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CASE REPORT

Timing of Whole Lung Lavage in Autoimmune Pulmonary Alveolar Proteinosis with Concurrent Opportunistic Infection: A Case Report and Systematic Review

Jiaqi Pu[1,2], Yifan Zhou[3], Haixia Zhou[1,2], Yongjiang Tang[1,2], He Yu[1,2], Jian-Qing He[1,2]

[1]Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan Province, People's Republic of China; [2]State Key Laboratory of Respiratory Health and Multimorbidity, West China Hospital, Sichuan University, Chengdu, Sichuan Province, People's Republic of China; [3]Department of Respiratory and Critical Care Medicine, Guizhou Aerospace Hospital, Zunyi, Guizhou Province, People's Republic of China

Correspondence: Jian-Qing He; He Yu, Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan University, Guo-Xue-Xiang 37#, Wuhou District, Chengdu, Sichuan Province, 610041, People's Republic of China, Email jianqing_he@scu.edu.cn; 27902682@qq.com

Background: Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare lung disorder characterized by abnormal accumulation of surfactant in the alveoli, often leading to progressive respiratory failure. While whole lung lavage (WLL) remains the standard therapeutic intervention, its timing and safety in the context of active infection remain a critical clinical dilemma.

Case Presentation: We present a fatal case of a 42-year-old Tibetan female with aPAP and progressive respiratory failure requiring V–V ECMO. Critically, serological tests were negative, but targeted next-generation sequencing (tNGS) of bronchoalveolar lavage fluid revealed a dominant mixed opportunistic infection (*Cryptococcus neoformans*: 3,877 reads; *Enterococcus faecium*: 118,062 reads). Despite this finding, the patient underwent emergent WLL and subsequently succumbed to the uncontrolled infection. To contextualize our findings, we conducted a systematic literature search in PubMed and Embase from their inception to November 21, 2025, which identified 27 relevant case reports and series. This review demonstrated that the majority of WLL procedures were performed after the active infection was controlled or had resolved following the initiation of antimicrobial therapy. The outcome was generally favorable, with clinical improvement reported in 23 cases (85.2%).

Conclusion: This fatal aPAP case suggests a staged management approach whereby WLL should be deferred until infection control is achieved. Early tNGS-guided pathogen identification appears crucial for directing antimicrobial therapy. This target-then-lavage strategy merits further validation but offers a prudent framework for managing these high-risk patients.

Keywords: pulmonary alveolar proteinosis, *Cryptococcus neoformans*, whole lung lavage, targeted next-generation sequencing, opportunistic infection

Introduction

Pulmonary alveolar proteinosis (PAP) is a rare lung disorder with an estimated incidence of 0.2 cases per million population.[1] It is characterized by the abnormal accumulation of surfactant lipids and proteins in the alveoli, primarily due to impaired clearance by GM-CSF-dependent macrophages.[2] Autoimmune PAP (aPAP), mediated by neutralizing anti-GM-CSF antibodies, accounts for over 90% of cases and often presents with nonspecific respiratory symptoms, leading to frequent diagnostic delays.[3]

A critical and life-threatening complication of aPAP is opportunistic infection, occurring in 13%–22% of patients and contributing significantly to mortality.[3–5] The immunopathological basis for this susceptibility is well-established: anti-GM-CSF antibodies disrupt critical pulmonary host defense by impairing alveolar macrophage phagocytosis and neutrophil antimicrobial functions.[6,7] This specific immunodeficiency creates a niche for intracellular pathogens, notably *Nocardia*

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and *Mycobacteria*.[8] Importantly, recent evidence underscores a particularly strong link between GM-CSF autoimmunity and susceptibility to Cryptococcus species.[9]

Despite this understanding, critical management gaps persist. Conventional microbiological tests often lack sensitivity in aPAP patients, while current guidelines offer no consensus on the timing of whole-lung lavage (WLL) during active infection. This creates a fundamental therapeutic dilemma: proceeding with WLL risks pathogen dissemination, while delay may perpetuate respiratory failure. Current guidelines lack specific recommendations on this risk-benefit calculus. Therefore, there is an urgent need for clinical strategies that enable earlier pathogen identification and inform the optimal sequencing of therapy. The recent application of targeted next-generation sequencing (tNGS) in respiratory infections offers a promising avenue for rapid and precise microbiological diagnosis, but its utility and implications for management timing in aPAP have not been defined.

