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Analysis and Perception of *Chlamydia psittaci* Pneumonia: Novel Insights of the Rare Disease in Infectiology

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Objective: To investigate and analyze the clinical features, diagnosis and treatment, and prognosis of rare *Chlamydia psittaci* pneumonia, and to improve the understanding of this rare disease.

Methods: A retrospective analysis and exploration was performed for 33 cases of patients with *Chlamydia psittaci* pneumonia in the First Affiliated Hospital of Gannan Medical University from January 2017 to March 2024, and the clinical features, diagnosis, treatment and key points for differential diagnosis were summarized and analyzed. Meanwhile, the latest literature from PubMed was retrieved to systematically discuss the research progress in *Chlamydia psittaci* pneumonia.

Results: A total of 33 patients with *Chlamydia psittaci* pneumonia were included in this study, including 21 males (63.64%) and 12 females (36.36%), with a median age of 59 (32–79) years. There were 27 cases (81.82%) of patients accompanied with a history of poultry contact, 22 patients (66.67%) had underlying diseases. In our study, patients with *Chlamydia psittaci* pneumonia were mainly affected in Autumn (21.21%) and Winter (54.55%). All patients had undergone bronchoscopy and obtained bronchoalverolar lavage fluid (BALF) for metagenomic next-generation sequencing (mNGS) detection, and mNGS results showed that all patients (100%) were co-infected with multiple pathogens including *Chlamydia psittaci*. All patients were given antimicrobial therapy after diagnosis, and no treatment-related adverse reactions or adverse events were observed in our study, the average length of hospitalization was 11.09 days. Fortunately, no death was observed in our study, and patients were all discharged from hospital after recovery and in favourable physical and psychological conditions after discharge.

Conclusion: *Chlamydia psittaci* pneumonia lacks specific clinical features or manifestations and tends to develop into severe exacerbation. mNGS could help to achieve an accurate diagnosis. Early administration of antibiotics can improve the prognosis of patients to the greatest extent.

Keywords: *Chlamydia psittaci* pneumonia, clinical features, diagnosis, differential diagnosis, precise treatment, mNGS, evidence-based medicine, prognosis

Introduction

Community-acquired pneumonia (CAP) is one of the most commonly treated diseases in the respiratory department and intensive care unit (ICU), while *Chlamydia psittaci* pneumonia is a clinically rare zoonotic disease caused by *Chlamydia psittaci* infection and also a zoonotic infectious disease, accounting for about 1% of CAP.[1–3] It can occur when exposed to contaminated faeces and nasal secretions from infected birds or poultry, resulting in widespread infection in humans and animals, posing significant socio-economic and public health security challenges, and is a truly notorious rare

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subtype of CAP. Patients with mild *Chlamydia psittaci* pneumonia may have no clinical manifestations or symptoms, while those with severe cases may have severe pneumonia, multiple organ failure, and even death.[4,5] Early diagnosis of *Chlamydia psittaci* infection is one of the keys to clinical diagnosis, treatment and prevention, and accurate detection results play an indispensable role in controlling disease progression, improving patient prognosis and reducing mortality.[6] However, the clinical manifestations of *Chlamydia psittaci* pneumonia are mainly characterized by fever, chills, sore throat, headache, fatigue and muscle pain and other non-specific influenza-like symptoms, which may also be accompanied by some symptoms or signs such as rash, vomiting, diarrhea,[7,8] which undoubtedly brings major difficulties and challenges to the early diagnosis of *Chlamydia psittaci* pneumonia. This leads to the aggravation of patients' condition and poor prognosis.

Due to the low incidence of *Chlamydia psittaci* pneumonia, which is rare in clinical practice and often accompanied by sudden and critical conditions, there have been few systematic and comprehensive clinical studies on *Chlamydia psittaci* pneumonia, and most of them are the case reports from single-center. Meanwhile, the studies on the diagnosis and differentiation, diagnosis and treatment progress and prognosis of *Chlamydia psittaci* pneumonia are limited and single. To this end, this study retrospectively analyzed the clinical data of 33 patients with *Chlamydia psittaci* pneumonia admitted to the First Affiliated Hospital of Gannan Medical University from January 2017 to April 2024, and deeply explored the clinical characteristics and main points of diagnosis and treatment of *Chlamydia psittaci* pneumonia, in order to provide references for basic research and clinical diagnosis and treatment of *Chlamydia psittaci* pneumonia.

Materials and Methods

Research Object

This study retrospectively analyzed the clinical data of 33 patients with *Chlamydia psittaci* pneumonia diagnosed by bronchoalveolar lavage fluid (BALF) metagenomic next-generation sequencing (mNGS) combined with medical imaging and laboratory examination in the First Affiliated Hospital of Gannan Medical University from January 2017 to March 2024. All cases included in this study met the diagnostic criteria for CAP in the guidelines.[9,10] This study was approved by the medical ethics committee of the First Affiliated Hospital of Gannan Medical University, and all the patients or their families signed informed consent.

