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CASE SERIES

Coxiella burnetii Should Not Be Ignored: Two Cases of Q Fever Pneumonia Diagnosed by Metagenomic Next-Generation Sequencing

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Background: Q fever is a globally distributed zoonotic disease caused by *Coxiella burnetii* (*C. burnetii*). As an obligate intracellular bacterium, *C. burnetii* is primarily transmitted from domestic animals to humans, with ticks also serving as potential vectors. The clinical manifestations of Q fever are often nonspecific and highly variable, making its diagnosis particularly challenging.

Case Presentation: Two male pneumonia patients were hospitalized in Deqing People's Hospital, one was 73 years old, and the other one was 30 years old, both of them presented with hyperpyrexia without a clear epidemiological history. However, initial empirical treatment was ineffective and microbiological cultures were all negative, then bronchoscopy was conducted for them and bronchoalveolar lavage fluid (BALF) was sent for metagenomic next-generation sequencing (mNGS) test. Ultimately, two patients were diagnosed with Q fever pneumonia, and the symptoms of patients were significantly improved after timely treatment with the special drug doxycycline and moxifloxacin, and lung inflammation in both patients were effectively absorbed in the subsequent follow-up examination.

Conclusion: Two cases of Q fever pneumonia were diagnosed through mNGS. As a new detection method, mNGS has advantages in the diagnosis of unknown infectious pathogens. As a zoonotic pathogen, *C. burnetii* should not be ignored. The One Health approach may be suitable for Q fever prevention and control.

Keywords: Q fever, *Coxiella burnetii*, pneumonia, metagenomic next-generation sequencing, case report

Introduction

Q fever is a zoonotic disease caused by the bacterium *C. burnetii* which has worldwide with the exception of New Zealand.[1,2] It was first reported by Dr Derrick in 1935 originating from an unexplained collective fever among slaughterhouse workers.[3] This pathogen showed properties of both virus and rickettsia and was then named *Coxiella burnetii*.[4] An influenza-like infection named "Balkangrippe" prevalented among soldiers in the Balkan regions in 1940 was finally identified as *C. burnetii* infection.[5]

Geographically, Q fever shows marked heterogeneity. In Europe, sporadic cases coexist with large outbreaks, exemplified by the Netherlands epidemic (2007–2010) with more than 4000 confirmed human cases linked to goat farms. France, Germany, Spain, and Italy also report endemicity, often with regionally distinct genotypes. In Africa, prevalence varies widely, reaching up to 32% in Egypt and more than 70% in camels in Algeria, though surveillance is limited. North America, Latin America, Asia, and Australia also document circulation, with underdiagnosis common outside Europe.[6]

C. burnetii is a gram-negative, strictly intracellular, pleomorphic bacterium that exists in two distinct antigenic forms, Phase-I and Phase-II, depending on the structure of lipopolysaccharide (LPS) on the cell surface.[7–9] Phase I variants are highly infectious forms found in naturally infected hosts, whereas Phase II variants are less infectious and are obtained after serial passages in cell culture systems or embryonated eggs.[10–12]

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Domestic animals such as cattle, sheep and goats act as the major reservoirs of *C. burnetii* with the pathogen shed in the milk, urine, feces, and semen of infected animals.[13] When infected animal discharges dry and mix with dust, they may lead to human infection through contaminated aerosols which can be dispersed over long distances (up to several tens of kilometres).[1,6,14,15] In addition, drinking contaminated unpasteurized dairy products and contacting with contaminated milk, urine, feces, semen are also transmission routes of the disease.[16,17] Besides, tick bites can also transmit *C. burnetii* to humans in a manner similar to its transmission among animals.[1,13,18] On the other hand, *C. burnetii* is extremely virulent, even a single organism can cause disease.[19,20] Therefore, *C. burnetii* was considered as a potential bioterrorism agent in the United States and included in the list of nationally notifiable infectious diseases in 1999, and the same level of emphasis was also found in Australia, Japan, and the Netherlands.[21–24]

The clinical presentation of Q fever is often nonspecific and highly variable. Approximately half of infected individuals remain asymptomatic, whereas the others may develop flu-like symptoms such as fever, headache, and myalgia, or present with pneumonia or hepatitis.[13,25,26] Acute Q fever is considered as a self-limiting disease; however, 3%−5% of patients with acute Q fever develop into chronic Q fever, which mainly manifests as blood culture-negative endocarditis.[27–29] In addition, approximately 20% of acute patients develop Q fever fatigue syndrome (QFS) which is not a life-threatening condition but may result in serious social and economic consequences in the form of loss of person's quality of life and inability to work.[30,31]

Although several Q fever outbreaks have occurred in various regions of China over the past 70 years, the disease is not a notifiable condition and may therefore be considered neglected.[15,21,25] The present case report describes the diagnosis of Q fever using mNGS in two adult patients presenting with severe pneumonia and fever. Timely diagnosis and prompt treatment resulted in a favorable clinical outcome.