Herein, we report an instructive fatal case of aPAP complicated by a mixed opportunistic infection, which serves as a crucial demonstration of a sequential decision-making framework for managing infected aPAP patients. We will illustrate how early tNGS application is pivotal for resolving diagnostic uncertainty, and how this microbiological evidence must then directly inform the critical timing of WLL. By integrating our experience with a synthesis of recent literature, we aim to crystallize a management paradigm that prioritizes infection control before definitive lavage.

Methods

Targeted Pathogen Sequencing

Pathogen identification was performed on bronchoalveolar lavage fluid using tNGS with the IDseq Focus Respiratory Panel (Vision Medicals). This hybridization capture-based method targets a comprehensive panel of 302 clinically relevant pathogens and 35 resistance/virulence genes. The complete technical workflow, including detailed probe design strategy, hybridization conditions, and the bioinformatics pipeline (software, versions, and positive thresholds), is provided in Supplementary Method S1.

Case Presentation

A 42-year-old Tibetan female farmer was transferred to our tertiary center on May 8, 2025, with 30 days of progressive cough and dyspnea. Initial evaluation at a regional hospital (April 2025) revealed PAS-positive lipoproteinaceous material in BAL fluid, elevated serum KL-6 (4,322 U/mL), and absence of significant pathogenic microorganisms by tNGS. Sequential therapeutic lung lavage was performed (April 25–26) due to respiratory failure, retrieving 7,000 mL of brown-tinged effluent from 10,000 mL instilled (70% retrieval; Figure 1). Despite broad-spectrum antimicrobials (including moxifloxacin, sulfonamides, and piperacillin-tazobactam) and non-invasive ventilation, respiratory failure progressed.

Figure 1 Brown-colored bronchoalveolar lavage fluid obtained during the first whole lung lavage.
Notes: The single tube on the left contains the total pooled BALF obtained from the patient. The three tubes on the right represent aliquots that were subdivided from the total sample for parallel diagnostic tests. Written informed consent for the publication of this image was obtained from the patient's next of kin/the patient's legal guardian.

Upon admission, a physical examination showed bilateral fine crackles. Chest computed tomography demonstrated diffuse ground-glass opacities with reticulations and subpleural honeycomb shadows (Figure 2). Arterial blood gas confirmed type I respiratory failure (pH 7.488, PaO_2 41.6 mmHg, $PaCO_2$ 28.3 mmHg on 80% FiO_2). Laboratory studies noted leukocytosis (15.38×10^9/L) and elevated D-dimer (1.32 mg/L FEU), with normal inflammatory markers and autoimmune antibody. BALF tNGS (May 9) identified *Cryptococcus neoformans* as the dominant pathogen (3,877 reads). This finding highlighted the critical role of tNGS in uncovering an occult infection that conventional serology had failed to detect, thereby directly prompting the initiation of empirical amphotericin B and flucytosine despite negative cryptococcal antigen and galactomannan testing. Lumbar puncture was not pursued primarily due to written refusal from the patient's next of kin after thorough explanation of the procedure's rationale, risks, and potential benefits. This decision was supported by the absence of clinical signs suggesting meningoencephalitis (eg., no headache, meningism, or altered mental status) and the lack of significant abnormalities on non-contrast head CT scan. Pivotal diagnostic re-evaluation on May 11 revealed strongly positive anti-GM-CSF antibodies (>445 U/mL), definitively confirming aPAP and redirecting the initial suspicion of cryptococcus-secondary PAP to aPAP complicated by cryptococcal co-infection.

