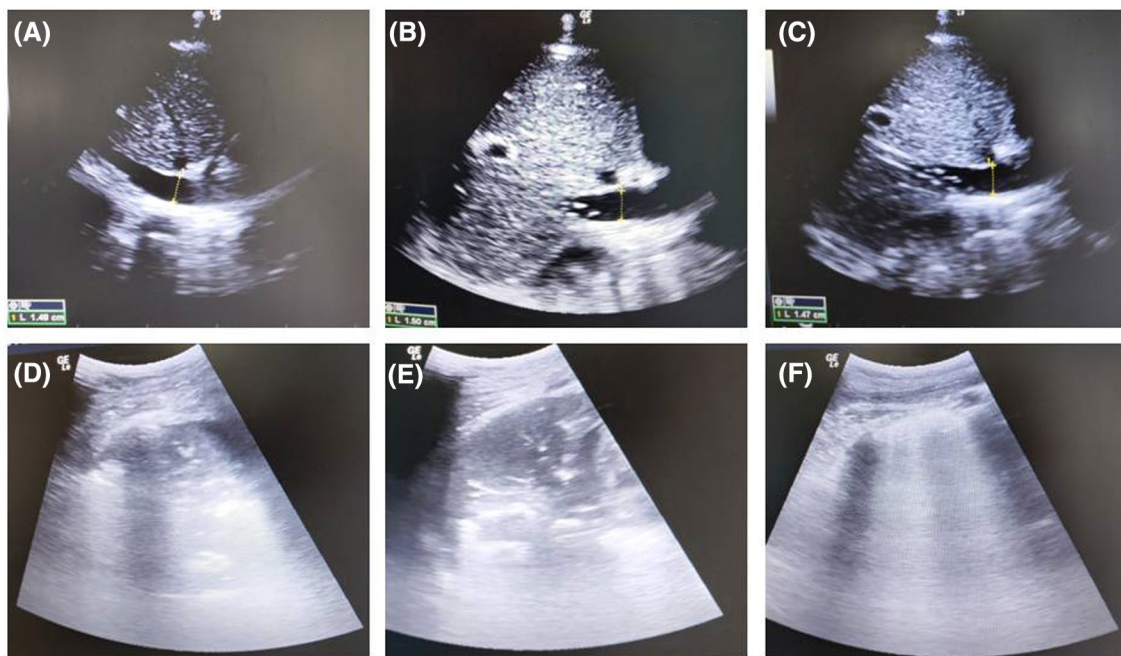


FIGURE 4 Thoracic ultrasound in the patient. The anteroposterior IVCD was kept at 1.5 cm below the diaphragm in the hepatic segment in supine position during normal inspiration and expiration (A, B, C, respective image). Comparison of the lung ultrasonography from HD 7 (D) and HD 8 (E), it was noticed the improvement of lung consolidation on HD 10 (F)

of lung consolidation, coincided with improvement of CXR (Figure 5).

2.6 | Intermittent use of Cidofovir

Based on the report of the NGS result in HD 4, Cidofovir was started as soon as possible (HD 7). Briefly, Cidofovir was administrated at a dose of 5 mg/kg in the first week, followed by the same dose in the next week. Hydration with normal saline before and after Cidofovir was used with probenecid (1.25 g/m²) to prevent renal toxicity. The concentrations of HAdV DNA in BALF had not dropped after the first dose of Cidofovir (Figure 3B). Then, the second dose of Cidofovir

was given on HD 14. On HD 15, the oral intubation was removed and sequenced with high-flow nasal cannula at FiO₂ 40%. Then, virus loads of HAdV were only analysed based on oropharyngeal swabs samples. It became undetectable in oropharyngeal swabs sample after the using of the second dose of Cidofovir (Figure 3B–D).