Research Method

Clinical data of all patients with *Chlamydia psittaci* pneumonia included in this study were collected and analyzed, including: (1) Gender, age, underlying diseases, epidemiological history and other baseline data; (2) Clinical symptoms and signs; (3) Blood routine examination, blood biochemical examination, arterial blood gas analysis and other laboratory examination results; (4) Changes of pulmonary imaging results such as computed tomography (CT) and mNGS results during hospitalization; (5) The results of bronchofiberscopy and pathological examination; (6) Treatment and prognosis during hospitalization. All patients included in this study were diagnosed by clinical doctors. Naturally, the multi-disciplinary team (MDT) collaboration involving microbiologists and specialists from other clinical disciplines within the hospital was also consulted.

mNGS Detection

The patients' condition failed to improve following the routine anti-infection treatment upon admission, and the symptoms gradually deteriorated, thus making it necessary to conduct the fiberoptic bronchoscopy. BALF specimens were retained during the bronchoscopy, and the time for each patient to obtain BALF specimens for mNGS detection varied. The workflow of mNGS sample collection and processing includes nucleic acid extraction, library construction, sequencing, and sequencing data analysis. The specific detection process was as follows: (1) BALF samples were collected, and the potentially contaminated part of the front segment was discarded, while 6 to 10 mL of the remaining sample was placed into a sterile tube. Additionally, 3 to 5 mL blood samples were collected from patients, placed in a sample storage tube free of DNA and stored at 4°C. (2) Fully automated nucleic acid extraction was carried out with NGSmaster™. (3) Library construction was conducted using PCR-free technology. The Agilent 2100 Bioanalyzer

Instrument and Qubit 3.0 (Thermo Fisher Scientific, USA) platform were used for library quality control. (4) An Illumina high-throughput sequencer was used for sequencing. (5) Pathogenic microbial gene data were analysis automatically using the provided software. High-quality sequencing data were obtained by removing low-quality and short (length <35 bp) reads.

Diagnostic Criteria

The diagnostic criteria for *Chlamydia psittaci* pneumonia included in this study were as follows: (1) In line with the latest version of the diagnostic criteria for CAP at the time of admission. (2) The patient was diagnosed with *Chlamydia psittaci* pneumonia by CT and mNGS. (3) Previous history of contact with poultry or birds or related poultry breeding history. In addition, severe pneumonia is diagnosed according to the guidelines of the American Thoracic Society/ Infectious Diseases Society of America,[10] that is, one or more of the following symptoms or signs can be diagnosed as severe pneumonia:[11] (1) Disturbance of consciousness; (2) Respiratory rate ≥30 times/min; (3) PaO_2 < 60mmHg; PaO_2 /FiO_2 < 300mmHg, need mechanical ventilation; (4) Arterial systolic blood pressure < 90mmHg; (5) Septic shock; (6) Chest X-ray shows bilateral or multiple lobe involvement, or the lesion enlarges ≥50% within 48 h of admission; (7) Urine volume <20mL/h, or <80mL/4h, or combined with acute renal failure, requiring dialysis treatment.

Exclusion Criteria

Exclusion criteria: (1) *Chlamydia psittaci* pneumonia was initially diagnosed in the respiratory department, infectious disease clinic or fever clinic without admission; (2) Patients with *Chlamydia psittaci* pneumonia referred to our hospital from treatment in other hospital(s); (3) Patients with *Chlamydia psittaci* pneumonia who have incomplete medical history, irregular diagnosis and treatment, or give up treatment midway; (4) Patients with *Chlamydia psittaci* pneumonia who did not agree to be included in this study due to privacy reasons.

Prognosis Follow-Up

The electronic inpatient record system was used to follow up the indicators of patients' recent return to the hospital for re-examination and hospitalization status, and the follow-up was conducted by telephone contact. The follow-up period was May 1, 2024.

Statistical Analysis

SPSS 26.0 software was used for statistical analysis. Measurement data conforming to normal distribution were expressed as mean ± standard deviation, and measurement data that did not conform to normal distribution were represented by median (quartile). Count data were expressed as cases or cases (%) using χ^2 test (Fisher's precision probability test). $P<0.05$ indicated that the difference was statistically significant.

Results

Baseline Data and Clinical Features

A total of 33 patients with *Chlamydia psittaci* pneumonia were included in this study, including 21 males (63.64%) and 12 females (36.36%), with a median age of 59 (32–79) years. There were 27 cases (81.82%) of patients in our study accompanied with a history of poultry contact, 22 patients (66.67%) had underlying diseases, and in the course of disease progression, 9 patients (27.27%) were converted into severe pneumonia. In our study, patients with *Chlamydia psittaci* pneumonia were mainly affected in Autumn (21.21%) and Winter (54.55%). In clinical manifestations, the first symptoms were mainly non-specific respiratory symptoms such as fever, chills, cough, sputum, and so on. Correspondingly, the patients were also accompanied by dizziness, headache, chest tightness, fatigue, poor appetite and other symptoms. Additionally, among the patients incorporated in this study, some cases presented adverse complications in the circulatory system and respiratory system, precisely encompassing cardiac insufficiency, respiratory insufficiency, sepsis or septic shock, which were the complications of *Chlamydia psittaci* pneumonia. The clinical characteristics and baseline data of all patients with *Chlamydia psittaci* pneumonia are shown in Table 1.

Table 1 Baseline Characteristics of Patients with *Chlamydia psittaci* Pneumonia

Characteristics	Results
Gender	
Male	21 (63.64%)
Female	12 (36.36%)
Age (years)	
≤60	18 (54.55%)
>60	15 (45.45%)
Poultry contact history	
Yes	27 (81.82%)
No or unclear	6 (18.18%)
First respiratory symptoms*	
Fever	32 (96.97%)
Cough	24 (72.73%)
Expectoration	19 (57.58%)
Chilliness	22 (66.67%)
Dyspnea	9 (27.27%)
Gasp	7 (21.21%)
Other non-specific symptoms or signs*	
Dizzy	19 (57.58%)
Headache	15 (45.45%)
Weakness or fatigue	14 (42.42%)
Thoracodynia	8 (24.24%)
Bloating or vomiting	7 (21.21%)
Muscle soreness	7 (21.21%)
Others	6 (18.18%)
Underlying diseases history*	
Cardiovascular diseases	11 (33.33%)
Neurological or psychiatric disorders	9 (27.27%)
Endocrine diseases	5 (15.15%)
Hematological or rheumatic diseases	3 (9.09%)
Others	2 (6.06%)

(*Continued*)

Table 1 (Continued).