Case Presentation (Case 1)

On November 15, 2023, a 73-year-old male patient with traveling history of Thailand one week ago was admitted to the Deqing People's Hospital. He presented with fever (maximum temperature was 39.2°C), cough, chest pain and tightness lasting for 4 days. Before seeking medical attention, he took cefdinir by self, but showed no improvement. The patient had history of chronic obstructive pulmonary disease (COPD) for 6 years without standard treatment and was accepted lung cancer surgery 3 years ago with currently receiving continuous treatment of osimertinib. Besides, the patient has no history of hypertension, diabetes, cardiovascular disease or other chronic disease. Respiratory medicine outpatient doctor conducted a blood routine revealed total white blood cell (WBC) count, 7.20×10^9 /L (normal range, 3.50×10^9-9.50×10^9 /L); neutrophil count, 6.0×10^9 /L (normal range, 1.80×10^9-6.30×10^9/L); lymphocyte count, 0.3×10^9/L (normal range, 1.10×10^9 −3.20×10^9/L); hemoglobin (Hb), 125 g/L (normal range, 130–175 g/L); platelet (PLT) count, 109×10^9/L (normal range, 125×10^9-350×10^9 /L); C-reactive protein (CRP), 113.5 mg/L (normal range, 0–10.0 mg/L) (Table 1).

After admission, physical examinations were performed and the results revealed: temperature, 39.2°C (normal range, 36.3–37.2°C); pulse rate 130 beats/minute (normal range, 60–100 beats/minute); respiratory rate, 25 breaths/minute (normal range, 12–18 breaths/minute); blood pressure, 114/64 mmHg (normal range, 90–140/60-90 mmHg); saturation of peripheral oxygen (SPO_2), 86% (normal range, 95–100%) (Table 1). The patient had thick breath sounds in both lungs and moist rale sounds in the right lower lung, and auscultation of the heart showed a heart rate of 130 beats per minute with regular rhythm, but no heart murmurs. Other physical examinations were normal.

The results of laboratory tests conducted after admission were as follows: arterial blood pH, 7.38 (normal range, 7.35–7.45); arterial blood PaO_2, 72 mmhg (normal range, 80–105 mmhg); arterial blood $PaCO_2$, 57 mmhg (normal range, 35–45 mmhg); arterial blood base excess (BS) 7.3 mmol/l [normal range, (−2.0)-(+3.0) mmhg]; arterial blood lactate 1.71 mmol/l (normal range, 0.50–2.20 mmol/lg); erythrocyte sedimentation rate (ESR), 85 mm/hour (normal range, 0–15 mm/hour); serum procalcitonin (PCT), 0.22μg/L (normal range, 0–0.06 μg/L); serum fibrinogen (FIB) content, 5.93 g/L (normal range, 2.00–4.00 g/L); serum D-dimer content, 2.14 mg/L (normal range, 0–0.55 mg/L). In addition, the results of serum carcinoembryonic antigen (CEA), serum total protein (TP), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), serum creatinine (SCR), serum viral hepatitis antigen, serum HIV 1p 24 antigen, treponema pallidum-specific antibody, and nucleic acid of influenza viruses A and B, parainfluenza virus 1 and 3,

Table 1 The Vital Signs and Laboratory Test Results with Reference Ranges of the Patient in Case 1

Item	Findings	Reference Range
Physical examinations		
Temperature (°C)	39.2	36.3–37.2
Pulse (beat/minute)	130	60–100
Respiratory (breath/minute)	25	12–18
Blood pressure (mmHg)	114/64	90–140/60–90
SPO_2 (%)	93	95–100
Blood routine test		
WBC ($\times 10^9$/L)	7.2	3.50–9.50
Neutrophils ($\times 10^9$/L)	6.0	1.80–6.30
Lymphocytes ($\times 10^9$/L)	0.3	1.10–3.20
Hb (g/L)	125	130–175
PLT ($\times 10^9$/L)	109	125–350
CRP (mg/L)	113.5	<10.0
Arterial blood gas analysis		
pH	7.38	7.35–7.45
PaO_2 (mmhg)	72	80–105
$PaCO_2$ (mmhg)	57	35–45
BS (mmol/l)	7.3	(−2.0)–(+3.0)
Lactate (mmol/l)	1.71	0.50–2.20
ESR (mm/h)	85	<15
Serum testing		
PCT (μg/L)	0.22	0–0.06
FIB (g/L)	5.93	2.00–4.00
D-dimer (mg/L)	2.14	0.00–0.55
CEA (μg/L)	1.63	<5.0
TP (g/L)	65.8	65.0–85.0
ALT (U/L)	28	9–60
AST (U/L)	37	15–45
SCR (μmol/l)	99	57–111
Pathogen antibody testing		
Viral hepatitis	Negative (-)	Negative (-)
HIV	Negative (-)	Negative (-)
Treponema	Negative (-)	Negative (-)

(*Continued*)

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Table 1 (Continued).

