

CASE REPORT

The role of gut microbiota and the gut–lung axis in sepsis: A case study of a pregnant woman with severe rickettsial pneumonia and septic shock complicated by MODS

Hongmei Qin  | Yaoqing Fu | Caixia Deng | Yanxing Chen | Keming Huang | Yiyang Ruan | Ke Liu

Department of Critical Care Medicine,
The First People's Hospital of Yulin,
Yulin, China

Correspondence

Ke Liu, Department of Critical Care
Medicine, the First People's Hospital of
Yulin, Yulin 537000, China.
Email: liuk1367791@163.com

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Key Clinical Message

In this case report, we describe the successful management of severe scrub typhus with pneumonia, sepsis, and multiple organ dysfunction in a pregnant woman. Despite initial challenges, the patient responded favorably to fecal microbiota transplantation and oral fecal microbiota capsule therapy.

Abstract

Scrub typhus, caused by *Orientia tsutsugamushi*, can lead to severe multiorgan dysfunction and carries a mortality rate of up to 70% if not treated properly. In this report, we present the case of a 27-year-old pregnant woman at 18 + 6 weeks gestation whose symptoms worsened 15 days after onset and progressed to severe pneumonia with sepsis and multiple organ dysfunction syndrome. After the pathogen was confirmed by next-generation sequencing analysis of bronchoalveolar-lavage fluid and blood samples, the patient's treatment was switched to antiinfective chloramphenicol. The patient also underwent uterine evacuation due to a miscarriage. Extracorporeal membrane oxygenation was discontinued once the pulmonary infection significantly improved. Subsequently, the patient had recurrent diarrhea, abdominal distension, and difficulty eating. The antibiotic regimen was adjusted according to the drug sensitivity, but the diarrhea and abdominal distension still did not improve. Following a comprehensive multidisciplinary risk assessment, we initiated fecal microbiota transplantation and oral fecal microbiota capsule therapy. As a result, the patient's condition was effectively managed, and they were gradually discharged. Fecal microbiota transplantation may be a safe and effective treatment for severe pneumonia and shock in pregnant women. This has significant implications for maternal health. However, further clinical cases are required to observe its long-term effectiveness.

KEYWORDS

fecal microbiota transplantation, multiple organ dysfunction syndrome, rickettsia tsutsugamushi, sepsis, severe pneumonia

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1 | INTRODUCTION

Scrub typhus is a rickettsial infection caused by the bacterium *Orientia tsutsugamushi*, which is transmitted to humans through the bite of infected chiggers.¹ The clinical manifestations typically include the presence of an eschar at the site of the chigger bite, accompanied by systemic symptoms such as fever, headache, myalgia, rash, and lymphadenopathy.² If the patient initially has respiratory symptoms, such as cough and difficulty breathing, it usually indicates some degree of inflammation or damage to the lungs.^{3,4} The infection can escalate to severe pneumonia, acute respiratory distress syndrome (ARDS), potentially advancing to sepsis without timely untreated.⁴ During sepsis, gut microbiome composition is severely affected, promoting disease-causing microorganisms, immune dysregulation, and reduced production of beneficial short-chain fatty acids.^{5,6} These changes decrease the threshold for the development of sepsis. Sepsis and antibiotic treatment can exacerbate microbiome disruption, creating a vicious cycle that can lead to systemic infections and eventually multiple organ dysfunction syndrome (MODS).⁷

However, patients with mild symptoms in the early stage of the disease may be difficult to diagnose *tsutsugamushi* infection even if they go to medical institutions for diagnosis and treatment. In this article, we describe a pregnant woman (18+6 weeks) who developed MODS and recurrent diarrhea after severe pneumonia due to rickettsial infection progressed to severe sepsis, and report her outcome after receiving fecal microbiota transplantation (FMT).

1.1 | Ethical approval

The study was approved by our hospital's ethics committee, and the patient consented in writing to the treatment and case publication.

2 | CASE HISTORY AND EXAMINATION

The patient was a 27-year-old female with persistent cough and sputum for over half a month, and her symptoms worsened. She was hospitalized at a local primary care center for treatment. During the hospitalization, she developed a fever, accompanied by asthma and fatigue. After worsening of asthma, the patient was transferred from the local basic health center to an external hospital for treatment. Preliminary diagnosis: (1) high fever (2) respiratory failure (3) 18+6 weeks of pregnancy (4) hypokalemia (5)

sinus tachycardia. The symptoms did not improve significantly after treatment with ceftazidime, aminophylline for anti-infection, antipyretic, potassium supplement, nebulized expectorant, and oxygen inhalation.

Due to the high risk of coinfection and the resulting severe disease progression, the patient was transferred to our hospital in early in the morning of July 24th. Admission diagnosis: pneumonia, respiratory failure, cardiac insufficiency, history of 5 deliveries, hypokalemia, and sinus tachycardia. In treatment, piperacillin sodium tazobactam sodium anti-infection, cough and phlegm, asthma, potassium, pressure, acid correction, and other symptomatic treatment. On the morning of July 24, the patient experienced increased shortness of breath, low pulse oxygen, and circulatory failure. She was given endotracheal intubation and mechanical ventilation for assisted breathing and changed to meropenem for anti-infection. The patient's condition did not improve, respiratory and circulatory failure was serious, and was transferred to the intensive care unit (ICU) in the afternoon.