Inhaled GM-CSF (150 μg bid) was immediately added to ongoing antifungal therapy. However, by May 19, the patient developed clinical deterioration marked by new-onset fever and severe neutropenia (absolute neutrophil count 0.74×10^9/L). Given concerns for potential disseminated infection, WLL was deferred. This decision underscored the clinical dilemma regarding WLL timing, balancing the risk of procedure-related infection dissemination against the progression of respiratory failure from the underlying PAP. Flucytosine was discontinued due to suspected bone marrow suppression, and granulocyte colony-stimulating factor (G-CSF) therapy was initiated. Notably, neutrophil counts normalized within 48 hours following these interventions. Repeat BALF tNGS detected *Enterococcus faecium* (118,062 reads) and *Acinetobacter baumannii* (734 reads), necessitating escalation to cefoperazone-sulbactam and linezolid. Amphotericin B was transitioned to fluconazole after completing a 14-day course. Despite maximal medical management and uninterrupted inhaled GM-CSF, refractory hypoxemia persisted (PaO_2/FiO_2 nadir 72). Due to the failure of conventional therapy and the rapid progression of respiratory failure, bilateral WLL was performed on May 29. Given the persistent decline in peripheral oxygen saturation that could not be maintained without advanced support, the

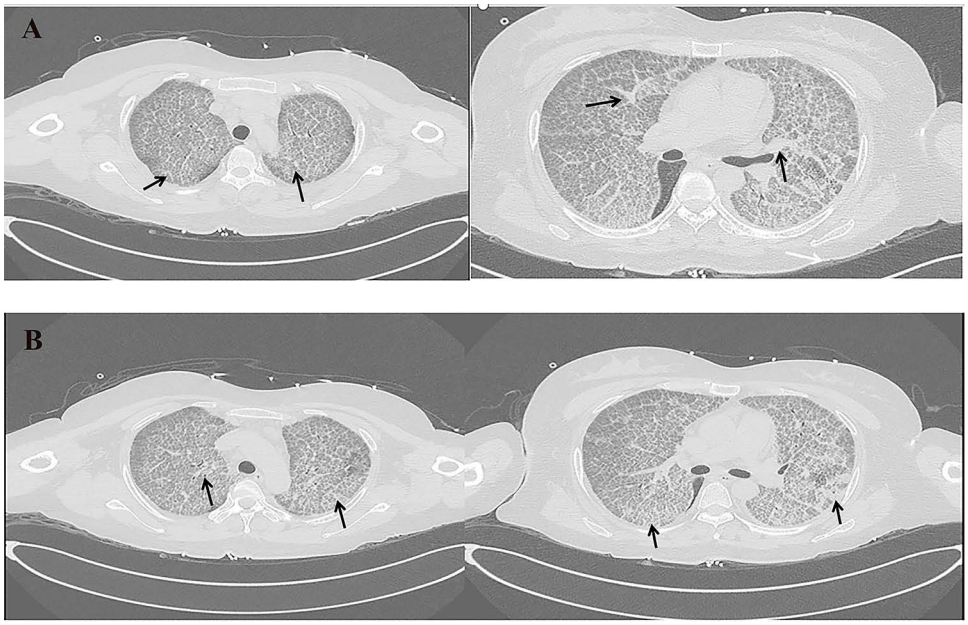

Figure 2 Chest computed tomography (CT) scans over the clinical course. (**A**) CT scan obtained on May 12, 2025, demonstrated diffuse ground-glass opacities with reticulations and subpleural honeycomb shadows. (**B**) Follow-up CT scan on May 19, 2025, showed unchanged extensive ground-glass opacities and honeycomb shadows despite 11 days of targeted antimicrobial therapy.

Notes: Black arrows in both panels highlight the key radiological features, including the diffuse ground-glass opacities with reticulations and the subpleural honeycomb shadows. Written informed consent for the publication of this image was obtained from the patient's next of kin/the patient's legal guardian.