Characteristics	Results
Onset season of *Chlamydia psittaci* pneumonia	
Spring	3 (9.09)
Summer	5 (15.15)
Autumn	7 (21.21)
Winter	18 (54.55)
Adverse complications*	
Cardiac insufficiency	7 (21.21)
Respiratory insufficiency	9 (27.27%)
Sepsis or septic shock	5 (15.15%)

Note: *indicates that some patients may have symptoms or signs of multiple organ systems at the same time, that is, a patient may have several clinical symptoms.

Blood Laboratory Examination results

Among the 33 patients with *Chlamydia psittaci* pneumonia included in this study, the white blood cell count (WBC) was normal in 20 cases (60.61%), increased in 10 cases (30.30%) and decreased in 3 cases (9.09%). Hemoglobin (HGB) was normal in 24 cases (72.73%) and decreased in 9 cases (27.27%). Neutrophil percentage (NE) increased in 29 cases (87.88%). C-reactive protein (CRP) was significantly elevated in all patients (100.0%). Procalcitonin (PCT) was elevated in 19 patients (57.58%). Lactate dehydrogenase (LDH) was elevated in 29 patients (87.88%). Correspondingly, 25 patients (75.76%) accompanied with hepatic insufficiency, 18 patients (54.55%) accompanied with renal dysfunction, 14 patients (42.42%) accompanied with coagulation disorders, and 28 patients (84.85%) accompanied with electrolytes disturbance.

Arterial Blood Gas Analysis and mNGS Detection

Among the 33 patients with *Chlamydia psittaci* pneumonia included in this study, except for 6 patients (18.18%) who had no obvious dyspnea and were not examined by arterial blood gas analysis, the remaining 27 patients (81.82%) showed different degrees of blood oxygen partial pressure reduction by arterial blood gas analysis, of which 14 patients (51.85%) accompanied with oxygenation index (OI) lower than 300 mmHg. All the 33 patients with *Chlamydia psittaci* pneumonia included in this study had undergone bronchoscopy and obtained BALF for mNGS detection, and mNGS results showed that all patients (100%) were co-infected with multiple pathogens including *Chlamydia psittaci*. Other major detected pathogens encompass the following: *Candida albicans* (17 cases, 51.52%), *Staphylococcus aureus* (13 cases, 39.39%), *Aspergillus fumigatus* (9 cases, 27.27%), *Streptococcus pneumoniae* (9 cases, 27.27%), *Klebsiella pneumoniae* (8 cases, 24.24%), *Haemophilus influenzae* (8 cases, 24.24%), *Pseudomonas aeruginosa* (7 cases, 21.21%), *Enterobacter cloacae* (4 cases, 12.12%), *human herpesvirus type B* (3 cases, 0.09%), *human herpesvirus type 1* (2 cases, 0.06%), *Acinetobacter baumannii* (2 cases, 0.06%), *Corynebacterium striata* (1 case, 0.03%), *Neisseria meningitidis* (1 case, 0.03%), *Micromonas micromonas* (1 case, 0.03%).

Imaging Findings

All patients included in this study have completed chest CT and other imaging examinations, and some patients showed a variety of imaging findings, including solid shadow, ground glass shadow, mass solid shadow, reverse halo sign, mediastinum and hilar lymph node enlargement. Typical imaging lesions of patients with *Chlamydia psittaci* pneumonia were shown in Figure 1. The chest X-ray anteroposteric film before treatment (Figure 1A) indicated that both lungs were infected, right pleural hypertrophy and adhesion, and small pleural effusion on the left. Before treatment, chest CT (Figure 1B and D) showed that bilateral lung infection, considering atypical pathogens, partial consolidation of lung

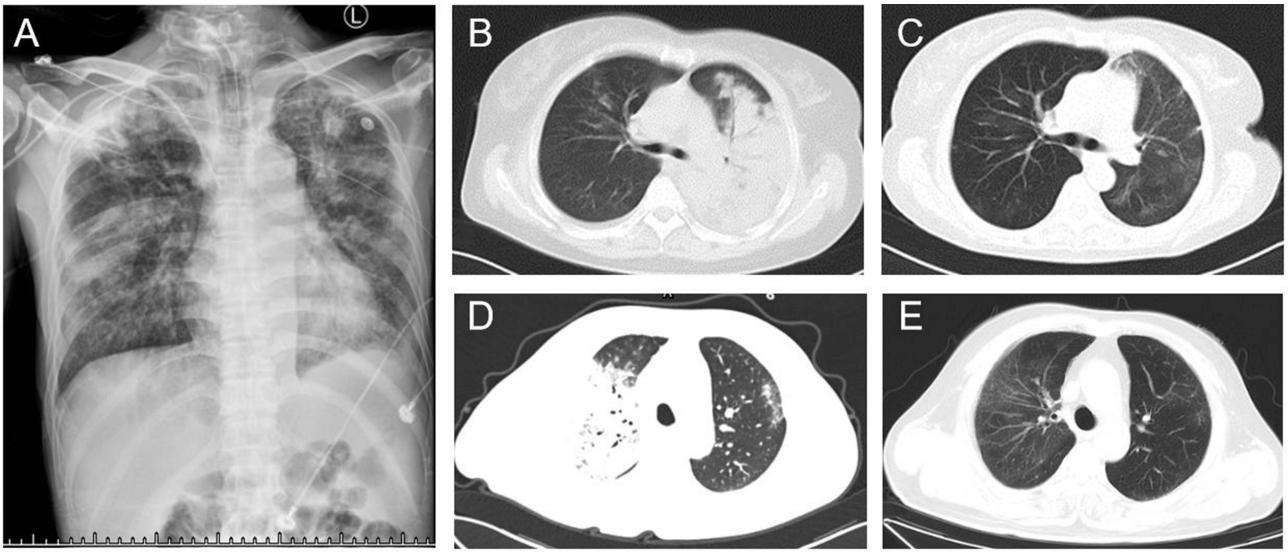

Figure 1 Typical imaging features of *Chlamydia psittaci* pneumonia.
Notes: (**A**) Chest X-ray of patients with *Chlamydia psittaci* pneumonia before treatment indicated 1. Double lung infection; 2. Right pleural hypertrophy and adhesion; 3. Left pleural effusion. (**B**), (**D**): Chest CT findings in patients with *Chlamydia psittaci* pneumonia before treatment showed that 1. Double lung infection, atypical pathogens were considered; 2. Pleural effusion. (**C**), (**E**): Chest CT of patients with *Chlamydia psittaci* pneumonia after treatment indicated that the lesions in both lungs were absorbed.