2.7 | Antimicrobial therapy

Initially, no particular exposure was known and the source of infection remains unclear. Hence, based on the clinical and laboratory findings suggesting sever CAP, we started treatment with Peramivir, Sulbactam/Cefoperazone,

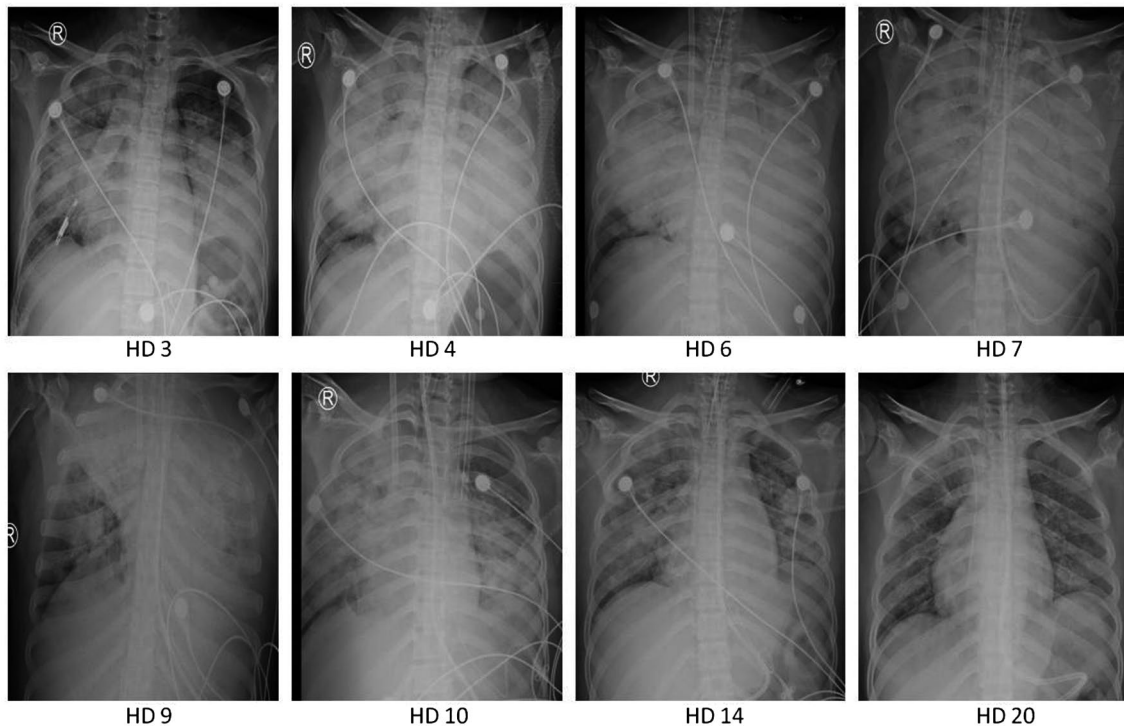


FIGURE 5 Serial changes of chest X-ray (CXR) study. Initial CXR showed progressive and bilateral pneumonic consolidation in whole lung (HD 3 and HD 4). From HD 7, pneumonic consolidation in right side began disappear. From HD 10, the image study showed evidence of obvious improvement of bilateral pneumonic consolidation, subsequently further improvement noticed by CXR on HD 14 and HD 20

Moxifloxacin, Linezolid, Ribavirin on admission to cover suspected pathogen, including influenza A, some respiratory viruses, PRRP, MASR and atypical pathogen. On HD 3, caspofungin was chose based on the tissue culture with candida growth. Until adenovirus was confirmed, Peramivir, Moxifloxacin and Linezolid were removed. From HD 8, carbapenem-resistant acinetobacter baumannii (CRAB) was repeatedly detected in both BALF and purulent secretion of airway, accompanied by increased N, PCT, and CRP, all representing sources of bacterial translocation. Repetitive blood cultures and secretion of airway did not show growth of relevant pathogens, included Penicillinase resistant *Streptococcus pneumoniae* (PRRP), Methicillin-resistant *Staphylococcus aureus* (MASR), *Pseudomonas aeruginosa* (PA) and Carbapenem-resistant *Klebsiella pneumoniae* (CRE). On HD 12, the patient was administrated with Meropenem and tigecycline to target CRAB. On HD 13, we switched to polymyxin B as a substitute for tigecycline due to diarrhoea. In the further course, the inflammatory parameters decreased gradually.