3 | METHODS

At the time of transfer, the patient was on auxiliary oxygen support with an F_{iO_2} of 100%, exhibiting a blood oxygen saturation of 80%, and a blood pressure of 112/52 mmHg, which was being sustained with the use of pressors (norepinephrine at a rate of 2.0 $\mu\text{g}/\text{kg}/\text{min}$). The heart rate was 177 beats per minute, and the respiratory rate was 46 breaths per minute. The patient presented with oliguria, metabolic acidosis, and elevated lactic acid levels, indicating a critical condition. The acute physiology and chronic health evaluation II (APACHE-II) score was 30 points, and the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score was 14 points. Lung ultrasound revealed a significant number of B-lines in the lungs. The diagnosis upon transfer included: severe pneumonia, acute respiratory distress syndrome, electrolyte metabolism disturbance (hypokalemia and hypocalcemia), sinus tachycardia, hypoproteinemia, mild hydronephrosis, and gallbladder deposits. The findings from lung ultrasound imaging and CT scans are depicted in [Figures 1, 2](#).

In view of the shock, the patient underwent venovenous extracorporeal membrane oxygenation (VV-ECMO) cannulation at the bedside with the consent of the family. After the cannulation, the patient was transitioned to ECMO support for further treatment, 40 min later. Despite this, the patient continued to experience persistent hypotension and hypoxemia, with the lowest blood pressure at 62/52 mmHg, elevated blood lactate levels peaking at 21.5 mmol/L, and poor peripheral circulation, indicating an extremely critical condition.

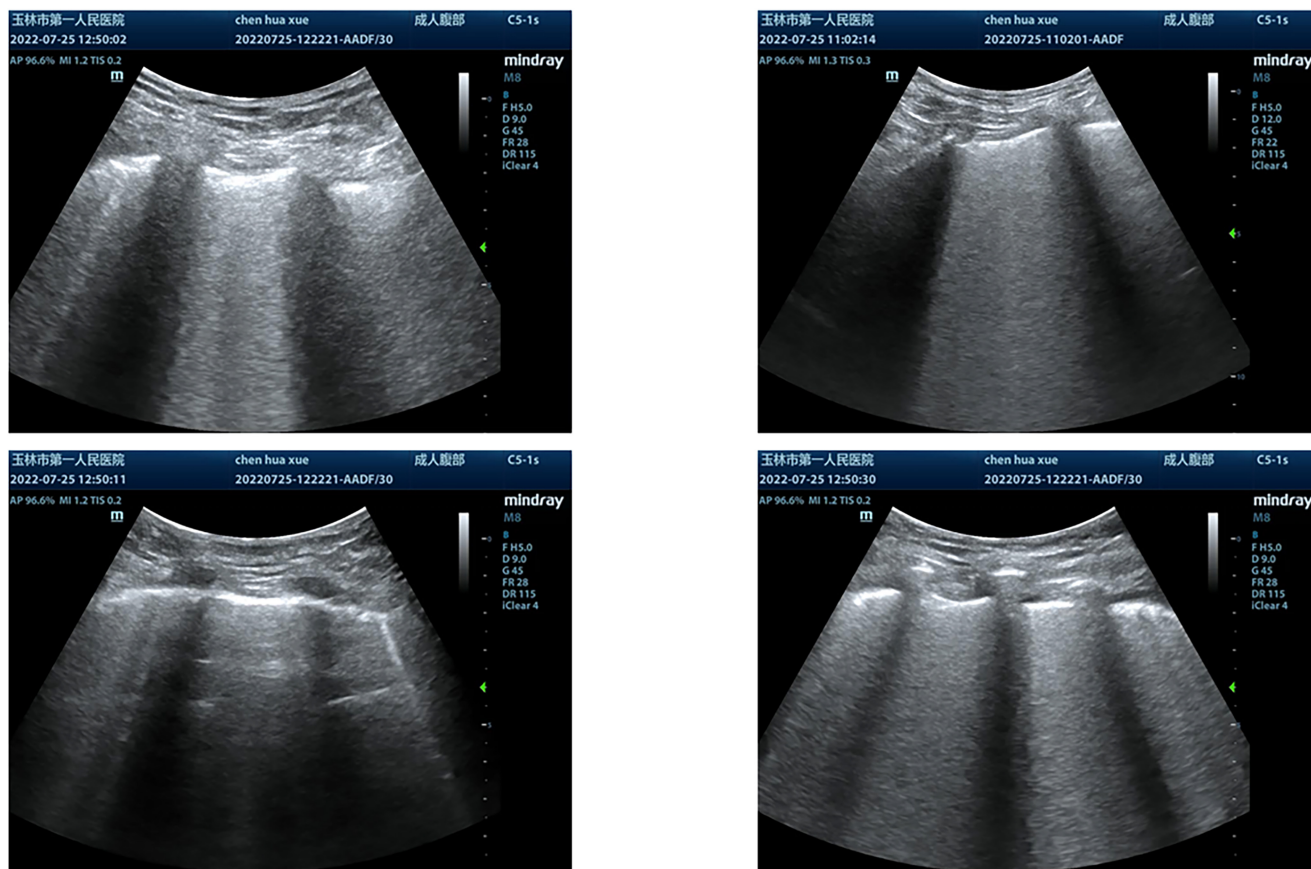


FIGURE 1 Lung ultrasound imaging prior to initiation of venovenous extracorporeal membrane oxygenation (VV-ECMO).