lobes, and the pleural effusion is visible. While after treatment, chest CT (Figure 1C and E) indicated that the thoracic morphology was normal, the lung field was clear, and the bronchus of both lobes and segments were unobstructed, no enlarged lymph nodes were found in the interstitial space of the mediastinum, and there was no effusion in both pleural cavities. The specific results of CT imaging features of 33 patients with *Chlamydia psittaci* pneumonia in this study are shown in Table 2.

Table 2 The CT Imaging Features of 33 Patients with *Chlamydia psittaci* Pneumonia

CT Imaging Features	Results
Lesion site *	
Unilateral lung lobe	25 (75.76%)
Bilateral lung lobes	8 (24.24%)
Confining the upper lobe	9 (27.27%)
Confining the lower lobe	19 (57.58%)
Multiple lung lobes	5 (15.15%)
Only the left lung is involved	11 (33.33%)
Only the right lung is involved	17 (51.51%)
Imaging features *	
Ground glass shadow	16 (48.48%)
Solid shading (including unilateral or bilateral)	18 (54.55%)
Pleural effusion (unilateral or bilateral)	14 (42.42%)
No pleural effusion	19 (57.58%)

Note: *indicates that the patients may have multiple lesions at the same time in results of cardiac instrumental examination, that is, a patient may accompany with several clinicopathological features.

Features and Manifestations Under Tracheoscopy

In this study, patients with *Chlamydia psittaci* pneumonia showed mostly hyperemia and edema of the trachea mucosa on the side of the patient under tracheoscopy, with only a small amount of secretions visible in 22 patients (66.67%), medium to large amounts of yellowish white secretions visible in 9 patients (27.27%), and hemorrhagic secretions in 2 patients (6.06%) under the tracheoscopy. Typical bronchoscopic features and manifestations of patients with *Chlamydia psittaci* pneumonia are shown in Figure 2.

Pathological Examination After Tracheoscopy

All patients included in the study underwent tracheoscopy, and 14 patients (42.42%) underwent bronchoscopic pulmonary biopsy and pathological examination. Typical pathological changes included widening of alveolar intervals with fibrous tissue hyperplasia, infiltration of lymphoplasma cells and neutrophils, active alveolar epithelial hyperplasia, inflammatory exudation and histopathocyte aggregation in the alveolar cavity, and bleeding in some alveolar cavities, which was consistent with the changes of alveolitis. Tracheoscopic pathology of 5 patients (15.15%) indicated Masson body formation, which was consistent with organizing pneumonia. The pathological results are shown in Figure 3.

Treatment and Prognosis

All patients with *Chlamydia psittaci* pneumonia included in this study were given antimicrobial therapy after diagnosis, of which 4 patients (12.12%) received extracorporeal membrane oxygenation (ECMO) adjuvant therapy, and 8 patients (24.24%) received monotherapy after diagnosis. There were no significant differences in prognosis and length of hospital