2.8 | Further course of the disease

The course of the clinical parameters is shown in Figures 5–7. Comparison of the chest radiographs from H 9 and

H 10 showed improvement of infiltration, subsequently improvement noticed by chest CT on HD 13. Despite an initial lymphocytopenia, lymphocytes count rose until HD 13, and subsequently normalised. It was suggested that the observed clinical improvement coincided with normalisation of lymphocytopenia. Almost simultaneously, plasma LDH and CK level fell continuously. The inflammatory parameters interleukin-6 (IL-6) and C-reactive protein (CRP) had also dropped. Albumin concentrations were decreased to levels as low as 23 g/L, then, the patient received albumin substitution until HD 23. Of note, thrombocytopenia developed later, with a peak at HD 20, and a late restore. After the removal of ECMO, we continued to give anticoagulation treatment for the patient. The patient improved continuously and discharged on HD 30 without any further sever complications.

3 | DISCUSSION

Here, we reported a case of critical ARDS caused by a highly virulent strain of adenovirus. Management including antiviral agents, extracorporeal membrane oxygenation (ECMO) and prone ventilation was the focus of interest.

Several antiviral agents, including Cidofovir, ribavirin and ganciclovir, have shown in vivo and in vitro anti-adenoviral

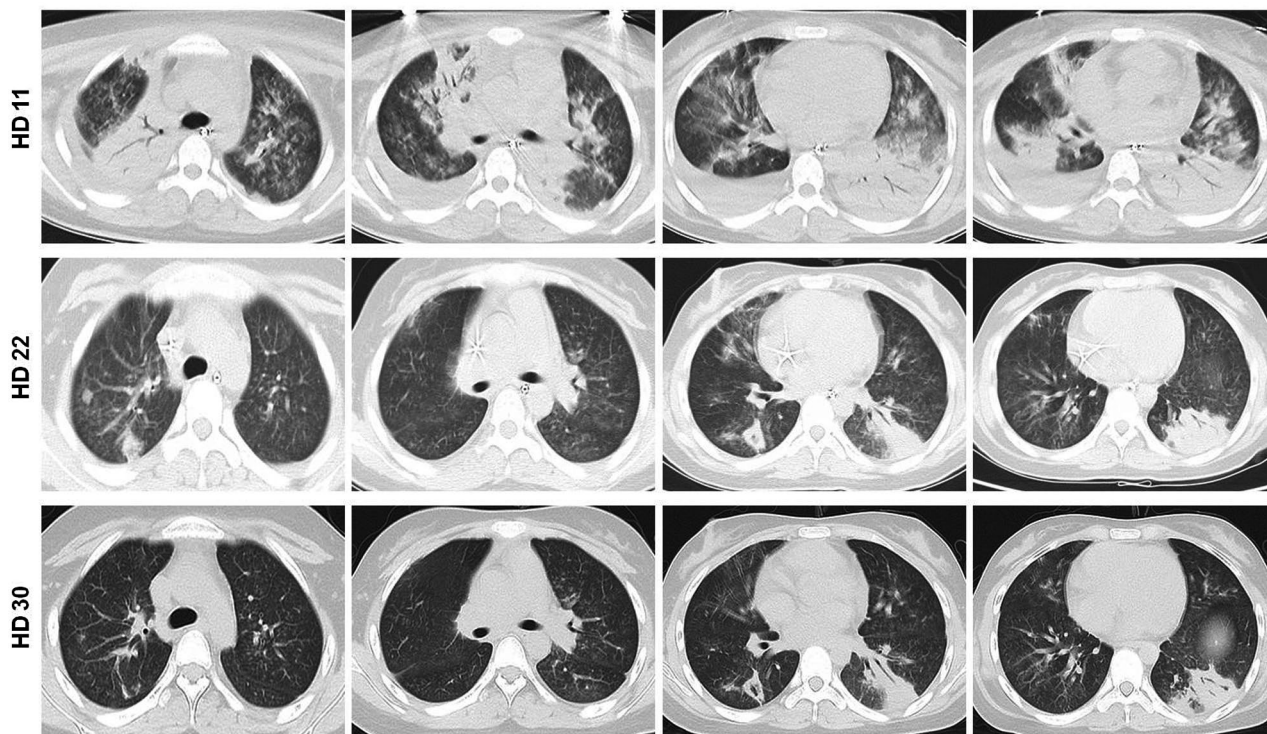


FIGURE 6 Serial changes of chest CT scan study. On HD 11, V-V ECMO was weaned. Chest CT scan showed bilateral consolidation and multiple patchy infiltrations with right pleural effusion. In HD 22, bilateral lobe pneumonic infiltrations and right pleural effusion were improved, follow-up CT scan (HD 30) shows continual improvement of lung abnormality