Item	Findings	Reference Range
Virus nucleic acid testing		
Influenza viruses A and B	Negative (-)	Negative (-)
Parainfluenza virus 1 and 3	Negative (-)	Negative (-)
Adenovirus	Negative (-)	Negative (-)
Respiratory syncytial virus	Negative (-)	Negative (-)
Mycoplasma pneumoniae	Negative (-)	Negative (-)
COVID-19	Negative (-)	Negative (-)
Bacteriological testing		
Blood culture	Negative (-)	Negative (-)
Sputum culture	Negative (-)	Negative (-)
Putum tuberculosis smear	Negative (-)	Negative (-)

Abbreviations: SPO_2, saturation of peripheral oxygen; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; CRP, C-reactive protein; pH, potential of hydrogen; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial Pressure of carbon dioxide; BS, base excess; ESR, erythrocyte sedimentation rate; PCT, procalcitonin; FIB, fibrinogen; CEA, carcinoembryonic antigen; TP, total protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SCR, serum creatinine; HIV, human immunodeficiency virus; COVID-19, coronavirusdisease2019.

adenovirus, respiratory syncytial virus, *Mycoplasma pneumoniae*, and COVID-19 in throat swabs were all negative. The blood culture, sputum culture, and sputum tuberculosis smear were also sterile in 5 days (Table 1).

The results of imaging examination were as follows: chest computed tomography (CT) scan revealed bronchopathy, emphysema, inflammatory lesions in right lung, postoperative changes in left lower lobe lung with pleural effusion and pleural changes. Cardiac color Doppler ultrasound revealed left ventricular diastolic function decreased and mild mitral and tricuspid regurgitation. Abdominal color Doppler ultrasound revealed left renal cyst, alteration after partial prostatectomy and no abnormalities were found in the liver, gallbladder, pancreas and spleen. Twenty-four-hour dynamic electrocardiogram revealed sinus tachycardia, frequent atrial premature beats (1013 times/24-hour), ventricular premature beats (3939 times/24-hour), and occasional ventricular premature triad. Considering the patient's history of COPD, piperacillin-tazobactam (4.5 g, q8h) intravenously was chosen for empirical anti-infective therapy. Unfortunately, the patient presented with a persistent fever in the next 3 days, with the maximum body temperature of 38.6–38.8°C.

Considering the possibility of existing drug-resistant pathogens, piperacillin sulbactam was replaced with cefoperazone sulbactam (3.0 g, q12h, Pfizer Inc., USA) on November 18. Bronchoscopy was conducted for the patient, and BALF was sent for mNGS testing, using the Illumina HiSeq platform (Illumina, San Diego, CA, USA) on November 21. Bronchoscopy revealed a large amount of purulent secretion in the basal segment of the lower lobe of the right lung, and the mNGS result returned on November 23, suggesting the existence of *C. burnetii* (number of homogenized sequences 3989, relative abundance, 99.28%) (Figure 1). Combining the patient's travelling history of Thailand, symptoms, signs

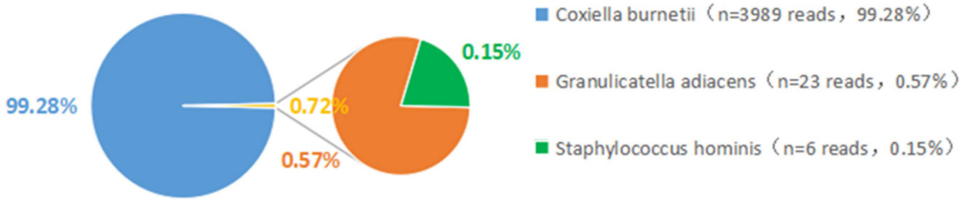

Figure 1 The sequences number and relative of pathogen data from mNGS of BALF, the sequence number of C. burnetii was 3989, accounting for 99.28%.

and auxiliary examination results, the patient was diagnosed with acute Q fever infection in pneumonia on November 23, and doxycycline hydrochloride entericcoated capsules were administered orally (0.1 g twice daily) to the patient instead of cefoperazone sulbactam (Figure 2). The patient had no fever, and other symptoms were significantly relieved in the next 4 days before discharge, and the doxycycline anti-infection treatment was sustained for 2 weeks.

The patient did not return to the hospital for chest CT one month later as instructed, but no physical discomfort or recurrence of fever was reported in the telephone follow-up. Ten months later, the patient returned for a follow-up chest CT scan. The inflammatory lesions in the right lung had completely absorbed comparing that before, but unfortunately, the cancer recurrence occurred in the left lung (Figure 3).

Case Presentation (Case 2)

On February 17, 2025, a 30-years-old young male patient presented with fever (maximum temperature was 39.0°C), cough, headache and fatigue for 3 days treated in the fever clinic of Deqing People's Hospital. The patient had no clear epidemiological history before the onset of illness. Chest CT scan conducted at the fever clinic revealed inflammatory lesions in both lungs and laboratory tests conducted simultaneously revealed an elevated CRP level of 141.1 mg/L, the WBC count of 14.80×10^9/L, SCR level of 112 μmol/L and negative results of influenza A and B virus (Table 2). The patient was empirically administered ceftriaxone (2.0 g, qd) intravenously for infection and ibuprofen orally for fever.

