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CASE REPORT

Neonatal methicillin-resistant *Staphylococcus aureus* pneumonia–related recurrent fatal pyopneumothorax: A case report and review of literature

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Abstract

BACKGROUND

Although neonatal *Staphylococcus aureus* pneumonia is common and usually curable, it can also be refractory and life-threatening. Herein, we report a case of severe neonatal community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) necrotizing pneumonia with bilateral recurrent pyopneumothorax, respiratory failure, heart failure, and cardiac arrest. We hope our report will add to the understanding of this disease.

CASE SUMMARY

An 18-d-old boy presented with cough for five days, fever for three days, and dyspnea for two days. Preadmission chest radiograph revealed high-density shadows in both lungs. On admission, his oxygen saturation fluctuated around 90% under synchronized intermittent mandatory ventilation. He was unconscious, with dyspnea, weak heart sounds and hepatomegaly. Moist crackles were present throughout his left lung, while the breath sounds in the right lung were decreased. After high-frequency oscillatory ventilation, empiric antimicrobials (meropenem and vancomycin), improved circulation, and right pleural cavity drainage for right pneumothorax (approximately 90% compression), his oxygen saturation level stayed above 95%, and recruitment of the right lung was observed. His condition did not deteriorate until the 5th day of hospitalization (DOH 5). On the morning of DOH 5, his oxygen saturation decreased. Subsequent chest radiograph showed bilateral pneumothorax with nearly 100% compression

of the left lung. Desaturation was not relieved after urgent left pleural cavity drainage, and cardiac arrest occurred soon thereafter. Although his spontaneous heartbeat returned through emergency resuscitation and salvage antibacterial therapy (linezolid and levofloxacin) was administered given the detection and antimicrobial susceptibility of MRSA, he showed no improvement, with recurrent pyopneumothorax and continued drainage of purulent fluid and necrotic lung tissue fragments from the pleural cavity. Eventually, his parents refused extracorporeal membrane oxygenation (ECMO) and gave up all the treatments, and the newborn passed away soon after withdrawal on DOH 13.

CONCLUSION

Neonatal MRSA pneumonia can be refractory and lethal, especially in cases where necrotizing pneumonia leads to extensive lung necrosis and recurrent pneumothorax. Despite treatment with linezolid and other medical measures, it may still be ineffective. Currently, ECMO has been a remedial therapy, but if the lung tissue is too severely eroded to be repaired, it may be useless unless the infection can be controlled and lung transplantation can be performed. Regardless of whether ECMO is initiated, the key to successful treatment is to achieve control over the pneumonia caused by MRSA as soon as possible and to reverse lung injury as much as possible.

Key Words: Newborn; Methicillin-resistant *Staphylococcus aureus*; Pyopneumothorax; Linezolid; Extracorporeal membrane oxygenation; Case report

Core Tip: Neonatal pneumonia can usually be prevented, controlled and cured, regardless of whether it is caused by hospital-associated methicillin-resistant *Staphylococcus aureus* or community-acquired methicillin-resistant *Staphylococcus aureus*, but sometimes it is refractory or incurable. We report a case of severe neonatal community-acquired methicillin-resistant *Staphylococcus aureus* necrotizing pneumonia with bilateral recurrent pyopneumothorax, respiratory failure, heart failure, and cardiac arrest. We hope our report furthers our understanding of this disease.

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INTRODUCTION

With the development and widespread application of antibiotics, methicillin-resistant *Staphylococcus aureus* (MRSA) has spread globally[1-3], exhibiting multidrug resistance and extensive colonization[1-2,4-5]. MRSA causes both hospital-associated infections and community-acquired infections[2,6-10]. In addition to skin and soft tissue infections (SSTIs)[5,9], MRSA can lead to pneumonia, sepsis, intracranial infections, *etc.*[6,9], which are common in the elderly population, children, patients with neutrophil dysfunction, and inpatients[6]. Pneumonia caused by MRSA is severe and refractory, with acute onset, rapid progression and high mortality, manifested by repeated episodes of fever, symptoms of severe infection and dyspnea, and it can lead to shock and multiple-organ failure[11-12]. The characteristics of MRSA pneumonia on chest imaging vary, including such features as pneumothorax[11], empyema[11,13], and pneumatoceles [11,14-15]. Neonatal MRSA infections usually occur in critically ill newborns with long-term hospitalization[16-17], such as extremely premature infants[18-19], low-birth-weight infants[17,20], term infants undergoing surgery[18], and neonates with congenital heart disease[17]. MRSA infections in newborns can also involve multiple systems (*e.g.*, SSTIs [17], pneumonia[13-15,17,19,21], bacteremia[13,15,17], central nervous system infections[17], bone and joint infections[17,22], peritonitis[17], and liver abscess[23]) and cause related injuries that are severe and refractory[17,23].