efficacy. Cidofovir is a nucleotide analogue and shows in vitro and in vivo antiviral activity. This agent is used mainly in critical adenoviral infection and immunocompromised patients, including children and stem cell and solid organ transplantation recipients. Despite several reports of treatment failure and the absence of randomised controlled trials, most studies showed that Cidofovir is clinically effective against adenoviral infection in immunocompromised patients.^{7,8} Although the efficacy of Cidofovir in adenoviral infection is not established in immunocompetent patients, it showed clinical benefit and improvement in oxygenation in several clinical trials in immunocompetent military trainees.⁹ In fact, most immunocompetent patients overcame adenovirus pneumonia without antiviral agents, even in case reports, some patients overcame adenovirus pneumonia complicated by ARDS without the use of antiviral agents. Clinical, in some cases of critical pneumonia caused by adenovirus serotype 55, the disease course is more aggressive, and antiviral agents are used more frequently.¹⁰ In this report, as the clinical response to ribavirin was not good, Cidofovir was added to ribavirin, with subsequent virological improvement.

ECMO has been used for salvage therapy in intractable hypoxia in patients with ARDS.^{11,12} With ECMO, the ventilator settings are changed to permit lung rest and to minimise ventilator-induced lung injury. There have been reported cases of adenovirus pneumonia complicated by ARDS using

ECMO, some used ECMO therapy to overcome intractable hypoxia.¹³ Sun et al reported five cases of adenoviral ARDS. Despite ECMO therapy in one patients, only one survived.¹⁴ In survivors, the time lag between invasive MV and ECMO therapy was shorter than in nonsurvivors. Here, the time lag between invasive MV and ECMO was less than 1 day in our case. In conclusion, early ECMO therapy is a potential option for the treatment of intractable hypoxia and can avoid ventilator associated lung injury.

Improvement in oxygenation in the prone position is thought to result from a reduction in intrapulmonary ventilation perfusion mismatch, ventilator-induced lung injury and better drainage of secretions.¹⁵⁻¹⁸ In our case, we found improvement in haemodynamic and oxygenation was possibly attributed to synergy. The patient showed gradual improvement in oxygenation and haemodynamic with prone ventilation for 16 hours.

There are several limitations in this report. We did not use PiCCO system to determine pulmonary vascular leak, which was an instant and objective method of quantification of pulmonary vascular leak by the extravascular lung water index (EVLWI). And efficacy was presumed based on the clinical course, including Lac level, HCT, urine output and superior vena cava diameter.

Taken together, this report emphasised the complexity and specific challenges of intensive care treatment of patients with