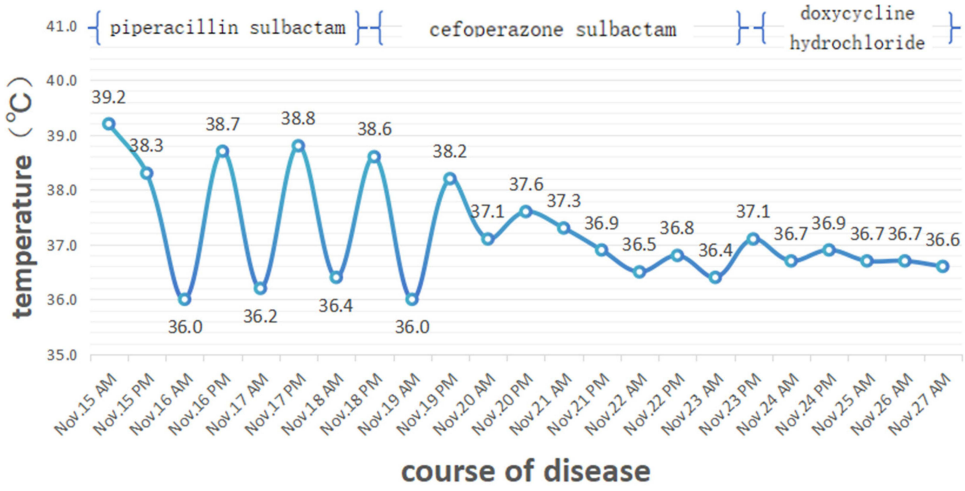

Figure 2 Analysis of patients' medication information and temperature changes. The temperature gradually decreased after using cefoperazone and sulbactam, but did not completely return to the normal range. The temperature returned to normal after using doxycycline.

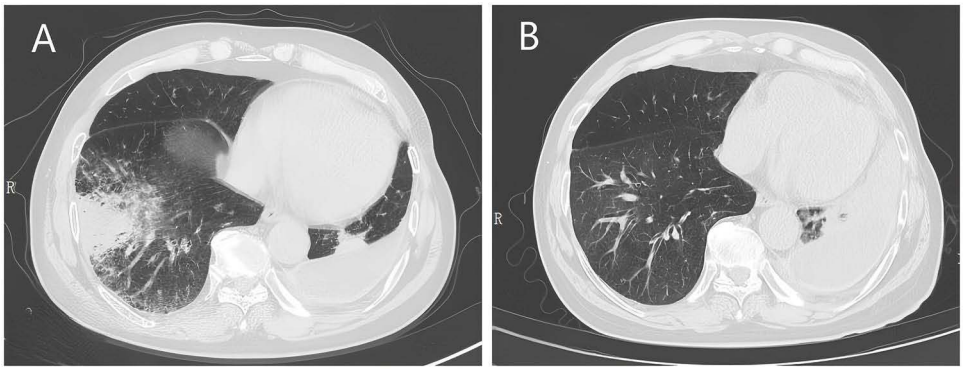

Figure 3 The contrast of chest CT before and after. The image (**A**) completed on November 15, 2023 and image (**B**) completed on August 20, 2024. The inflammatory lesion in the right lung had completely absorbed after treatment.

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Table 2 The Vital Signs and Laboratory Test Results with Reference Ranges of the Patient in Case 2

Item	Findings	Reference Range
Physical examinations		
Temperature (°C)	39.2	36.3–37.2
Pulse (beat/minute)	110	60–100
Respiratory (breath/minute)	18	12–18
Blood pressure (mmHg)	116/78	90–140/60–90
SPO_2 (%)	93	95–100
Blood routine test		
WBC ($\times 10^9$/L)	14.8	3.50–9.50
CRP (mg/L)	141.1	<10.0
Arterial blood gas analysis		
pH	7.42	7.35–7.45
PaO_2 (mmhg)	73	80–105
$PaCO_2$ (mmhg)	37	35–45
BS (mmol/l)	–1.0	(–2.0)–(+3.0)
Lactate (mmol/l)	1.10	0.50–2.20
Routine urine test		
Hemoglobin	Positive (2+)	Negative (-)
Protein	Positive/negative (±)	Negative (-)
APTT	31.6s	25.0–31.3 s
Antigen test of influenza A and B virus	Negative (-)	Negative (-)
ESR (mm/h)	43	<15
Serum testing		
PCT (μg/L)	0.08	0-0.06
FIB (g/L)	6.1	2.00–4.00
D-dimer (mg/L)	0.65	0.00–0.55
TP (g/L)	65.7	65.0–85.0
ALT (U/L)	118	9–60
AST (U/L)	55	15–45
SCR (μmol/l)	112	57–111
Pathogen antibody testing		
Viral hepatitis	Negative (-)	Negative (-)
HIV	Negative (-)	Negative (-)
Treponema	Negative (-)	Negative (-)

(*Continued*)

Table 2 (Continued).