Hospital-associated MRSA (HA-MRSA) infection is common[19,24-26], while community-acquired MRSA (CA-MRSA) infection[6,21,27], especially severe neonatal CA-MRSA refractory necrotizing pneumonia[13,15], is relatively rare. Although some neonates with MRSA pneumonia will recover[13-15,21], some cases cannot be cured[17]. Caregivers must pay attention to the importance of hand hygiene and other protective measures in the daily care of newborns and try to avoid MRSA infections in multiple ways[16,20,26,28-29].

Herein, we report a case of severe neonatal CA-MRSA necrotizing pneumonia with bilateral recurrent pyopneumothorax, respiratory failure, heart failure, and cardiac arrest.

CASE PRESENTATION

Chief complaints

An 18-d-old boy presented with cough for five days, fever for three days, and dyspnea for two days.

History of present illness

His body temperature peaked at 37.5 °C. Chest radiograph revealed high-density shadows in both lungs (Figure 1A). Antibiotics (meropenem and vancomycin) and mechanical ventilation had been performed at the local hospital. For further treatment, the newborn was transferred to our neonatal intensive care unit through a vehicle-mounted ventilator by ambulance.

Personal and family history

The boy, G3P2, was born to a 34-year-old woman at 38 wk 3 d of gestational age with a birth weight of 4.5 kg and an Apgar score of 9 points at 1 min after birth. His parents were not close relatives and were in good health. They lived in a rural area.

Physical examination

He had a fever of 38.2 °C, a heart rate of 210 beats/min, a respiratory rate of 100 breaths/min, a blood pressure of 95/65 mmHg, and a body weight of 4.75 kg. His oxygen saturation fluctuated around 90% under synchronized intermittent mandatory ventilation (FiO_2 100%). He was unconscious, with dyspnea, weak heart sounds and hepatomegaly. Moist crackles were present throughout his left lung, while the breath sounds in the right lung were decreased.

Laboratory examinations

Changes in leukocyte, erythrocyte, hemoglobin, platelet, neutrophil (%), C-reactive protein, creatine kinase-MB, lactate dehydrogenase, and hydroxybutyrate dehydrogenase parameters (Table 1) indicated that the above items had increased to varying degrees, except for the decreases in erythrocytes, hemoglobin, and platelets. MRSA infection was confirmed by multiple cultures (sputum and pleural fluid) (Table 2), while other pathogen tests, such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, cytomegalovirus, herpes simplex virus, rubella virus, *Toxoplasma gondii*, *Mycobacterium tuberculosis*, adenovirus, parainfluenza virus 2, parainfluenza virus 3, human coronavirus 229E/NL63, influenza virus A, rhinovirus, and respiratory syncytial virus, along with cerebrospinal fluid culture and blood cultures, were all negative.

Imaging examinations

Chest radiographs at the local hospital (Figure 1A) and in Taihe Hospital (Figure 1B and C and Figures 2-4) are shown in detail in the History of present illness and Treatment sections, respectively. The latter revealed recurrent bilateral pyopneumothorax, multiple high-density shadows and pneumatoceles (Figure 4, orange arrows) in both lungs.

FINAL DIAGNOSIS

According to the clinical definition of CA-MRSA infection used by the United States Centers for Disease Control and Prevention[30], the diagnosis was severe neonatal CA-MRSA necrotizing pneumonia.

TREATMENT

Upon admission, after timely high-frequency oscillatory ventilation (HFOV), empiric antimicrobials (meropenem 40 mg/kg IV q8h plus vancomycin 15 mg/kg IV q8h), improved circulation, and right pleural cavity drainage for right pneumothorax (approximately 90% compression) (Figure 1B), his oxygen saturation level stayed above 95%, and recruitment of the right lung was observed (Figure 1C). Dynamic monitoring was performed by chest radiography (Figure 2), and his condition did not deteriorate until the 5th day of hospitalization (DOH 5).