The patient received active fluid resuscitation, blood transfusion, albumin supplementation, and vasopressor support (including norepinephrine, pituitary hormone extract, dopamine, and hydrocortisone for maintaining hemodynamic stability) as part of the anti-shock therapy. Antimicrobial therapy with meropenem, peramivir, and oseltamivir was administered, along with amiodarone for anti-arrhythmic management and gamma globulin for immunomodulatory and anti-inflammatory effects. Life support measures, including mechanical ventilation, were implemented. The following day, combined continuous renal replacement therapy (CRRT) and intermittent hemodialysis were initiated.

After achieving hemodynamic stability, the patient underwent prone position ventilation, with fiberoptic bronchoscopy-guided alveolar lavage performed 1–2 times daily and mechanical assisted sputum drainage carried out 4 times daily. Alveolar lavage fluid next-generation sequencing (NGS) identified *Candida albicans*, *Klebsiella pneumoniae*, and *Orientia tsutsugamushi*, while blood NGS confirmed the presence of *Orientia tsutsugamushi* and human herpesvirus type 4. The patient was treated with a combination of imipenem, chloramphenicol, caspofungin, and ganciclovir for anti-infective therapy. In addition, enteral nutrition, organ support, and fluid

management were provided as part of the comprehensive treatment regimen.

On July 27th, the patient underwent an evacuation due to a miscarriage. On July 29, the patient's circulation and oxygenation were improved, and pulmonary infection and exudation were reexamined. Two days later, on July 29th, the patient's circulatory and respiratory status improved, and the lungs were reassessed for infection and exudates. As a result of the treatment, the patient's lung lesions improved significantly. The ECMO was removed on July 31st, and the lung CT findings are presented in Figure 3. The lung CT results obtained 25 days post-ECMO removal are depicted in Figure 4, indicating that the patient's pulmonary lesions were largely resolved. However, the patient developed worsening jaundice, with peak bilirubin levels reaching $328 \mu\text{mol/L}$, leading to the administration of artificial liver support therapy.

On August 3rd, patients presented with limb muscle weakness and refractory diarrhea, abdominal distension, difficulty weaning from mechanical ventilation, difficulty eating, and an average of 4–9 times of progressive diarrhea per day. Figure 5 demonstrates the abdominal CT results of the patient, which suggest intestinal obstruction, bowel dilation, and significant gas accumulation.

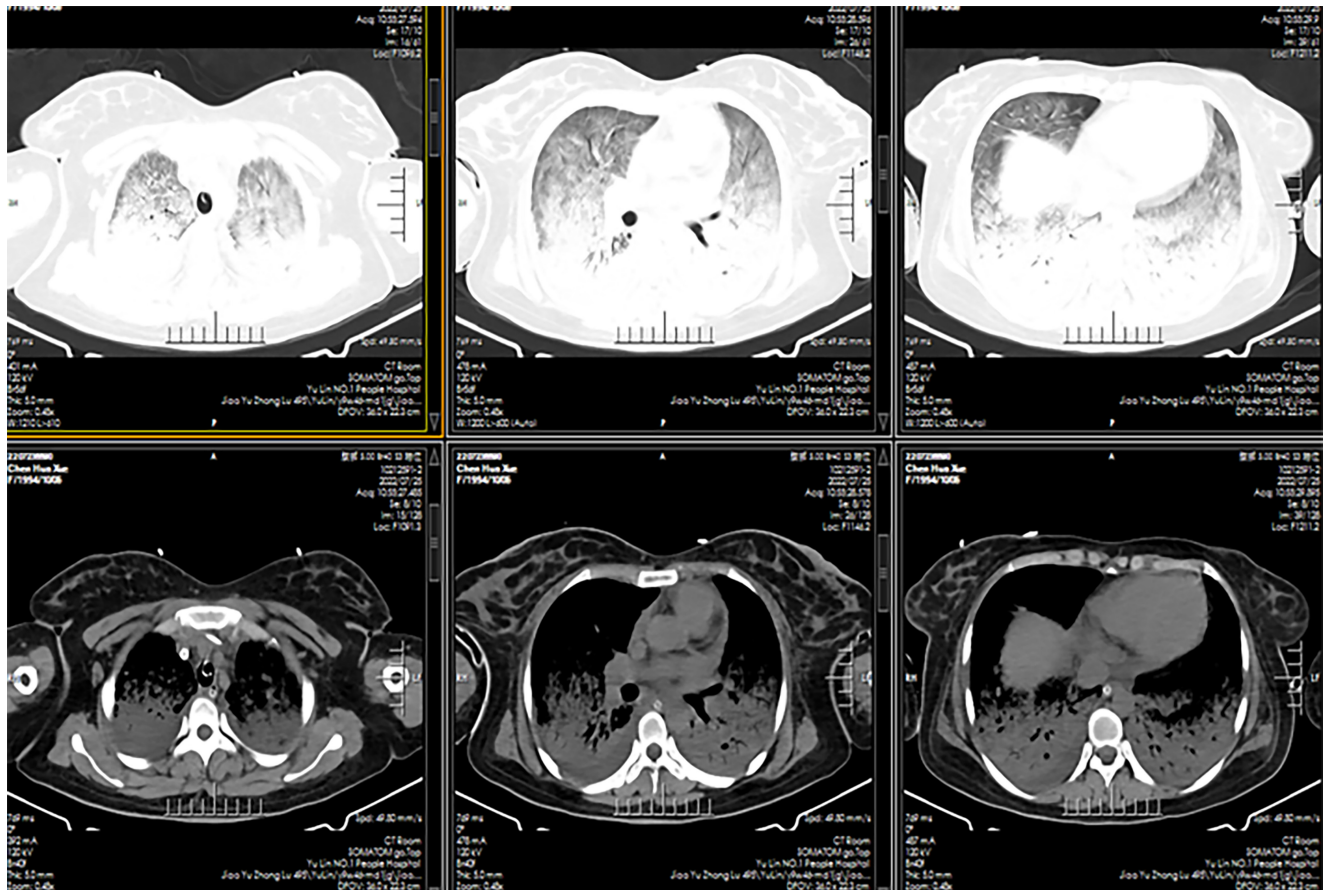


FIGURE 2 Pulmonary computed tomography (CT) prior to initiation of VV-ECMO. On July 24th, two areas of pneumonitis were observed, indicative of pulmonary edema; a small amount of fluid was present in both pleural cavities.