Item	Findings	Reference Range
Virus nucleic acid testing		
Parainfluenza virus 1 and 3	Negative (-)	Negative (-)
Adenovirus	Negative (-)	Negative (-)
Respiratory syncytial virus	Negative (-)	Negative (-)
Mycoplasma pneumoniae	Negative (-)	Negative (-)
COVID-19	Negative (-)	Negative (-)
Bacteriological testing		
Blood culture	Negative (-)	Negative (-)
Sputum culture	Negative (-)	Negative (-)
Putum tuberculosis smear	Negative (-)	Negative (-)

Abbreviation: APTT, activated partial thromboplastin time; SPO_2, saturation of peripheral oxygen; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; CRP, C-reactive protein; pH, potential of hydrogen; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial Pressure of carbon dioxide; BS, base excess; ESR, erythrocyte sedimentation rate; PCT, procalcitonin; FIB, fibrinogen; CEA, carcinoembryonic antigen; TP, total protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SCR, serum creatinine; HIV, human immunodeficiency virus; COVID-19, coronavirusdisease2019.

However, outpatient treatment was ineffective, and the patient was admitted to the general medicine ward for further treatment on February 18.

The patient had no history of disease, except for a high BMI of 32.05 kg/m^2. After admission, physical examination was performed, and the results were as follows: temperature, 39.2°C; pulse rate, 110 beats/min; respiratory rate, 18 breaths/minute; blood pressure, 116/78 mmHg; SPO_2, 93% (Table 2). Thick breath sounds were auscultated in both lungs without any wet rale sounds, and auscultation of the heart showed a heart rate of 110 beats/min with regular rhythm and no heart murmurs.

The following laboratory tests are as below: ESR, 43 mm/hour; serum PCT, 0.08 μg/L; serum FIB content, 6.10 g/L; serum D-dimer content, 0.65 mg/L; activated partial thromboplastin time (APTT), 31.6s (normal range, 25.0–31.3s); urinary hemoglobin positive (2+) (normal range, negative); urinary protein, positive/negative (±) (normal range, negative). In addition, the results of serum TP, ALT, AST, viral hepatitis antigen, HIV 1p 24 antigen, and treponema pallidum-specific antibody were all negative (Table 2).

Imaging examinations were as follows: electrocardiogram (ECG) was normal, cardiac color Doppler ultrasound revealed mild tricuspid regurgitation, and abdominal color Doppler ultrasound revealed fatty liver. In terms of treatment, piperacillin-tazobactam (4.5 g, q8h) was administered intravenously; however, there was no sign of improvement in the patient's condition, with peak temperature remaining 38.6°C–39.2°C in the next 2 days. Considering the complexity of the disease, the patient was referred to respiratory medicine on February 21.

On admission to the department of respiratory medicine, physical examination revealed the following: temperature, 38.0°C; pulse rate, 100 beats/min; respiratory rate, 17 breaths/min; blood pressure, 131/70 mmHg; SPO_2, 93%; lung and heart auscultation were similar to previous phases.

Further laboratory tests implemented were as follows: arterial blood pH 7.42; arterial blood PaO_2, 73 mmhg; arterial blood $PaCO_2$, 37 mmhg; arterial blood BS −1.0 mmol/l; arterial blood lactate, 1.10 mmol/l. Nucleic acid of parainfluenza virus 1 and 3, adenovirus, respiratory syncytial virus, *Mycoplasma pneumoniae* and COVID-19 in throat swabs were all negative. Blood culture, sputum culture and sputum tuberculosis smear were also sterile for 5 days (Table 2).

Considering the possibility of atypical pathogen infection, moxifloxacin (0.4 g, qd) by intravenous infusion was selected for further therapy instead of piperacillin sulbactam. Besides, Bronchoscopy was conducted for the patient, and

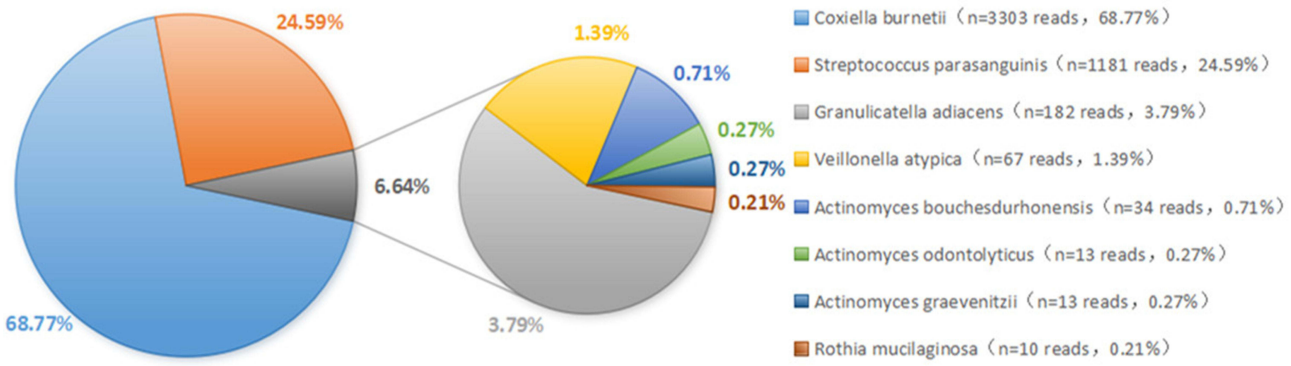

Figure 4 The sequences number and relative of pathogen data from mNGS of BALF, the sequence number of C. burnetii was 3303, accounting for 68.77%.