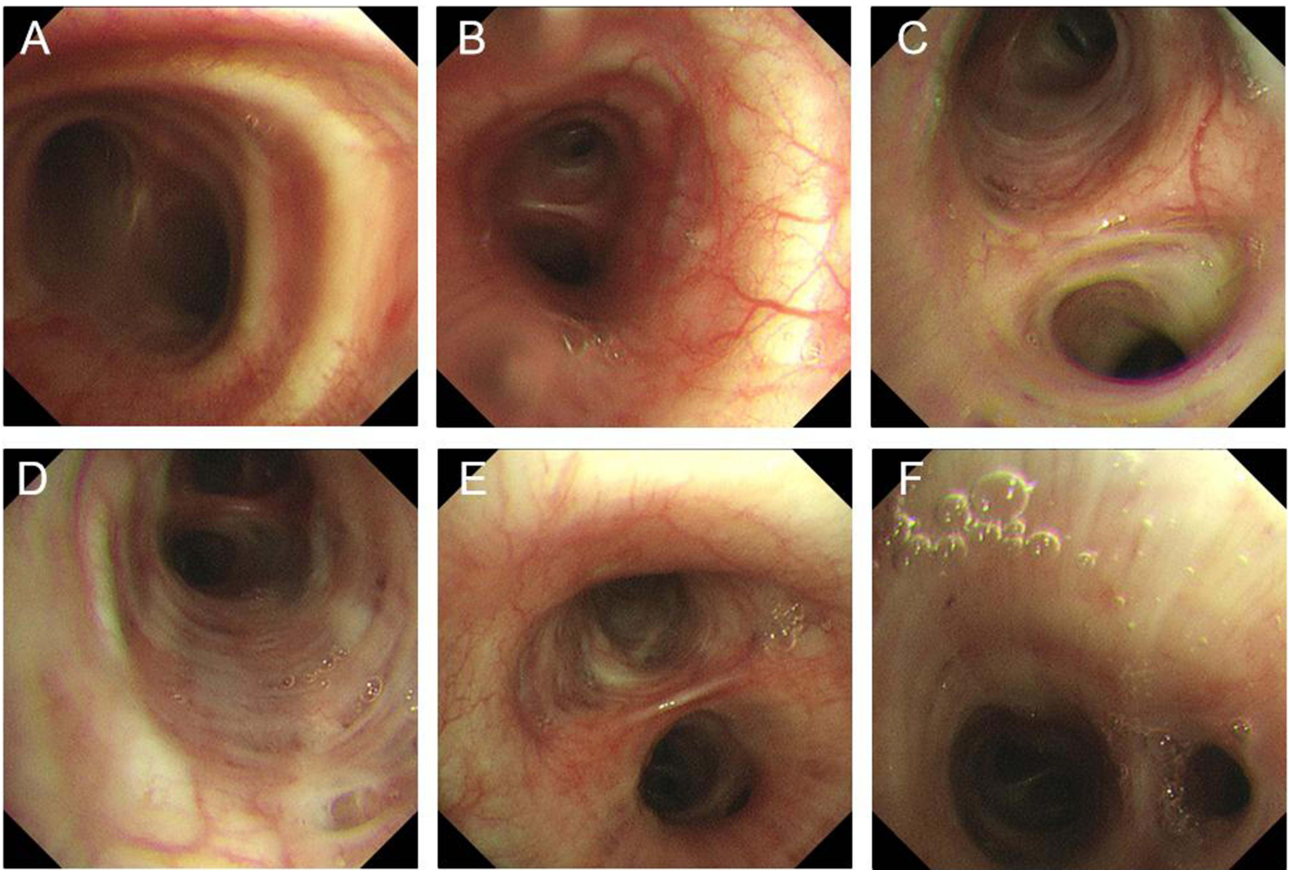

Figure 2 Typical tracheoscopic manifestations of *Chlamydia psittaci* pneumonia. Tracheoscopy indicated sharp tracheal carina and good motion. The bronchial tube lumen of trachea and each lobe of both lungs were unobstructed and the mucosa was smooth. The upper lobe of the right lung and the upper lobe of the left lung were obviously congested. The bronchial mucosa of other parts was mildly congested, and no bleeding or new organisms were observed.
Notes: (**A**) carina of trachea; (**B**) left main bronchus; (**C**) left superior lobar bronchus; (**D**) right superior lobar bronchus; (**E**) right median segmental bronchus; (**F**) right inferior lobar bronchus.

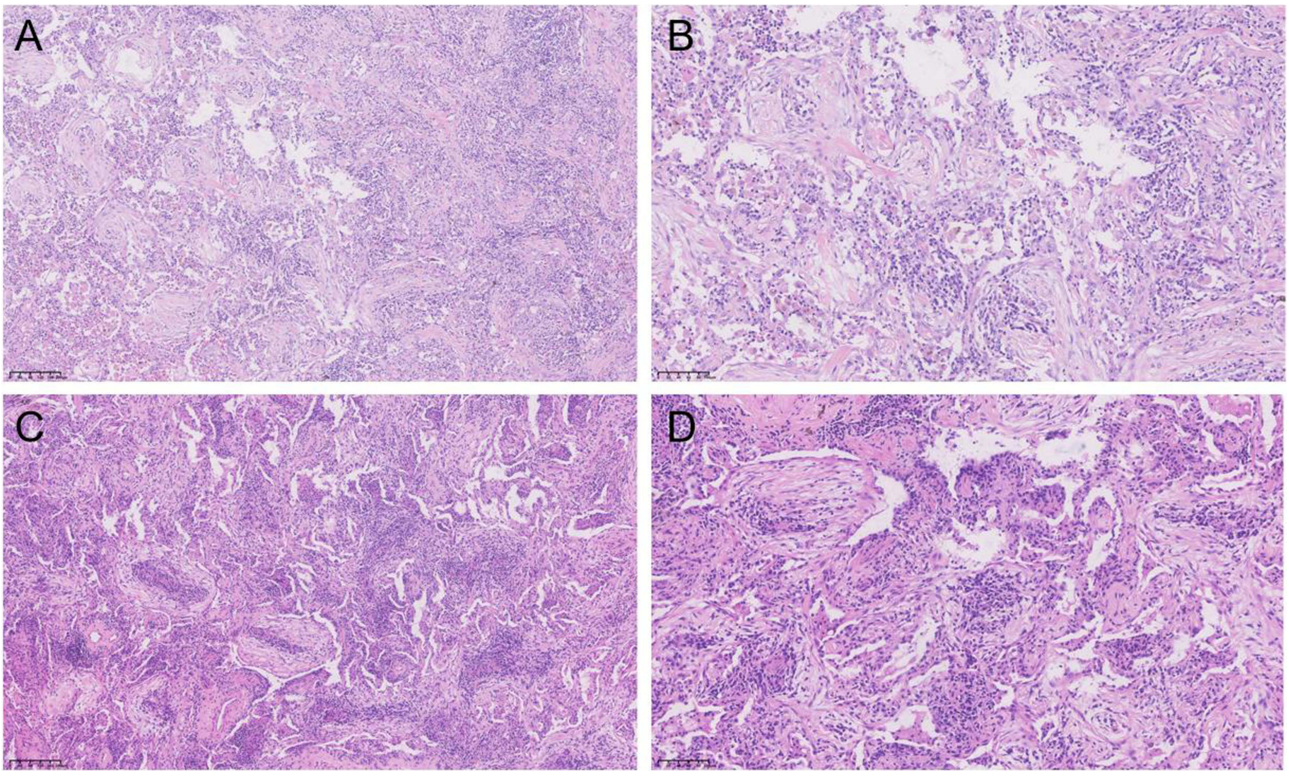

Figure 3 Pathological findings of tracheoscopic lung biopsy in patients with *Chlamydia psittaci* pneumonia. (**A**). Widening of alveolar septum with fibrous tissue proliferation and lymphocyte infiltration; (**B**). Alveolar epithelial cells proliferated and macrophage aggregation was observed in the alveolar cavity; (**C**) Multiple light-stained, fibrous cell mass structures (Masson bodies) in the alveolar cavity; (**D**) Masson corpuscles were mainly composed of layered fibroblasts, inflammatory cells and mucoid matrix.
Notes: (**A**), (**C**) is hematoxylin-eosin (HE) staining, ×10. (**B**), (**D**) is HE staining, ×20.