Bacterial cultures and next-generation sequencing (NGS) indicated the presence of multiple bacterial and fungal infections, including *Candida albicans*, *Enterobacter cloacae*, *Aspergillus fumigatus*, *Pseudomonas aeruginosa*, and *Escherichia coli*. The patient was treated with oral vancomycin, intensive rehabilitation, immunoglobulin therapy, traditional Chinese medicine, tracheostomy, and jejunal feeding tube placement. Despite the aforementioned interventions, the patient continued to experience diarrhea and abdominal distension, prompting concerns regarding dysbiosis secondary to sepsis and antibiotic-induced alterations in the gut microbiome.

On August 29th, antibiotic treatment was discontinued, and fecal microbiota transplantation (FMT) was initiated on August 30th, with 200 mL qd (once daily) administered via gastric tube for three consecutive days, followed by oral fecal microbiota capsules. The patient's abdominal distension and diarrhea gradually improved, and she continued to receive rehabilitation, nutritional support, immune enhancement, and intensified airway care, leading to gradual improvement in her condition. On October 10th, she achieved stable respiratory and circulatory functions, without abdominal bloating or diarrhea,

with normal urine output, no signs of jaundice, and limb strength rated at grade 3 for the upper limbs and grade 3 for the lower limbs. The patient was able to eat normally and was fully weaned from the ventilator. On November 8th, she was transferred to a local hospital for ongoing rehabilitation. A follow-up visit on December 8th indicated that her upper limb strength had improved to grade 4, while her lower limb strength remained at grade 3. She was discharged on January 4, 2023. The timeline of the patient's treatment is depicted in Figure 6, which shows the main clinical events during the treatment process. Figure 7 illustrates the changes in the patient's oxygenation index and blood lactate levels during treatment. The oxygenation index is a crucial metric that reflects the status of pulmonary function and overall oxygenation. A notable increase in this index during the course of treatment signifies an enhancement in the patient's respiratory function. On the contrary, blood lactate levels serve as a reliable indicator of tissue hypoxia and systemic metabolic disturbances. Notably, the blood lactate level reached its peak on July 25th, recording at 21.5 mmol/L, and subsequently decreased, indicating an amelioration in tissue hypoxia and metabolic derangements.