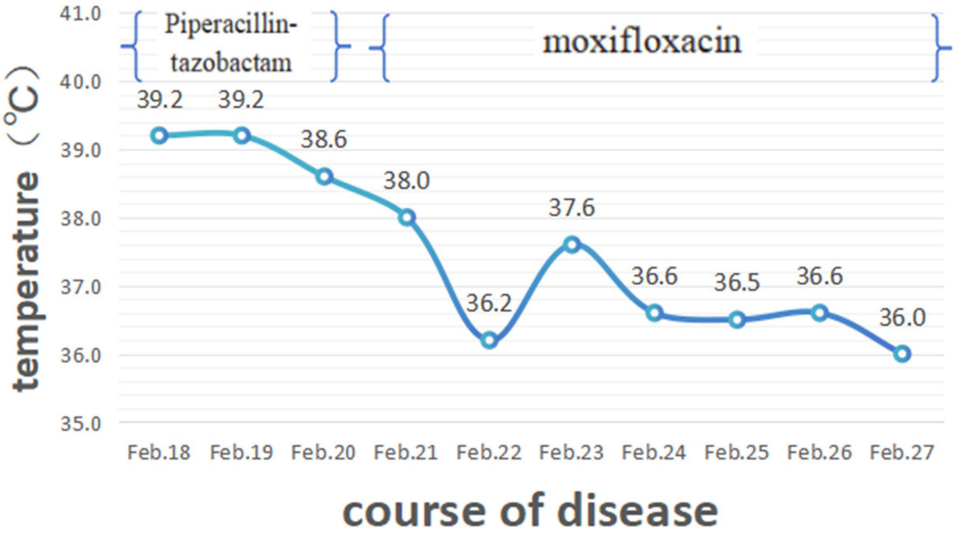

Figure 5 Analysis of patients' medication information and temperature changes. The temperature gradually decreased after using moxifloxacin.

BALF was sent for mNGS test on February 24. Bronchoscopy revealed inflammatory changes in the trachea and bilateral bronchitis, and the mNGS result returned on November 26 suggested the existence of *C. burnetii* (number of homogenized sequences 3303, relative abundance, 68.77%) (Figure 4). *C. burnetii* reads were abundant in all microbial species and the patient was diagnosed with acute Q fever infection in pneumonia.

Considering that moxifloxacin is theoretically effective for *C. burnetii* as doxycycline and that the patient had no fever since February 23, we decided not to change the treatment, and the patient was discharged on February 27 with no fever and significant improvement in respiratory symptoms (Figure 5). After discharge, moxifloxacin orally anti-infection treatment was administered for the patient lasting 2 weeks. It is encouraging that the patient had no physical discomfort and no recurrence of fever in follow-up and the reexamined Chest CT scan at one month later after discharge revealed that most of inflammatory lesions in both lungs achieved absorption (Figure 6).

Discussion

As a worldwide zoonotic disease, domestic animals act as the major reservoirs of *C. burnetii* leading human infection. In addition, a small number of infections were due to tick bites. However, except for the patient in case 1 who had a history of traveling to Thailand before the onset of the disease, both patients had no history of tick bites, consumption of unpasteurized dairy products, direct contact with ruminants or their body fluids. They may be exposed in aerosols containing *C. burnetii* leading the patients could not confirm how to get infected. Tissot-DuPont et al once reported that

