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RESPONSE TO LETTER

Diagnosis of Acute Q Fever in a Patient by Using Metagenomic Next-Generation Sequencing: A Case Report [Response to Letter]

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Dear editor

We would like to thank you for giving us the opportunity to respond to the letter "Diagnosis of Acute Q Fever in a Patient by Using Metagenomic Next-Generation Sequencing: a case report". We were also delighted to receive comments from three authors on our recent article published in the *Infection and Drug Resistance* journal.[1] Their professional suggestions and opinions on the article will guide our clinical diagnosis and treatment of Q fever and other diseases in the future. In addition, we would like to provide clarifications on the specific comments.

Metagenomic next-generation sequencing (mNGS) is a powerful tool for detecting pathogens, including bacteria, viruses, fungi, and parasites, without the need for targeted amplification or prior knowledge of pathogen genomic sequences.[2,3] In addition to detecting the presence of pathogens, mNGS can also identify pathogen resistance and virulence genes, as well as other relevant information about pathogen characteristics and mechanisms.[2] As a result, mNGS is increasingly being used for direct detection of pathogens in clinical specimens. Although mNGS is capable of detecting pathogenic bacteria, it cannot determine whether they are alive or dead. Therefore, we concur with Dany et al that supplementary techniques should be employed for confirmation purposes. Identifying certain microorganisms solely through mNGS can be challenging. It is necessary to take into account the makeup of the microbial community and its interactions with the host and the environment. Objective reasons have hindered us from collecting environmental and animal samples for mNGS from the patient's work and living area, which is located far from our hospital. Consequently, we are unable to accurately determine the source of exposure to *Coxiella burnetii*, and can only make a probable inference.

Q fever presents with diverse and non-specific clinical manifestations, making it challenging to diagnose in clinical practice. Acute Q fever is characterized by symptoms such as high fever, headache, muscle aches, general malaise, and may be accompanied by pneumonia, hepatitis, heart damage, and neurological symptoms.[4] Chronic Q fever is mostly complicated by endocarditis, with clinical manifestations similar to subacute bacterial endocarditis.[4] Clinicians need to make the diagnosis based on the medical history (history of contact with livestock, history of bite) and the above clinical manifestations, and then combined with relevant auxiliary examination results (such as serum immunological test, cell culture, PCR, mNGS, etc.) can make the diagnosis. During the diagnostic process, it is important to exclude other diseases such as influenza, dengue fever, and tick-borne illnesses. In addition, mNGS detected only 79 reads covering 0.20% of the *C. burnetii* genome in this study. The low pathogen load in the sample, insufficient amount of total extracted nucleic acid, or high amount of human genomic material relative to pathogens may have contributed to this outcome. To enhance the reliability of future clinical applications, standardization of specimen collection, nucleic acid extraction, sequencing, and bioinformatics analysis processes should be implemented.

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Due to the patient's progressive disease and negative results of traditional microbiological tests (eg blood culture, pharyngeal swab culture, etc.), we gave empirical treatment with piperacillin-tazobactam and levofloxacin to control the infection when the causative organism could not be identified. However, in China, mNGS is often used as a second-line test in case of poor previous treatment because it is more expensive. Indeed, the early application of antibiotics has an impact on mNGS test results, which may be smaller than that of conventional microbiological tests. A related study showed that among 96 patients who received antibiotics 2 weeks prior to mNGS testing, the detection rate of mNGS pathogens in blood specimens was 47.9%, compared with 19.6% in blood cultures.[5] Our study did not mention microbial resistance characteristics as they were not detected in the mNGS results. Despite orally taking tetracycline tablets for 2 weeks, the patient continued to experience intermittent low-grade fever. However, after the patient completed the full course, he did not experience any further fever or physical discomfort. Therefore, we suspect that the reason for this was that the full course of tetracycline was not completed. Finally, we fully agree with Dany et al that mNGS results should be interpreted with caution, especially regarding the diagnostic identification of infectious agents and the impact on the rational use of antibiotics after the emergence of antibiotic resistance issues.

Disclosure

The authors report no conflicts of interest in this communication.

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