stay between the monotherapy group (8 cases, 24.24%) and the combined treatment group (25 cases, 75.76%) (P>0.05). No treatment-related adverse reactions or adverse events were observed in all patients, and the average length of hospitalization was 11.09 days. Fortunately, no death was observed in our study, and all of them were discharged from hospital after recovery. Our follow-up showed that all the patients were in favourable physical and psychological condition after discharge. The details of treatment and prognosis of patients with *Chlamydia psittaci* pneumonia are shown in Table 3.

Discussion

CAP is a common and severe respiratory disease in clinical practice, which often leads to aggravation of patients in the department of respiratory, cardiology, and ICU wards in hospitals, and is associated with high mortality.[12,13] *Chlamydia psittaci* pneumonia is a rare kind of CAP that can infect a wide range of animal hosts and then cause human infection with *Chlamydia psittaci* through corresponding vectors.[14] As a typical zoonotic infectious disease, the severity of *Chlamydia psittaci* pneumonia can range from mild to severe. In addition to special epidemiological contact history, the clinical manifestations of patients with *Chlamydia psittaci* pneumonia lack specificity, and it is difficult to distinguish them from other types of CAP, and it is easy to misdiagnose and miss diagnosis. As a result, some patients were delayed in diagnosis and treatment and developed into severe pneumonia.[15] In the past, due to the limitations of relevant detection methods and poor diagnosis and treatment standards, there were few academic reports on *Chlamydia psittaci* pneumonia, and the existing case reports were mostly single-center case reports, lacking systematic clinical research, diagnosis and treatment analysis of *Chlamydia psittaci* pneumonia. With the popularization and application of mNGS technology in clinical practice, the confirmed cases of *Chlamydia psittaci* pneumonia are increasing year by year, which is likely to pose a public health risk and deserves the attention of academic circles and clinical practitioners.

Table 3 Treatment and Prognosis of 33 Patients with *Chlamydia psittaci* Pneumonia

Case Number	Treatment Options After Diagnosis	Adverse Reaction	Length of Stay (days)	Medication and Course of Treatment After Discharge	Prognosis
1	Doxycycline + Meropenem + Moxifloxacin	None	9	Moxifloxacin for 9 days	Rehabilitate and survive
2	Azithromycin	None	15	Moxifloxacin + azithromycin for 9 days	Rehabilitate and survive
3	Piperacillin sodium tazobactam sodium + levofloxacin	None	8	Moxifloxacin for 6 days	Rehabilitate and survive
4	Imipenem and cilastatin sodium + moxifloxacin + doxycycline + voriconazole + piperacillin sodium and tazobactam sodium, VV-ECMO adjuvant	None	14	Voriconazole + doxycycline + moxifloxacin for 9 days	Rehabilitate and survive
5	Meropenem + azithromycin + doxycycline + moxifloxacin + piperacillin sodium and tazobactam sodium	None	30	Cefaclor + moxifloxacin for 9 days	Rehabilitate and survive
6	Moxifloxacin + cefoperazone sodium and sulbactam sodium	None	7	Moxifloxacin for 9 days	Rehabilitate and survive
7	Azithromycin + doxycycline + cefoperazone sodium and sulbactam sodium	None	20	Azithromycin + cefaclor for 9 days	Rehabilitate and survive
8	Moxifloxacin	None	7	Moxifloxacin for 6 days	Rehabilitate and survive
9	Moxifloxacin	None	16	Moxifloxacin for 15 days	Rehabilitate and survive
10	ECMO, moxifloxacin + doxycycline + piperacillin sodium and sulbactam sodium	None	45	Moxifloxacin + cefaclor for 15 days	Rehabilitate and survive
11	Moxifloxacin	None	10	None	Rehabilitate and survive
12	Piperacillin sodium and tazobactam sodium + doxycycline	None	9	Moxifloxacin + doxycycline for 9 days	Rehabilitate and survive
13	Moxifloxacin + doxycycline	None	9	Moxifloxacin + doxycycline was treated for 12 days	Rehabilitate and survive
14	Piperacillin sodium and tazobactam sodium	None	9	Cefaclor + doxycycline for 7 days	Rehabilitate and survive

(*Continued*)

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Table 3 (Continued).