On the morning of DOH 5, his oxygen saturation decreased. Subsequent chest radiograph showed bilateral pneumothorax with nearly 100% compression of the left lung (Figure 3A). Desaturation was not relieved after urgent left pleural cavity drainage, and cardiac arrest with nonshockable rhythm occurred soon thereafter. Emergency neonatal cardiopulmonary resuscitation (CPR) (including intravenous 1:10000 epinephrine 0.2 mL/kg every 3 to 5 min) was performed for 42 min, but he still had no spontaneous heartbeat. Then, his spontaneous heartbeat returned within 18 minutes by adjusting the resuscitation [infusion of 5% sodium bicarbonate (3 mL/kg), 1:10000 epinephrine (0.2 mL/kg), atropine (0.02 mg/kg), and 10% calcium gluconate (2 mL/kg) *via* a preset peripherally inserted central catheter (PICC) sequentially], and the left lung was partially recruited (Figure 3B and C).

Afterward, MRSA infection was confirmed by multiple cultures (Table 2). Although salvage antibacterial therapy (linezolid 10 mg/kg IV q8h plus levofloxacin 10 mg/kg IV q12h) was administered on DOH 6 according to the culture and antimicrobial susceptibility test results and the child did not experience cardiac arrest again, his condition showed no improvement. He had recurrent pyopneumothorax (Figure 4) and continued drainage of purulent fluid and necrotic lung tissue fragments from the pleural cavity.

Table 1 Laboratory data of this child

	DOH 1	DOH 2	DOH 3	DOH 4	DOH 5	DOH 6	DOH 7	DOH 8	DOH 9	DOH 10	DOH 11	DOH 12
Leukocyte (10^9/L)	6.69	5.18	12.58	22.31	75.77	35.57	43.45	35.73	27.9	25.73	22.69	19.95
Erythrocyte (10^{12}/L)	3.78	3.36	3.14	3.18	3.44	3.44	3.44	2.93	3.13	3.92	3.12	3.09
Hemoglobin (g/L)	134	119	113	111	125	122	122	102	109	133	106	103
Platelet (10^9/L)	290	197	199	187	269	105	149	166	88	169	115	95
Neutrophil (%)	63.2	75.6	75.6	74.9	80.6	80.0	NA	79.9	76.6	75.5	80.4	80.4
CRP (mg/L)	290.41	260.3	152.96	114.7	132.6	128.0	227.3	187.8	151.2	129.0	126.6	229.7
CK-MB (U/L)	-	-	-	171	150	-	47	-	-	-	-	-
LDH (U/L)	-	-	-	865	1885	-	1128	-	-	-	-	-
HBDH (U/L)	-	-	-	548	1006	-	684	-	-	-	-	-

CRP: C-reactive protein; CK-MB: Creatine kinase-MB; DOH: Day of hospitalization; HBDH: Hydroxybutyrate dehydrogenase; LDH: Lactate dehydrogenase; NA: Not available.

OUTCOME AND FOLLOW-UP

Eventually, owing to the high probability of poor prognosis, the parents refused extracorporeal membrane oxygenation (ECMO) and gave up all the treatments, and the newborn passed away soon after withdrawal on DOH 13.

DISCUSSION

As this case shows, neonatal MRSA pneumonia can be extremely challenging. The following aspects of this case are discussed in a clinical problem-oriented manner.

How was the initial antibacterial therapy selected, and then how was the antibiotic adjusted?

On admission, given the severity and rapid progression of the child's condition and the presence of pneumothorax, the primary diagnosis was severe neonatal community-acquired pneumonia. Initial antibacterial therapy with meropenem and vancomycin was administered for coverage of gram-negative bacteria and gram-positive bacteria.

Afterward, the diagnosis of severe neonatal CA-MRSA necrotizing pneumonia with bilateral pyopneumothorax was made. Based on the culture and antimicrobial susceptibility test results (Table 2) and a literature review, the antibiotics were switched to linezolid[9,31-35] and levofloxacin[36] for further salvage antibacterial therapy.

Table 2 Culture and antimicrobial susceptibility results of this child

	DOH 6	DOH 6	DOH 6	DOH 6	DOH 10	DOH 12
Specimen	Sputum	Sputum	Sputum	Pleural fluid	Pleural fluid	Pleural fluid
Pathogen	MRSA	MRSA	MRSA	MRSA	MRSA	MRSA
Chloromycetin	S	S	S	S	S	S
Erythromycin	R	R	R	R	R	R
Cefoxitin	R	R	R	R	R	R
Gentamicin	S	S	S	S	S	S
Oxacillin	S	R	R	R	S	S
Penicillin	R	R	R	R	R	R
Rifampin	S	S	S	S	S	S
Teicoplanin	S	S	S	S	S	S
Vancomycin	S	S	S	S	S	S
Clarithromycin	R	R	R	R	R	R
Clindamycin	R	R	R	R	R	R
Linezolid	S	S	S	S	S	S
Tigecycline	S	S	S	S	S	S
Amikacin	S	S	S	S	S	S
Azithromycin	R	R	R	R	R	R
Levofloxacin	S	S	S	S	S	S
Moxifloxacin	S	S	S	S	S	S

DOH: Day of hospitalization; MRSA: Methicillin-resistant *Staphylococcus aureus*; S: Sensitive; R: Resistant.