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procedure was successfully conducted under V–V ECMO, with 87,000 mL of proteinaceous brown fluid evacuated (98.2% retrieval; Figure 3). Post-procedural imaging showed persistent diffuse infiltrates without improvement (Figure 4). Due to refractory hypoxemia (PaO_2/FiO_2 86 mmHg) unresponsive to maximal medical therapy and the family's socioeconomic constraints, the family requested voluntary discharge against medical advice. Subsequent telephone follow-up revealed that the patient had expired on the day of discharge (June 3, 2025) (Table 1). The fatal outcome following the lavage procedure provided a stark illustration of the perils of performing WLL in the setting of uncontrolled infection.

Review of Literature

A systematic literature search was conducted across two databases, PubMed and Embase, from their inception until November 21, 2025, to identify case reports and case series detailing the management of PAP with co-infections treated

Figure 3 Sequential effluent evolution during salvage whole-lung lavage under V–V ECMO: from right to left: dark-brown → light-brown → clear and transparent.
Notes: Written informed consent for the publication of this image was obtained from the patient's next of kin/the patient's legal guardian.

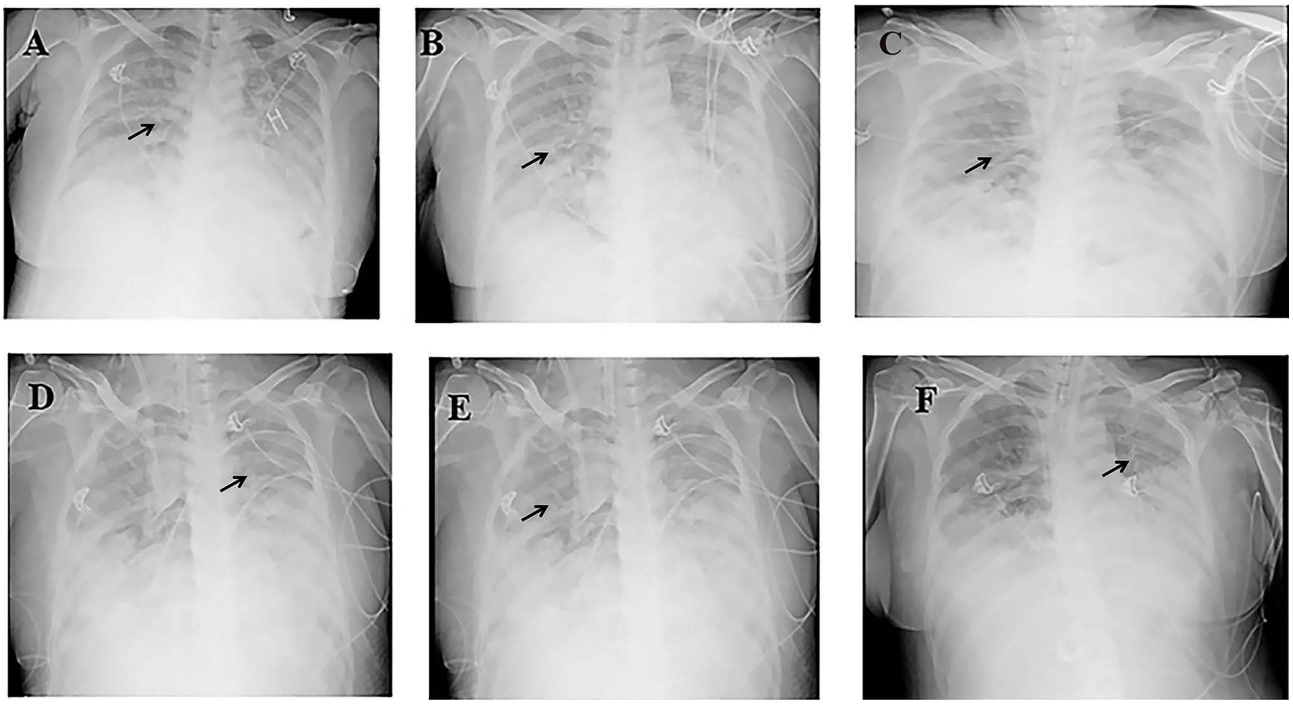

Figure 4 Serial chest radiographs pre- and post-whole lung lavage (WLL) under ECMO support. (**A**) (May 16, 2025) and (**B**) (May 27, 2025): Pre-lavage radiographs showing persistent bilateral diffuse infiltrates. (**C**) (May 30, 2025), (**D**) (May 31, 2025), (**E**) (June 1, 2025), and (**F**) (June 3, 2025): Sequential post-lavage radiographs revealing unabated consolidation despite the procedure, indicating no significant improvement in lung infiltration. Black arrows in each panel indicate representative areas of pathology. Written informed consent for the publication of this image was obtained from the patient's next of kin/the patient's legal guardian.

Table 1 Chronology of Clinical Events, Diagnostic Findings, and Therapeutic Interventions

Date (2025)	Clinical Status & Events	Key Diagnostic Findings	Therapeutic Interventions	Clinical Rationale & Decision Basis
Apr 8	Symptom onset			
Apr 25–26	Progressive respiratory failure	PAS-positive material in BALF; elevated KL-6; **NGS: no significant pathogens**	Sequential therapeutic lung lavage; broad-spectrum antibiotics	To relieve alveolar burden and correct hypoxemia in suspected primary PAP.