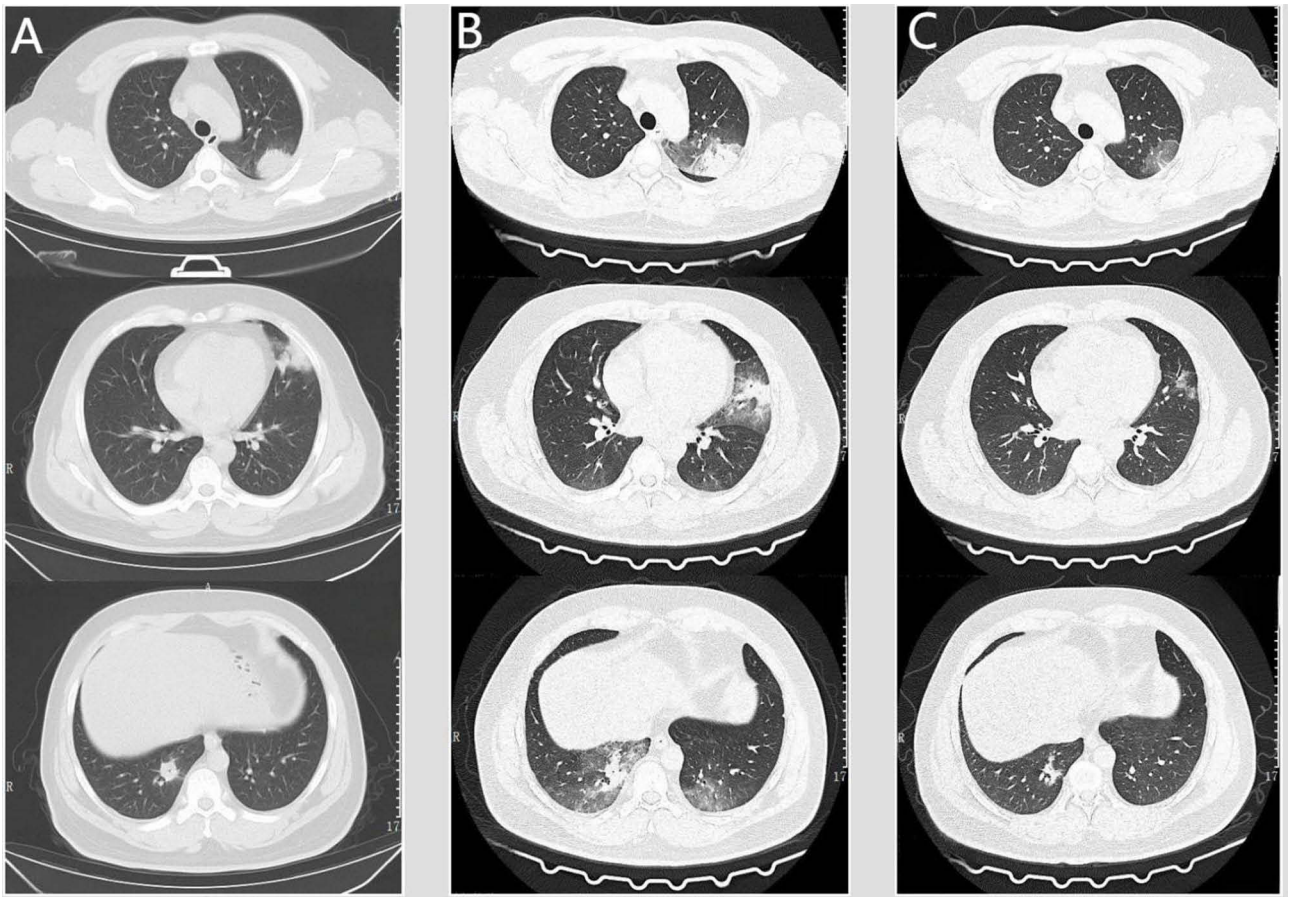

Figure 6 The contrast of chest CT before and after. The image (**A**) completed on February 17, 2025, image (**B**) completed on February 22, 2025 and image (**C**) completed on March 20, 2025. The inflammation in the patient's lungs progressed during hospitalization, but was eventually absorbed after treatment.

contaminated aerosols could spread over 30 km by wind.[32] Therefore, disease surveillance, regular monitoring and implementation of proper preventive and control strategies are necessary to reduce further disease outbreaks in an area. These strategies pose economic and public health significance in reducing reproductive losses in the livestock industry and to avoid potential risk of transmission of infection to human beings. Determination of herd-level prevalence of a disease in a population could help in proper planning and implementation of preventive and control measures.[33–35]

In recent years, the One Health approach was gradually applied in neglected zoonotic diseases, which is based on holistic thinking about the interface between humans, animals, and the environment, aiming to promote the health and sustainable development of these sectors through multisectoral and interdisciplinary collaboration at the local, national, and global levels.[36,37] Coordinated and collaborative strategies to combat Q fever, as well as other zoonoses, need to incorporate the human, animal, and environmental domains within the One Health framework. These strategies include improving human surveillance, implementing animal surveillance, and ensuring data sharing and intelligence exchange between the public health and veterinary sectors. Furthermore, it is essential to improve communication, develop the proactivity of people involved in managing Q fever, strengthen laboratory infrastructure, improve veterinary control measures, promote human and animal serosurveillance, and conduct environmental monitoring and vaccination.[36,38]

As for clinical manifestations, both patients showed high fever, similar to the case reported by Wang et al.[18] Arterial blood analysis revealed both patients developed respiratory failure, which may be related to the severe infections in their lungs. Fortunately, neither patient developed liver impairment which were common among patients with Q fever. In the case reports of Dong Wang, Jinwei Huang, Stephen R Graves, Toshihiro Matsui and Hang Jin Jeong, patients all arised varying degrees of liver function impairment.[18,30,39–41] In addition, the patient in case 2 developed mild renal impairment, which may be due to insufficient water intake during fever; adequate fluid replacement eventually improved the

renal impairment. Chest CT imaging of two patients indicated that the infection position of *C. burnetii* in the lungs was not fixed, which was similar to the results reported by Felipe Mussi von Ranke et al. In their report, 6 soldiers simultaneously developed Q fever pneumonia at different positions in the lungs.[26]