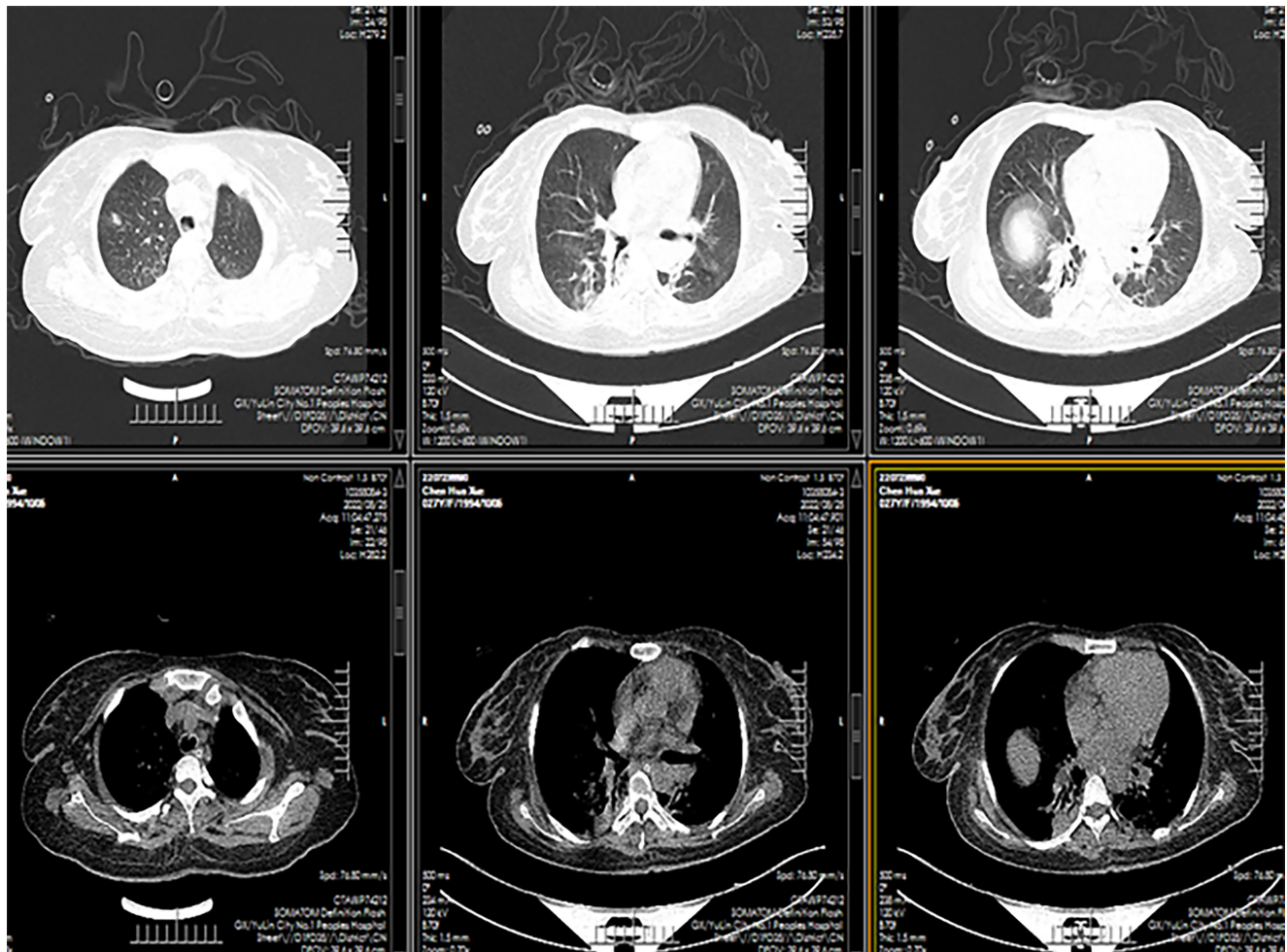


FIGURE 3 Pulmonary CT on the day of ECMO removal. On July 31, the two pneumonia lesions had decreased in size, and the pleural effusion on both sides had largely resolved.

3.1 | FMT procedure

The patient received three FMT treatments from a healthy donor, who tested negative for blood-borne infections and common fecal pathogens. On the infusion day, 80 g of fresh feces were collected, diluted with 350 mL sterile saline, and filtered through a presterilized metal sieve. The patient was then infused with 200 mL of the filtrate via a gastric tube.

4 | CONCLUSION AND RESULTS

We present, to our knowledge, the first documented case in the literature of a pregnant patient experiencing severe post-septic diarrhea. She was treated with ECMO, prone positioning ventilation, CRRT, blood adsorption, and subsequent FMT, with preliminary results. The patient's pregnancy, amidst the gravity of her condition encompassing pneumonia, respiratory failure, and sepsis, underscores the urgent necessity for rigorous

monitoring and prompt intervention to ensure the welfare of both the mother and fetus. Managing such intricate cases necessitates a multidisciplinary approach, meticulously weighing therapeutic options that strike a balance between risks and benefits for both the mother and the developing fetus.

The successful implementation of FMT in this instance, notwithstanding the patient's critical condition and the inherent risks associated with the procedure, exemplifies the potential of innovative treatments to enhance outcomes in high-risk obstetric patients. This could prompt a reevaluation of current clinical protocols, particularly pertaining to sepsis and its associated complications during pregnancy, and foster the exploration of novel therapeutic strategies that prioritize the safety of both mother and fetus.

While FMT has demonstrated potential value in the treatment of sepsis in this case, its widespread clinical application still faces a series of challenges and limitations. Firstly, donor screening is a critical step, requiring assurance of the donor's health status and the suitability of