Case Number	Treatment Options After Diagnosis	Adverse Reaction	Length of Stay (days)	Medication and Course of Treatment After Discharge	Prognosis
15	Moxifloxacin + Linezolid + doxycycline	None	9	Moxifloxacin + doxycycline for 18 days	Rehabilitate and survive
16	Imipenem cilastatin sodium + moxifloxacin + doxycycline	None	9	Doxycycline for 14 days	Rehabilitate and survive
17	Ceftazidime + moxifloxacin + doxycycline, piperacillin sodium and sulbactam sodium	None	8	Moxifloxacin + doxycycline for 9 days	Rehabilitate and survive
18	Moxifloxacin + doxycycline	None	9	Moxifloxacin + doxycycline for 9 days	Rehabilitate and survive
19	Imipenem and cilastatin sodium + doxycycline	None	12	Doxycycline for 9 days	Rehabilitate and survive
20	Cefoperazone sulbactam + moxifloxacin + doxycycline	None	8	Doxycycline + cefixime for 7 days	Rehabilitate and survive
21	Moxifloxacin + doxycycline	None	6	Moxifloxacin + doxycycline for 9 days	Rehabilitate and survive
22	Moxifloxacin + doxycycline	None	7	Moxifloxacin + doxycycline for 7 days	Rehabilitate and survive
23	Piperacillin sodium and tazobactam sodium	None	15	Doxycycline for 7 days	Rehabilitate and survive
24	Moxifloxacin + doxycycline	None	8	Moxifloxacin + doxycycline for 7 days	Rehabilitate and survive
25	Moxifloxacin + doxycycline	None	8	Moxifloxacin + doxycycline for 7 days	Rehabilitate and survive
26	Moxifloxacin + doxycycline + piperacillin sodium and sulbactam sodium	None	9	Doxycycline for 10 days	Rehabilitate and survive
27	Moxifloxacin	None	7	Moxifloxacin for 6 days	Rehabilitate and survive
28	Moxifloxacin + piperacillin sodium and sulbactam sodium	None	7	Moxifloxacin for 6 days	Rehabilitate and survive

29	Moxifloxacin + piperacillin sodium and sulbactam sodium	None	10	Moxifloxacin for 6 days	Rehabilitate and survive
30	Moxifloxacin + piperacillin sodium and sulbactam sodium	None	7	Moxifloxacin for 6 days	Rehabilitate and survive
31	Moxifloxacin	None	8	Moxifloxacin for 6 days	Rehabilitate and survive
32	Doxycycline + piperacillin sodium and sulbactam sodium	None	5	Doxycycline for 7 days	Rehabilitate and survive
33	Moxifloxacin + doxycycline	None	6	Doxycycline for 7 days	Rehabilitate and survive

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In terms of clinical characteristics, *Chlamydia psittaci* pneumonia is more common in elderly men, and it seems that patients with *Chlamydia psittaci* pneumonia were mainly affected in Autumn (21.21%) and Winter (54.55%) in our study. The early clinical symptoms or signs are atypical and the individual differences are obvious: clinical manifestations are often cough, phlegm, high fever, headache, chills, muscle aches and other non-specific symptoms, and there are no significant characteristic changes in imaging, making it difficult to distinguish it from CAP. In addition, some severe patients may have adverse outcomes such as dyspnea, acute respiratory distress syndrome, multiple organ failure, and death.[16,17] Among the 33 patients included in this study, male accounted for about two-thirds, and most of them were elderly. The clinical symptoms and signs of these patients were non-specific. In addition to respiratory symptoms, it was accompanied by symptoms of the nervous system, circulatory system and digestive system, indicating that *Chlamydia psittaci* could not only cause serious involvement and lesions of lung organs but also lead to multiple organ dysfunction and even failure. It is worth noting that in this study, except for 6 patients who had no definite poultry contact history, all the other patients had relevant epidemiological contact history. Therefore, in clinical practice, patients should be examined with detailed epidemiological history, and attention should be paid to whether they had poultry or bird contact history. In addition, in this study, 9 patients (27.27%) who were converted into severe pneumonia had underlying disease history, suggesting that underlying disease history is likely to be a risk factor for severe *Chlamydia psittaci* pneumonia.

In terms of the diagnosis of *Chlamydia psittaci* pneumonia, routine blood tests of patients often show the main characteristics of neutrophil elevation, normal or slight increase of white blood cells, and significant decrease of lymphocytes, and CRP and PCT are significantly increased. The vast majority of patients are complicated with abnormal liver and kidney function, abnormal coagulation function and electrolyte disturbance.[18] It is suggested that *Chlamydia psittaci* has strong pathogenicity, rapid disease progression, and can cause serious immune inflammatory response, which has certain reference value for early diagnosis and recognition of the disease. Previous studies have shown that *Chlamydia psittaci* pneumonia can involve multiple organ systems in addition to the lungs, such as heart, liver, kidney, digestive tract and central nervous system, etc., and symptoms, signs and laboratory abnormalities of the corresponding organ dysfunction may occur in a short period of time.[19,20]

Due to the lack of specificity of laboratory tests, the combination of imaging examinations will help to confirm the diagnosis. Despite the summary and analysis of lung imaging examinations of all patients in this study, we concluded that the lung imaging findings of patients with *Chlamydia psittaci* pneumonia are often characterized by lung consolidation, which is mostly lamellar exudation of unilateral or bilateral lung lobes, and the extent of consolidation is closely related to the severity of the disease. Some patients may have patellar or nodular ground glass shadows and may also have air bronchial signs. Pleural involvement may be accompanied by exudative pleural effusion. Laboratory examination of pleural effusion is dominated by lymphocytes, and the level of adenosine deaminase (ADA) may be elevated. However, there is no doubt that whether it is imaging examination or laboratory examination of pleural effusion, the above mentioned may lack the specificity and sensitivity of diagnosis, so the mNGS detection is still a key means for early diagnosis and differentiation.[21,22] The patients in this study were mostly accompanied by lung consolidation from the imaging perspective, and nearly half of the patients had unilateral or bilateral pleural effusion, which was also consistent with the conclusions of previous studies. In addition, patients with improved blood gas analysis were often accompanied by hypoxemia and respiratory failure, indicating once again that *Chlamydia psittaci* has strong virulence and severe immunoinflammatory response, resulting in rapid progression of lung lesions and significant imbalance of pulmonary ventilation/blood flow ratio.