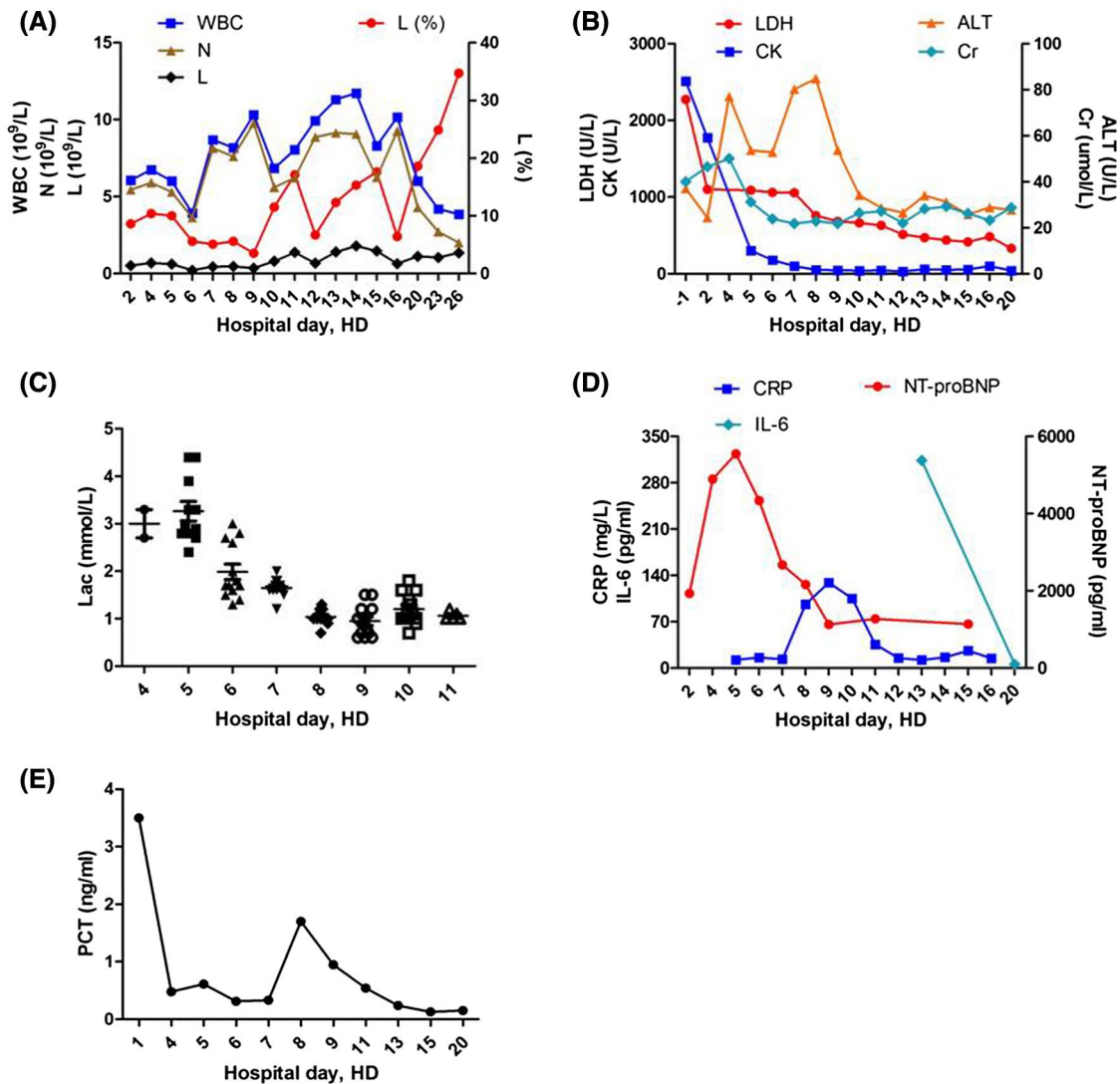


FIGURE 7 Serial changes of laboratory test study. The dynamic change of white cells (WBC), lymphocytes (L), level of LDH, CK, ALT, Cr, Lac, IL-6, CRP, NT-proBNP and PCT was observed over a 4 weeks period (A-E). HD was described as following, ECMO was applied on HD 4. Antiviral agent was changed to Cidofovir (HD 7, HD 14). The oxygenation and pneumonic infiltration were improved in HD 10, V-V ECMO was weaned on HD 11

critical adenovirus pneumonia. The efficacy of Cidofovir in more critical adenovirus pneumonia complicated by ARDS is promising, but more study is needed. Early ECMO therapy and prone ventilation is also a promising therapeutic option in adenoviral ARDS complicated by ARDS.

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CONFLICT OF INTEREST

The authors declared that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Literature research: CL and CC
Designed the study: JAH and CC
Analysed the data: CL, WWN, YBC, YHZ, JAH and CC
Interpreted the data: JAH and CC
Wrote the report: CL, HJA and CC
Edited the report: JAH
Involved in care of the patient: CL, WWN, YBC, YHZ, JAH and CC
Performed virological analysis: YX

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