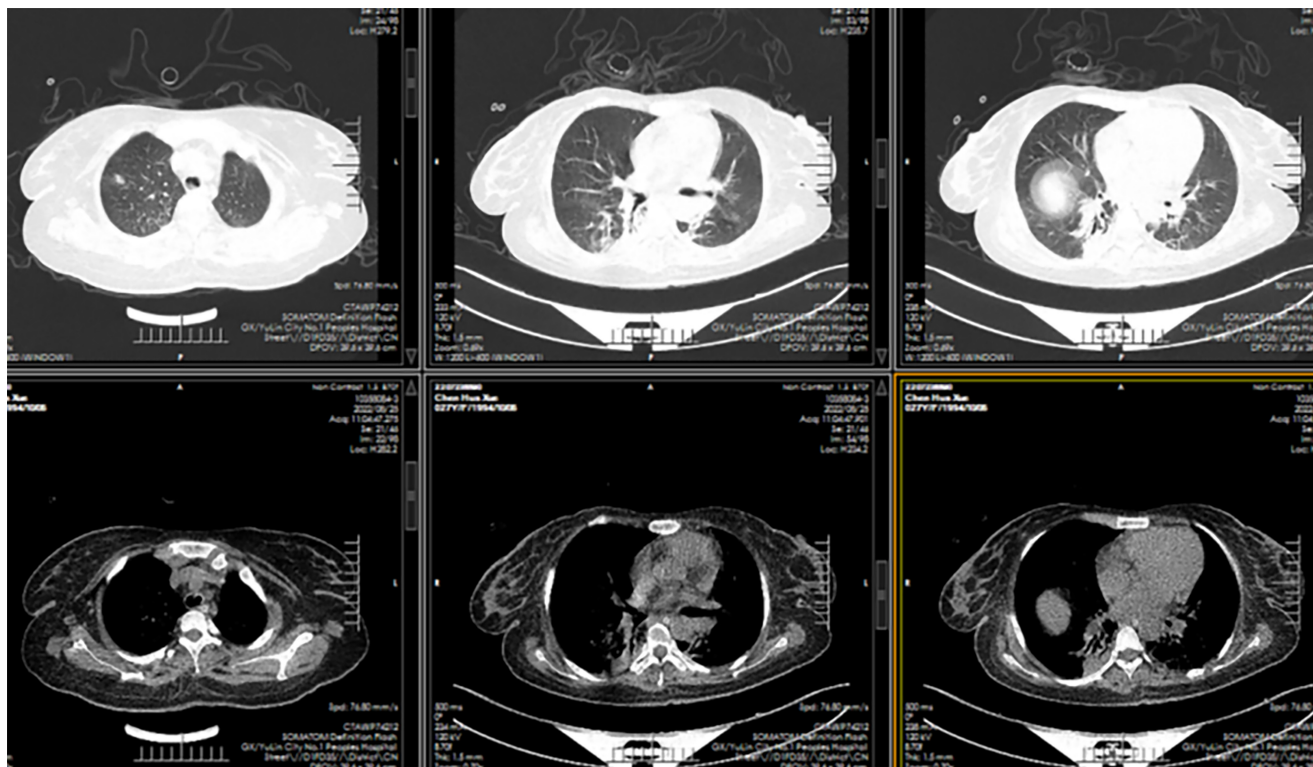


FIGURE 4 CT scan of the lungs 26 days post ECMO removal. On August 25th, the inflammatory lesions in both lungs were substantially resolved.

their gut microbiota. The donor's health history, infectious disease exposure, lifestyle factors, and antibiotic usage history all necessitate rigorous evaluation. However, the absence of standardized donor screening criteria may lead to disparities in FMT execution across different healthcare institutions, affecting the consistency and safety of treatment outcomes. Secondly, the procedural protocols for FMT are not yet fully standardized. Variations in FMT methods among different medical teams can result in inconsistent treatment effects. Establishing and disseminating standardized operating guidelines are crucial for enhancing the success rate and safety of FMT. Additionally, long-term monitoring of patients receiving FMT is essential. This includes not only assessing treatment efficacy but also monitoring for potential late-onset complications. However, the implementation of long-term monitoring may be constrained by resource limitations and patient compliance. Lastly, potential risks associated with FMT, such as infection transmission and immune responses, must also be thoroughly considered in clinical practice. Although these risks are infrequently reported in the current literature, as the application of FMT increases, understanding and developing preventive measures for these potential risks will become increasingly important. Future research should focus on addressing these issues

to ensure that FMT can maximize its therapeutic benefits while ensuring patient safety.

In conclusion, gut microbial communities play a crucial role in human health. FMT has potential applications in sepsis treatment and helps to improve patients' prognosis and quality of life. However, further studies are necessary to validate its safety and efficacy and to determine the optimal transplantation strategy and treatment regimen. For future research, we propose the following specific recommendations: Firstly, conduct prospective clinical trials with standardized protocols to ensure the reliability and reproducibility of the study results, including clear inclusion and exclusion criteria, randomized controlled design, and detailed treatment and assessment processes. Secondly, explore and establish operational standards for FMT, including the processing of donor feces, transplantation methods, dosage, and frequency, to enhance the consistency and reproducibility of treatment. Concurrently, implement long-term follow-up assessments to comprehensively understand the long-term effects and potential complications post-FMT treatment. Additionally, research and develop stringent donor screening and management guidelines to ensure the quality and safety of donors, thereby reducing the risk of infection transmission. By

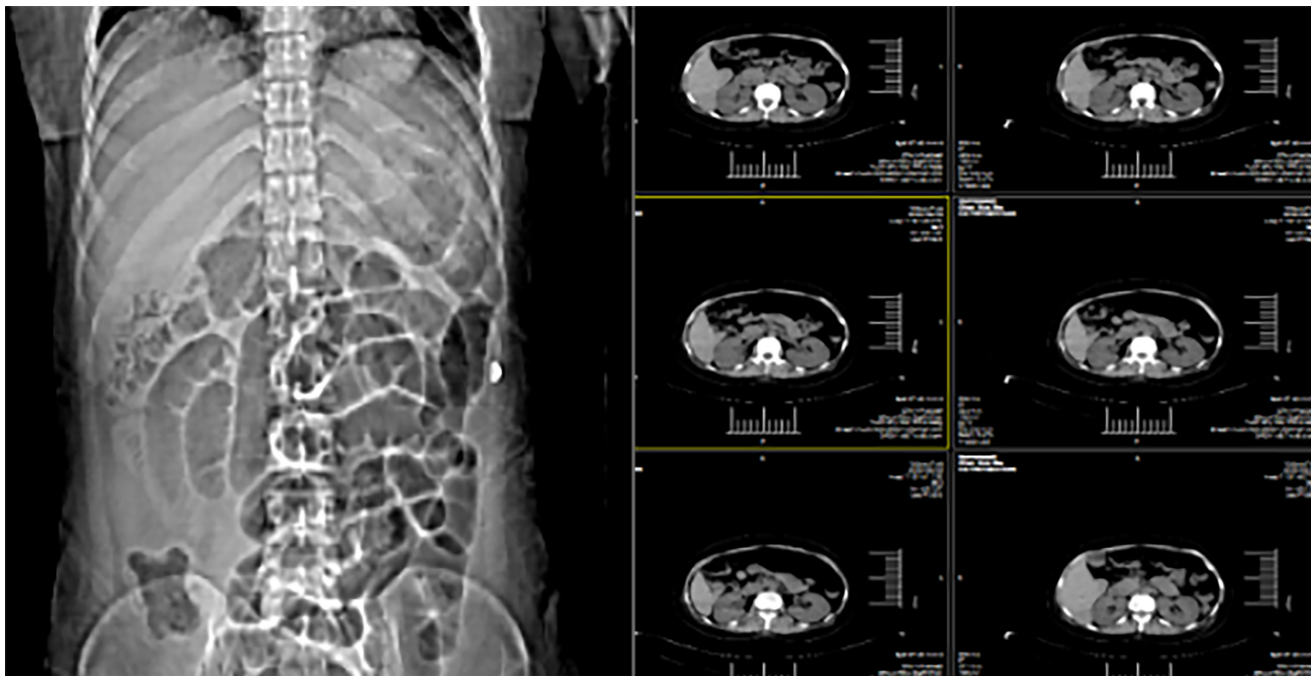


FIGURE 5 Abdominal CT of the patient. The CT on August 5th revealed intestinal obstruction, intestinal dilation, and significant gas accumulation.