It should be noted that previous laboratory tests for *Chlamydia psittaci* include etiological culture, serological test, polymerase chain reaction (PCR), and so on. However, these methods usually show difficulty in detection, low positive rate and poor sensitivity, and cannot be routinely carried out and popularized in clinical practice. However, it is gratifying that mNGS has now become an efficient and accurate detection method for identifying different pathogens including bacteria, fungi, viruses and eukaryotic parasites.[23] mNGS may be able to provide relatively rapid and accurate diagnosis, accelerate clinical treatment and interventions, and thus improve patient outcomes. Correspondingly, mNGS can generally be applied to a variety of sample types, including alveolar lavage fluid BALF, sputum, blood, cerebrospinal fluid. Through high-throughput sequencing of metagenomic sample nucleic acids, and then quantitative analysis and comparison with bioinformation tools, detailed pathogenic gene information can be obtained, which has advantages of

strong specificity, rapid sensitivity, and high accuracy.[24] The patients included in this study have undergone mNGS in alveolar lavage fluid, and *Chlamydia psittaci* nucleic acid sequences have been detected in all of them, indicating that mNGS detection has high practical value in the clinical diagnosis and differentiation of *Chlamydia psittaci* pneumonia. The comprehensive analysis of the results of mNGS detection and the clinical manifestations, laboratory tests, imaging examinations, and pathological findings of patients with *Chlamydia psittaci* pneumonia will be conducive to rapid diagnosis and avoid misdiagnosis and mistreatment.

In terms of the treatment of *Chlamydia psittaci* pneumonia, unfortunately, there is no consensus on unified treatment guidelines at home and abroad. The pathogen of *Chlamydia psittaci* pneumonia is chlamydia. Studies have shown that antibiotics or antibacterial drugs such as tetracycline, quinolones and macrolides can interfere with DNA and protein synthesis, and are the first recommended therapeutic drugs in clinical practice.[12,25] In clinical practice, the first-line drugs for *Chlamydia psittaci* pneumonia include doxycycline, minocycline and other tetracycline drugs, similarly, macrolide antimicrobials can be used as an alternative treatment for pregnant women or children and when contraindicated with tetracycline, while oxytetracycline and beta-amide drugs combined with quinolones are also effective in severe patients.[26,27] In addition, relevant studies have confirmed that quinolones have a certain effect on patients with mild *Chlamydia psittaci* pneumonia, but the effect is lower than that of tetracycline drugs.[24,28] It is noteworthy that *Chlamydia psittaci* pneumonia can cause multiple organ dysfunction and turn into severe pneumonia in a short period of time. Therefore, considering the cost and timeliness of the detection of mNGS, BALF mNGS should be improved as soon as possible when the clinical empirical antibiotic treatment is not effective, and the potential epidemiological contact history and recent diagnosis and treatment history of patients should be paid attention to avoid the prolongation and deterioration of the disease. In clinical practice, it is more urgent to pay attention to the complications and severe clinical intervention and treatment of *Chlamydia psittaci* pneumonia. The combination of multi-antibiotics and advanced respiratory support therapy when necessary will benefit patients.

There is undoubtedly a certain limitation in our study: this study is a single-center retrospective one with a relatively small sample size. In future studies, we will increase the sample size, prolong the study period, and conduct a multi-center study to support and confirm our findings, while utilizing and accumulating more cases of *Chlamydia psittaci* pneumonia for analysis and discussion.

To sum up, all patients with *Chlamydia psittaci* pneumonia included in this study after mNGS diagnosis were treated with tetracycline, quinolones or macrolides and other antibiotics, and their condition improved, the efficacy and prognosis were reasonable, and no clinical adverse events occurred. The above indicates that although *Chlamydia psittaci* pneumonia is a relatively rare CAP, mainly characterized by non-specific respiratory symptoms and prone to severe development, it mostly relies on evidence-based medical testimony such as etiological mNGS gene detection to achieve early diagnosis and then early anti-infection treatment, and the course of disease in most patients is controllable. In clinical practice, for patients with no typical epidemiological history or poor treatment effect of conventional CAP and rapid disease progression, bronchoscopy should be improved as soon as possible to perform BALF mNGS detection, early antibiotic treatment, and active prevention and treatment of complications, so as to maximize the prognosis of patients.

Conclusion

In general, although *Chlamydia psittaci* pneumonia is rare clinically, patients with CAP who do not respond to conventional anti-infectional therapy should be asked specifically about their personal history and disease history, and whether there is a history of contact with poultry or pigeons or other birds, which may be helpful in diagnosis and avoid missed diagnosis and misdiagnosis. The clinical specificity of *Chlamydia psittaci* pneumonia is poor, and it is easy to turn into severe pneumonia. After standard antibiotic treatment, the overall prognosis of patients is still optimistic. Compared with other auxiliary examination methods, mNGS generally has a more efficient detection rate and exhibits a wider pathogen spectrum. This is of great help and benefit for the subsequent combined anti-infective treatment of the patients with *Chlamydia psittaci* pneumonia. For related disciplines, it is of great practical significance to further explore the molecular mechanism of *Chlamydia psittaci* disease and actively develop new therapeutic drugs or means targeting *Chlamydia psittaci*.

Abbreviations

BALF, bronchoalveolar lavage fluid; mNGS, metagenomic next-generation sequencing; MDT, multi-disciplinary team; CAP, community-acquired pneumonia; ICU, intensive care unit; WBC, white blood cell count; HGB, hemoglobin; NE, neutrophil percentage; CRP, C-reactive protein; PCT, procalcitonin; LDH, lactate dehydrogenase; OI, oxygenation index; ECMO, extracorporeal membrane oxygenation; ADA, adenosine deaminase; PCR, polymerase chain reaction.

Ethics Statement

This study was conducted following approval from the Medical Ethics Committee of the First Affiliated Hospital of Gannan Medical University (approval number: LLSC-2023033102) under the ethical standards outlined in the Declaration of Helsinki.

Patient Consent

All patient data were anonymized and maintained with strict confidentiality throughout the study to protect privacy.

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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

We declare that we have no conflicts of interest.

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