May 8	Admission to our center	CT: Diffuse ground-glass opacities; ABG: Type I respiratory failure	Non-invasive ventilation	Worsening respiratory failure post-lavage.
May 9	Respiratory failure	**BALF-tNGS: *C. neoformans* (3,877 reads)**; Serology: Negative	Initiated amphotericin B + flucytosine	tNGS identified occult fungal infection missed by serology, guiding targeted therapy. **WLL deferred due to active infection.**
May 11	Diagnostic confirmation	**Serum anti-GM-CSF Ab: >445 U/mL**	Added inhaled GM-CSF	Confirmed autoimmune PAP (aPAP) etiology.
May 19	Clinical deterioration, fever, neutropenia	ANC: 0.74×10^9/L	Discontinued flucytosine; started G-CSF	To manage suspected drug-induced bone marrow suppression. **WLL further deferred due to systemic deterioration.**
May 21-29	Refractory hypoxemia	Repeat BALF-tNGS: ***E. faecium*** (118,062 reads), ***A. baumannii*** (734 reads); PaO_2/FiO_2: 72	Escalated to cefoperazone-sulbactam + linezolid; transitioned to fluconazole	tNGS revealed new/dominant bacterial pathogens, prompting antimicrobial escalation.
May 29			Bilateral WLL under V–V ECMO	**Rationale**: As a salvage therapy for progressive, life-threatening respiratory failure unresponsive to maximal medical management, including targeted antimicrobials and GM-CSF. **Goal**: To remove the profound surfactant burden mechanically.

Notes: Bold font is used to emphasize critical tNGS findings and the primary clinical rationale for key interventions, highlighting the direct linkage between diagnostic results and therapeutic decisions. The read numbers provided for pathogens detected by tNGS represent the number of sequenced reads uniquely aligned to the respective species genome.
Abbreviations: PAP, pulmonary alveolar proteinosis; BALF, bronchoalveolar lavage fluid; KL-6, Krebs von den Lungen-6; NGS, next-generation sequencing; CT, computed tomography; ABG, arterial blood gas; tNGS, targeted next-generation sequencing; C. neoformans, *Cryptococcus neoformans*; GM-CSF, granulocyte-macrophage colony-stimulating factor; Ab, antibody; aPAP, autoimmune pulmonary alveolar proteinosis; ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factor; *E. faecium*, *Enterococcus faecium*; *A. baumannii*, *Acinetobacter baumannii*; PaO_2/FiO_2, ratio of arterial oxygen partial pressure to fractional inspired oxygen; WLL, whole lung lavage; V–V ECMO, veno-venous extracorporeal membrane oxygenation.

with WLL. The search strategy, available in Supplementary Table 1, utilized keywords including "Pulmonary Alveolar Proteinosis" AND "infection" AND "WLL". There were no restrictions on language.