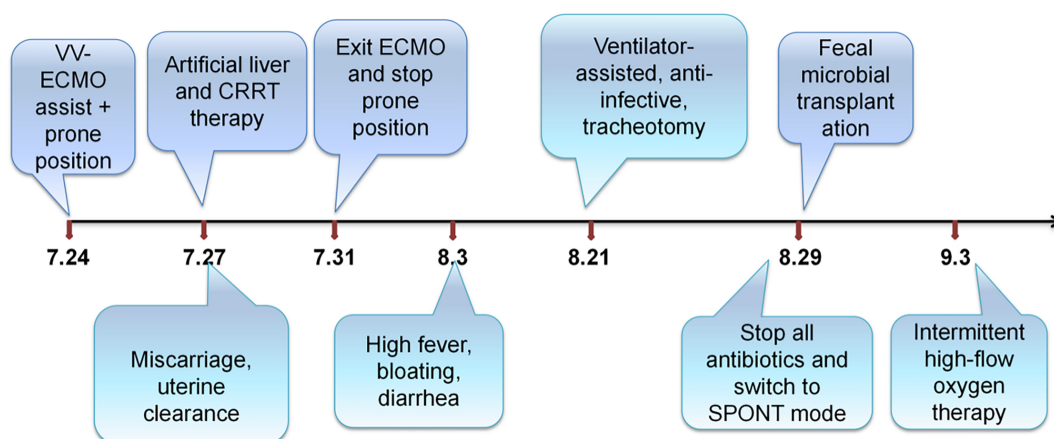


FIGURE 6 Patient treatment timeline. This timeline illustrates the principal clinical events throughout the patient's treatment course. CRRT, continuous renal replacement therapy; SPONT, spontaneous ventilation.

collecting and analyzing clinical data from patients, we can more accurately evaluate the efficacy and safety of FMT, providing robust support for clinical practice.

5 | DISCUSSION

A 27-year-old pregnant woman with persistent cough and sputum developed severe pneumonia and respiratory failure, leading to ECMO support. Despite aggressive treatment, her condition worsened, including a miscarriage and intestinal complications. FMT was initiated, which improved her abdominal symptoms and overall condition. The case highlights the role of the gut-lung axis,

with microbiome changes potentially contributing to pulmonary inflammation and sepsis. This outcome parallels previous cases, including one involving a patient with severe sepsis and diarrhea following vagotomy, who also achieved successful treatment with FMT.⁸

Scrub typhus, caused by *O. tsutsugamushi*, is characterized by the formation of eschars, which may be crusty red or black, and can also present with ulcerations, providing diagnostically significant symptoms.⁹ Literature reports that 7%–97% of patients suffering from scrub typhus develop eschars, although a minority of patients may present without eschars or ulcerations, complicating diagnosis.^{10–12} In this case, the absence of eschar symptoms and normal initial white blood cell count

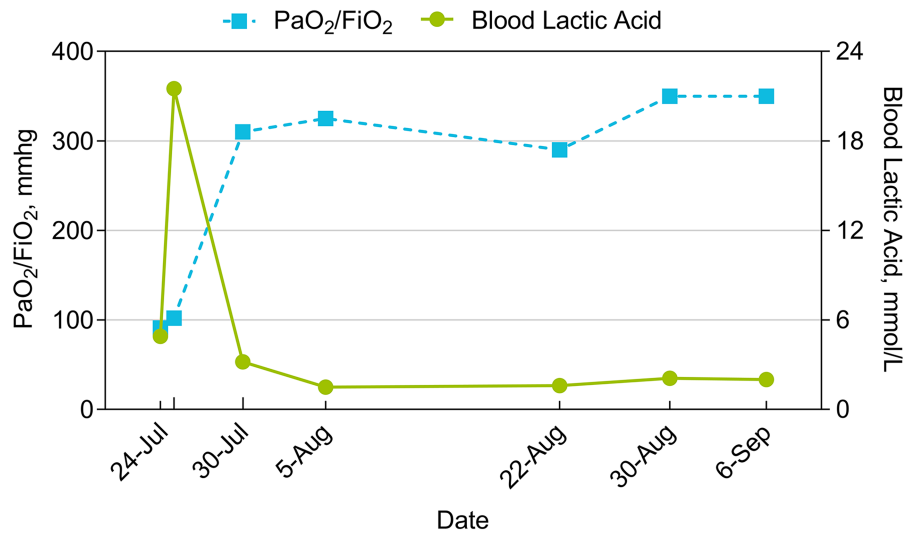


FIGURE 7 Oxygenation index and blood lactic acid during treatment. The oxygenation index progressively increased and stabilized, while the blood lactic acid levels initially rose and then gradually declined.

underscored the pivotal role of alveolar lavage fluid and blood NGS in confirming the pathogen. This approach is of significant importance for cases where clinical presentation does not facilitate diagnosis, albeit time-consuming. The patient presented with shock on July 24th, and it was not until July 28th that the pathogen was identified, leading to an adjusted treatment regimen. Due to the atypical clinical presentation, the initial therapy did not include targeted antibiotics against *O. tsutsugamushi*, which exacerbated the condition, triggering a systemic inflammatory response syndrome, resulting in damage to the lungs and other vital organs. Following a series of comprehensive salvage measures, including ECMO, prone positioning ventilation, CRRT, blood adsorption, and extracorporeal liver support, the patient's pulmonary lesions improved. However, subsequent developments of muscle weakness, intestinal obstruction, and intestinal failure, unresponsive to antibiotic therapy, suggested that these complications may have arisen from gut microbiota dysbiosis, leading to impaired intestinal function.