Since *C. burnetii* is an intracellular pathogen, it is almost impossible to confirm infection through conventional microbiological culture.[42] Serodiagnostic techniques including immunofluorescence assay (IFA), complement fixation test (CFT) and enzyme-linked immunosorbent assay (ELISA) are preferable for Q fever diagnosis. Serology can recognize the difference in antibody titers in acute and chronic infection. In acute infection, IgG antibody titers are higher against Phase II antigen only, while in chronic form, both IgG and IgA antibody titers are high against both Phase I and Phase II of the bacterium.[43] Therefore, serodiagnostic techniques were considered as the gold standard for diagnosis of Q fever. However, this technique is not suitable for detection of early acute Q fever because of the lag in antibody titer development (7–15 days after the onset of clinical disease).[1] In addition, PCR for nucleic acid detection is also highly suggestive for confirmatory Q fever diagnosis.[14,44] Nevertheless, the lack of *C. burnetii* testing reagents in most hospitals may lead to a failure to diagnose Q fever in time.[18]

As a new diagnostic technique, mNGS can directly determine the microbial nucleic acid sequence in the sample by high-throughput sequencing technology and compare the measured sequence with the existing sequence in the database. This approach can quickly and objectively identify the pathogenic microorganisms (including viruses, bacteria, fungi, and parasites) in a single sample without using any probes or primers, making it especially suitable for the diagnosis of difficult or infrequent clinical cases.[45,46] In recent years, the prices of this technique are gradually falling with widespread use in China. Therefore, bronchoscopy and mNGS tests of BALF were performed for the patients after initial treatment failure avoiding abuse. Ultimately, both patients were diagnosed with Q fever pneumonia. In fact, it's was beneficial to patients, reducing their fear of unknown diseases and hospital costs.

As treatment, the first-choice drugs for acute Q fever are doxycycline and hydroxychloroquine, while other antibiotics, such as quinolones, erythromycin, rifampin, roxithromycin and clarithromycin, can be used as alternative therapy.[47–49] A dose of 100 mg doxycycline 2 times a day for 2–3 weeks is recommended for patients with acute Q fever patients. It can be combined with hydroxychloroquine if necessary. Cotrimoxazole can be used safely in pregnant women and children under 8 years of age for Q fever.[50]

In this report, both patients received piperacillin-sulbactam as initial treatment, but no relief was achieved. In case 1, the patient's temperature improved after switching to cefoperazone-sulbactam, that might be related to the self-limiting nature of Q fever, as there was no evidence that cefoperazone-sulbactam is effective against Q fever. In order to avoid recurrence and subsequent possible of chronic Q fever, doxycycline was used for follow-up treatment and continued for more than 2 weeks. In case 2, moxifloxacin was empirically selected for further therapy after transferring to the department of respiratory medicine. The improvement of patient's symptoms and theoretical efficacy of quinolones against Q fever led no change in medication after diagnosis. Ultimately, both patients recovered completely without QFS or chronic Q fever and reexamined Chest CTs indicated significant absorption of pulmonary lesions.

The limitation of this study is that the transmission chain of the disease in 2 patients was not clear, which may lead to infection in some potential vulnerable groups such as their colleagues or family members. However, tracing the source of infection require cooperation between public health and veterinary sectors, which is difficult to actualize in sporadic cases. This report aims to enhance medical professionals' understanding of Q fever by sharing successful diagnostic and treatment experiences. Because Q fever remains neglected, underreported and unknown to many medical professionals in many countries. This impacts underdiagnosis, lack of timely treatment, and the risk of patients developing the disease in the chronic phase, which can progress to a serious condition and even death. Furthermore, misdiagnosis and treatment can contribute to unnecessary increases in costs in the public health system. In this context, Q fever needs to be widely disseminated among medical professionals.[36,51]

Conclusion

Two cases of Q fever pneumonia were diagnosed through mNGS and prompt, effective treatment resulted a favorable clinical outcome. As a new detection method, mNGS has advantages in the diagnosis of unknown infectious pathogens. For unknown infection with empirical treatment failure, early mNGS testing should be conducted to identify pathogens,

in order to avoid abuse and increasing economic burden of the patient. As a zoonotic disease, Q fever should not be ignored but ought to be reported promptly once diagnosed to avoid further transmission. The One Health approach may be suitable for Q fever prevention and control.

Data Sharing Statement

All the data in this study are included in the published articles.

Ethics Approval and Consent to Participate

All the two patients consented to treatment and provided written consent for publication of this study, which was performed in accordance with the principles of the Declaration of Helsinki. According to the regulations formulated by the ethics committee of Deqing People's Hospital, ethics approval was not required because of the nature of this study (case report).

Author Contributions

All authors made a significant contribution to the work reported, whether 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

The authors report no conflicts of interest in this work.

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