The study selection process was performed independently by two investigators (JQP and YFZ). Our initial search identified 183 records from databases. After removing 18 duplicates, 165 records were screened by title and abstract. This led to the exclusion of 113 records for the following reasons: not case or case series (eg., reviews, animal studies; n=15) and irrelevance to the research question (n=98). Subsequently, 52 full-text articles were assessed for eligibility. Of these, 25 were excluded because they involved PAP without co-infection (n=3) or had an unclear chronology between infection and WLL (n=22). This process culminated in the inclusion of 27 studies for the final analysis, as detailed in the PRISMA flow diagram (Figure 5).

Data from the final included studies were extracted into Supplementary Table 2. The extracted variables included first author, publication year, patient age and sex, the type of infecting pathogen, the timing of WLL relative to anti-infective therapy, and patient outcome. The systematic review included 27 unique cases of PAP with co-infection treated with WLL.[10–36] The cohort comprised 18 male and 9 female patients, with ages ranging from 22 to 69 years. The identified pathogens were diverse, including viral (eg., *SARS-CoV-2*),[24] bacterial (eg., *Nocardia spp., Mycobacterium spp., Pseudomonas*),[18,23,32] and fungal agents (eg., *Aspergillus, Cryptococcus, Histoplasma*).[12,33,34] Management strategies regarding the timing of WLL varied: it was performed

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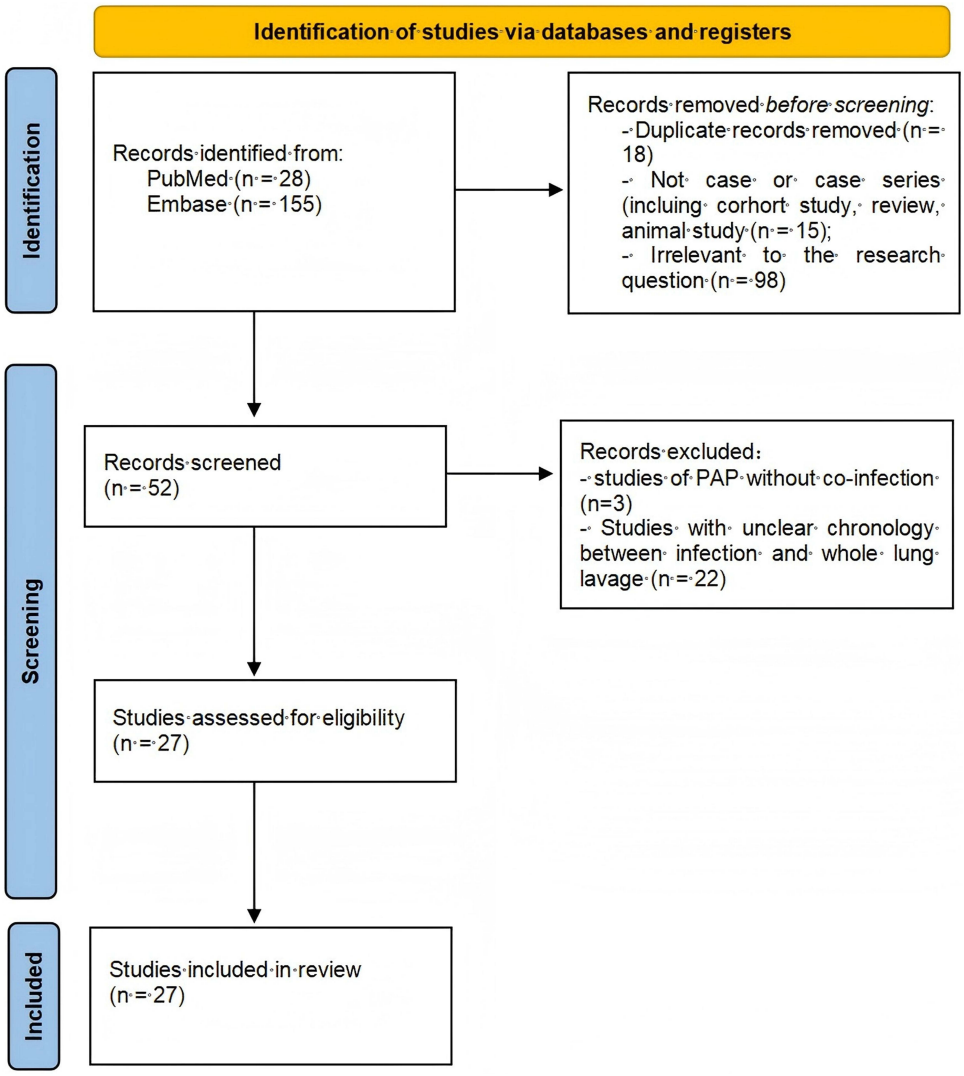