The gut–lung axis describes the bidirectional interactions between the gastrointestinal tract and the lungs, with the gut microbiota playing a significant role in regulating immune responses, metabolic products, and signal transduction between the gut and lungs.^{13,14} There is a cross talk of microbial metabolites between the lungs and the gut,¹⁵ where changes in the structure and quantity of the pulmonary microbiome can alter the secreted metabolic products, which then enter the gut via the bloodstream, influencing the growth of the gut microbiota.¹⁶ During the administration of broad-spectrum antibiotics, these agents not only eradicate pulmonary pathogens but also impact the normal gut microbiota, leading to dysbiosis.¹⁷

Moreover, systemic oxygen supply deficits and malnutrition associated with disease progression can affect the growth and metabolism of gut cells, thereby influencing the gut microbiota.¹⁸

Dysbiosis of the gut microbiota also impacts pulmonary microbial colonization and immune function. Metabolic products generated by gut bacteria, such as bacterial lipopolysaccharides (LPS),¹⁹ short-chain fatty acids (SCFAs),^{20,21} and immune cells (e.g., T-regulatory cells), circulate through the bloodstream, stimulating immune responses in the lungs, which in turn influence the colonization of the pulmonary microbiome.²² Furthermore, gut microbiota imbalance can also affect nutrient absorption and metabolism. The gut microbiota participates in the digestion and absorption of nutrients, and when dysbiosis occurs, nutrient absorption may be compromised, thereby impacting the patient's immune capacity and recovery potential.²³

The gut microbiota and gut–lung axis play a role in the development and progression of sepsis. Studies have shown changes in the gut microbiota composition in sepsis patients. During hospitalization, microbial diversity decreases rapidly, which becomes more evident with longer stays.^{24–26} These changes are partially attributed to clinical interventions such as enteral feeding, mechanical ventilation, and the widespread use of proton pump inhibitors, opioids, vasopressors, and especially antibiotics.⁵

To restore the intestinal microecological balance, several strategies can be employed, including the administration of probiotics, prebiotics, or FMT. These approaches promote the growth and reproduction of beneficial bacteria in the gut, thereby inhibiting the proliferation and translocation of pathogenic bacteria,

leading to improved patient outcomes.²⁷ FMT involves the transplantation of fecal microbiota from a healthy donor into the recipient's gut to restore intestinal flora and improve gut function. FMT has effectively treated four patients with refractory sepsis and diarrhea, one patient with MODS due to drug-induced hypersensitivity syndrome (DIHS), and 20 critically ill patients with antibiotic-associated diarrhea (AAD).^{8,28–31} Preliminary studies have shown that during sepsis, the reintroduction of healthy microbiota through FMT can correct intestinal ecological imbalances and promote the recovery of the gut microbial barrier, which in turn can improve the treatment outcomes of ICU sepsis. In this case, the patient's exposure to multiple antibiotic regimens, including piperacillin-tazobactam, meropenem, paracetamol, and oseltamivir, likely led to a disruption of the gut microbiota. Following treatments such as ECMO support, CRRT, hemoperfusion, and artificial liver therapy, the patient developed refractory diarrhea and abdominal distension, which did not improve despite adjustments to the antibiotic protocol. As the condition progressed, the patient exhibited severe manifestations such as muscle weakness, intestinal obstruction, and intestinal failure, further suggesting a significant disruption of the gut microbiome. Conventional antibiotic therapy failed to achieve the desired clinical outcomes, and probiotic and prebiotic treatments may also be insufficient to correct such a profound dysbiosis. Given the complexity of the patient's condition, involving multiple organ systems, there was a need for a comprehensive approach to improve intestinal function. In this context, FMT emerged as a novel therapeutic intervention, demonstrating its potential to restore gut microbiota balance and enhance intestinal function. Consequently, after experiencing recurrent diarrhea, abdominal distension, and difficulty weaning from mechanical ventilation, and following the failure of conventional strategies involving antibiotics and probiotics, the patient underwent FMT and oral fecal microbiota capsule therapy. The patient's condition was brought under control, and they gradually improved, leading to discharge. This further substantiates the efficacy of FMT as a treatment modality.

AUTHOR CONTRIBUTIONS

Hongmei Qin: Conceptualization; data curation; formal analysis; investigation; methodology; software; validation; visualization; writing – original draft. **Yaoqing Fu:** Conceptualization; data curation; formal analysis; methodology. **Caixia Deng:** Software; validation; visualization. **Yanxing Chen:** Software; validation; visualization. **Keming Huang:** Validation; visualization. **Yiyang Ruan:** Validation; visualization. **Ke Liu:** Funding

acquisition; project administration; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicting interests to declare.

DATA AVAILABILITY STATEMENT

The data used to support the results of this study can be obtained from correspondents upon request.

ETHICS STATEMENT

This study was approved by the Medical Ethics Committee of our hospital.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Hongmei Qin  <https://orcid.org/0009-0008-1002-2744>

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