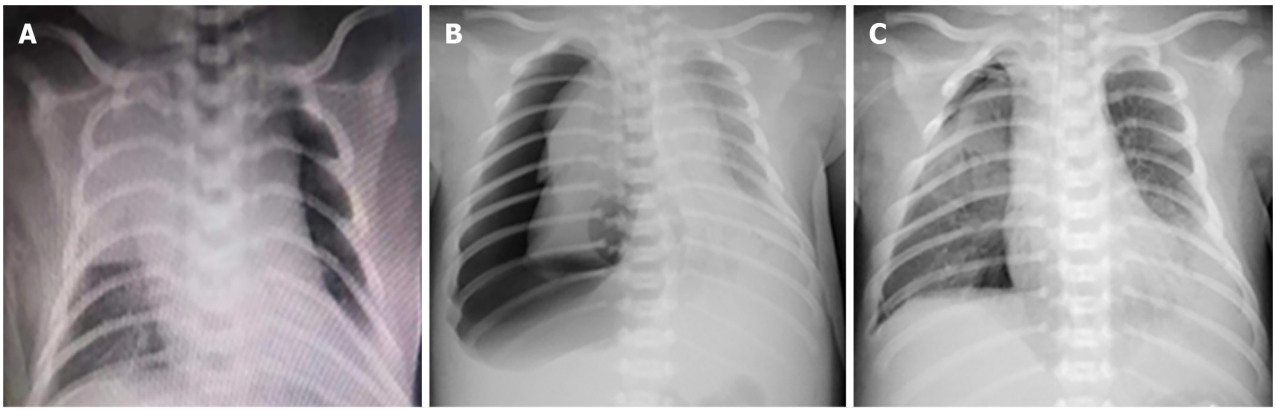

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Figure 1 Chest radiographs one day before admission and on the first day of hospitalization. A: High-density shadows in the right upper lung and left lower lung (one day before admission); B: Right pneumothorax (approximately 90% compression) with a blunt right costophrenic angle, blurring in the left lung, and a disappeared left costophrenic angle (on admission); C: High-density shadows in the right lung and left lower lung, with right pneumothorax, and blurred left diaphragm and costophrenic angle (after drainage of the right pleural cavity on the first day of hospitalization).

What caused the transient stability of the child after initial treatment, and what caused the subsequent rapid deterioration?

First, pathogens such as MRSA invade the body, proliferate, and cause damage in a gradual process. Second, neonatal diseases (including MRSA pneumonia) tend to be atypical and relatively less serious in the early stage. Third, MRSA strains should proliferate to a certain critical level and cause extensive damage before the patient's outward condition rapidly deteriorates. Furthermore, the various treatments administered (*e.g.*, vancomycin, HFOV, and pleural cavity drainage in this case) may have slowed the progression of the disease to a certain extent. However, the initial vancomycin

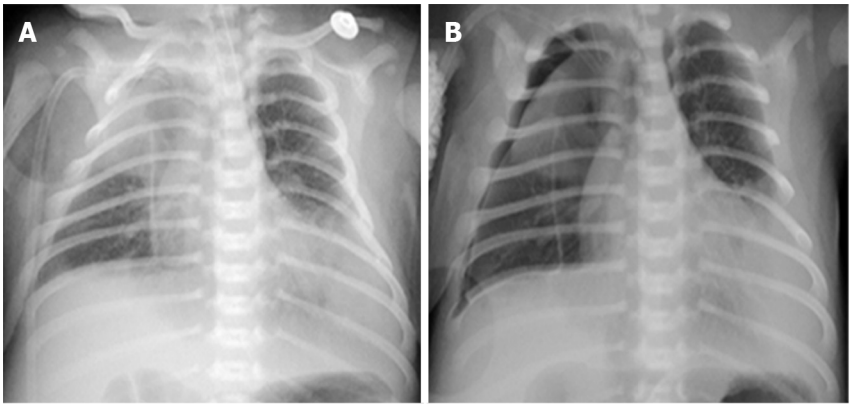

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Figure 2 Chest radiographs on the third and fourth days of hospitalization. A: High-density shadows in the right upper lung and left lower lung, with blurred left diaphragm and costophrenic angle (on the third day of hospitalization, DOH 3); B: High-density shadows in the right upper lung and left lower lung, with blurred left diaphragm, costophrenic angle, and right pneumothorax (on DOH 4).