Figure 5 PRISMA flow diagram of the study selection process for the systematic review of pulmonary alveolar proteinosis with co-infection.
Abbreviation: PAP, pulmonary alveolar proteinosis.

during active anti-infective therapy in one cases,[24] after the active infection was controlled or had resolved following the initiation of antimicrobial therapy in the majority (25 cases),[11–23,25–36] and before antifungal treatment in one case.[10] The outcome was generally favorable, with clinical improvement reported in 23 cases (85.2%).[10–16,18–23,25–32,34,36] One patient experienced limited improvement,[33] one had disease progression,[17] and one mortality was reported.[24] The outcome for one case was unknown.[35]

Discussion

The fatal outcome in this aPAP case, despite aggressive support with V–V ECMO and WLL, compels a critical re-evaluation of the standard therapeutic sequence in the context of co-infection. Our experience, contextualized by the literature review, crystallizes a critical management framework built upon two sequential pillars. First, our case underscores the paradigm-shifting role of targeted next-generation sequencing (tNGS) in the diagnostic algorithm for aPAP with suspected infection. The immunodeficiency inherent in aPAP not only predisposes to opportunistic infections but also likely contributes to the documented inadequacy of conventional microbiological methods. In this context, the superior sensitivity of tNGS proves decisive. As exemplified in our patient, tNGS successfully identified *Cryptococcus neoformans* as the dominant pathogen despite concurrent negative serological tests, a finding that directly and correctly guided the initial antimicrobial strategy. This aligns with growing evidence from other complex respiratory infections,

where BALF-tNGS has demonstrated significantly higher sensitivity (87.5%) compared to traditional assays (43.8%) and serum GM testing (21.9%).[37] Therefore, we posit that the integration of tNGS early in the diagnostic workup is essential to establish the etiological basis for targeted therapy—the foundational step in managing infected aPAP patients.

The distinction between nucleic acid detection and active infection warrants discussion. While tNGS does not prove viability, several factors supported invasive cryptococcosis in our patient: the high fungal read count, the severe aPAP-related immunodeficiency, and the characteristic clinical-radiological picture. Notably, the negative cryptococcal antigen in both serum and BALF aligns with the documented low sensitivity of these tests in cases of isolated pulmonary cryptococcosis without dissemination.[38] This known limitation of antigen testing in immunocompromised hosts justified the initiation of targeted antifungal therapy based on the strong molecular and clinical evidence, highlighting tNGS's critical role in diagnosing occult invasive fungal disease when conventional assays are falsely negative.[39]

Second, and most critically, our experience provides compelling evidence to define the optimal therapeutic sequence: infection control must unequivocally precede WLL. The central dilemma lies in balancing the risk of infection dissemination during lavage against the consequences of progressive respiratory failure. Our analysis identified a single fatality among the 27 reported cases. This death, which includes our present case, occurred in a patient who underwent WLL during active infection and significant systemic inflammation.[24] This consistent pattern strongly indicates that performing WLL in the setting of uncontrolled infection is associated with a prohibitive mortality risk. Consequently, WLL should be reconceptualized not as an emergent rescue therapy, but as an elective procedure deferred until after confirmed microbiological clearance and resolution of systemic inflammation.

In this case, inhaled GM-CSF before WLL demonstrated limited therapeutic efficacy, likely attributable to impaired drug delivery caused by accumulated lipoprotein-rich material within the alveolar space. This treatment failure necessitated consideration of more definitive therapy, leading to the crucial question of optimal timing for WLL. Crucially, our analysis of reported PAP cases with co-infections underscores that the timing of WLL relative to infection control is a critical determinant of survival. This is starkly illustrated by the sole fatality in our cohort, reported by Coirier et al, where WLL performed during uncontrolled COVID-19 was followed by fatal hemorrhagic shock.[24] These collectively indicate that WLL is contraindicated in active bacteremia/fungemia or significant systemic inflammation. Conversely, most survivors underwent elective WLL deferred until microbiological clearance: Cases from Shiohira et al,[40] Lee et al,[41] and Martin et al[31] achieved sustained remission after targeted antimicrobial therapy, while Melhem et al[27] reported successful salvage WLL for post-COVID respiratory failure without evidence of ongoing viral replication. While current guidelines lack specific recommendations regarding the optimal timing of WLL in PAP patients with concurrent infections, our analysis of these clinical outcomes strongly suggests that deferring the procedure until confirmed microbiological clearance and resolution of systemic inflammation may significantly improve patient safety and treatment efficacy. Although these findings are consistent across reported cases, publication bias from underreported negative outcomes may inflate the observed effect size.

This case exhibits distinct clinical features compared to 27 previously reported PAP-coinfection cases: (1) Polymicrobial coinfection involving drug-resistant Gram-negative bacteria (including *carbapenem-resistant but non-MDR A. baumannii*) and fungi, indicating enhanced therapeutic complexity; (2) Accelerated disease progression to respiratory failure within 1 month, underscoring the need for vigilant monitoring in infected aPAP patients; (3) Refractory clinical course culminating in fatal outcome despite ECMO support and aggressive antimicrobial therapy, highlighting synergistic challenges of uncontrolled infection and compromised immunity.

Based on integrated evidence from this case and literature review, we emphasize: (1) proactive infection risk assessment in PAP patients upon detecting fever, new radiological changes, or elevated inflammatory biomarkers, mandating prompt microbiological evaluation; (2) early adoption of molecular diagnostics (eg., tNGS) to enhance pathogen identification and precision antimicrobial therapy; (3) Strictly evaluate the timing of WLL to avoid clinical deterioration (4) personalized, multidisciplinary regimens tailored to pathogen profiles, infection foci, and host immunity. Future priorities should develop validated infection-risk prediction models and establish evidence-based protocols through multicenter cohorts to optimize therapeutic sequencing and outcomes.

Several limitations in our analysis warrant consideration. First, the conclusions regarding WLL timing are drawn from a relatively small sample size of reported cases, which limits the statistical power of our findings. Second, there is a high potential for publication bias, as cases with fatal outcomes or unusual presentations are more likely to be published, potentially

inflating the perceived strength of the association between WLL during infection and mortality. Third, the lack of data consistency across the heterogeneous case reports, with varying details on inflammatory markers and microbial burden, precluded a more formal quantitative meta-analysis. Fourth, while tNGS proved critical for pathogen identification in our case, the specific read count thresholds used for clinical significance were not specified in the report. Finally, the tNGS findings could not be independently validated by conventional microbial cultures, as both BALF and sputum cultures returned no growth, a discrepancy likely reflecting prior antimicrobial therapy. Despite these limitations, the consistent clinical narrative across all available cases provides a compelling argument for a cautious, staged management approach.

Conclusion

This fatal aPAP case suggests a staged management approach whereby WLL should be deferred until infection control is achieved. Early tNGS-guided pathogen identification appears crucial for directing antimicrobial therapy. This target-then-lavage strategy merits further validation but offers a prudent framework for managing these high-risk patients.

Ethics Statement

This study complied with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of West China Hospital.

Patient Consent

Informed consent for publication was obtained from the patient's next of kin. The family members were fully informed about the nature of the case report and agreed to the publication of clinical details and images.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declared no conflicts of interest in this work.

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