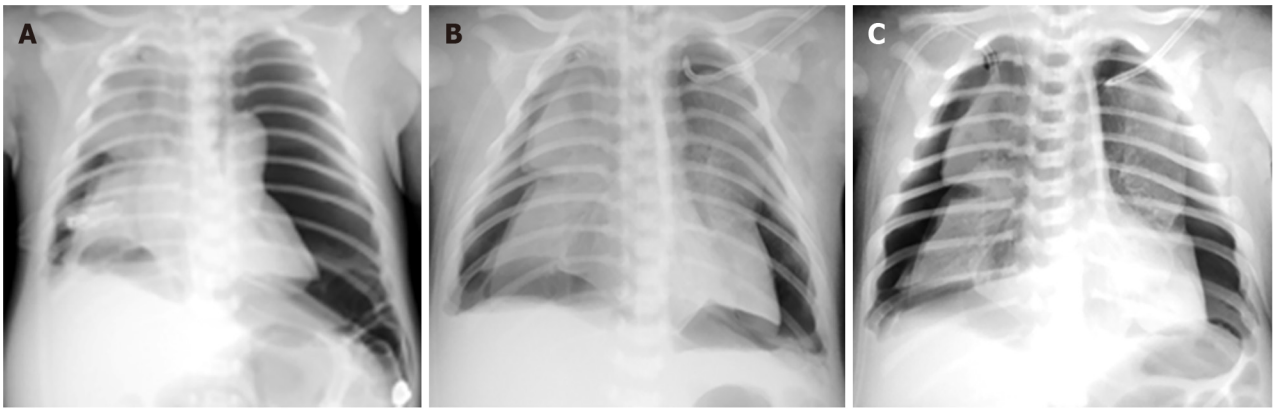

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Figure 3 Chest radiographs on the fifth day of hospitalization. A: Bilateral pneumothorax (nearly 100% compression of the left lung) with right lung consolidation (before cardiac arrest on the morning of the fifth day of hospitalization, DOH 5); B: Obvious recruitment of the left lung (after drainage of the left pleural cavity and successful resuscitation on DOH 5); C: Bilateral pneumothorax was more obvious than that in Figure 3B (at night on DOH 5).

probably could not eliminate the accumulated MRSA from the lungs, thereby increasing the chance of rapid replication of MRSA[33]. All of the above factors may have contributed to the transient stability of the child's condition after initial treatment and the subsequent rapid deterioration. Most importantly, this strain of MRSA caused severe necrotizing pneumonia with extensive necrosis of the lung tissue and recurrent pyopneumothorax, which may be the primary reason for the rapid deterioration of this child's condition.

Compared with vancomycin[35,37], linezolid has a stronger ability to penetrate tissues and is more likely to concentrate in the lungs[35,38-39], which may be more helpful for controlling pneumonia caused by MRSA[7,33,35]. Although MRSA detection methods have improved[1,29], it is still difficult to make an early diagnosis of MRSA infection and to determine which antibiotics will be effective in a timely manner, let alone to make an accurate prognostic prediction early on. Thus, it is difficult to choose linezolid as the initial therapy.

What was responsible for the cardiac arrest, and how to manage this unresponsive patient when conventional neonatal CPR was not successful?

Acute respiratory and circulatory dysfunction secondary to myocardial damage (*e.g.*, weak heart sounds, elevated creatine kinase-MB), heart failure and pneumothorax resulting from severe necrotizing pneumonia caused by MRSA led to cardiac arrest in this patient. Among these factors, pneumothorax was the most important, and the failure of conventional neonatal CPR may also be related to the negative effects of pneumothorax on his breathing and circulation.

In our case, apart from continuing to address the pneumothorax, the resuscitation strategy should be adjusted in a timely manner. While undergoing infusion of sodium bicarbonate, the child still had no heartbeat. Upon reinjection of 1:10000 epinephrine, although he had not yet regained his own heartbeat, short bursts of ventricular escape rhythm occurred. After administration of atropine, his spontaneous sinus rhythm was elicited, and the weak heart sounds became stronger subsequent to infusion of 10% calcium gluconate. Soon afterward, the oxygen saturation rose to 97%. All first-aid drugs were injected *via* a preset PICC. If the above treatments do not work, extracorporeal cardiopulmonary resuscitation

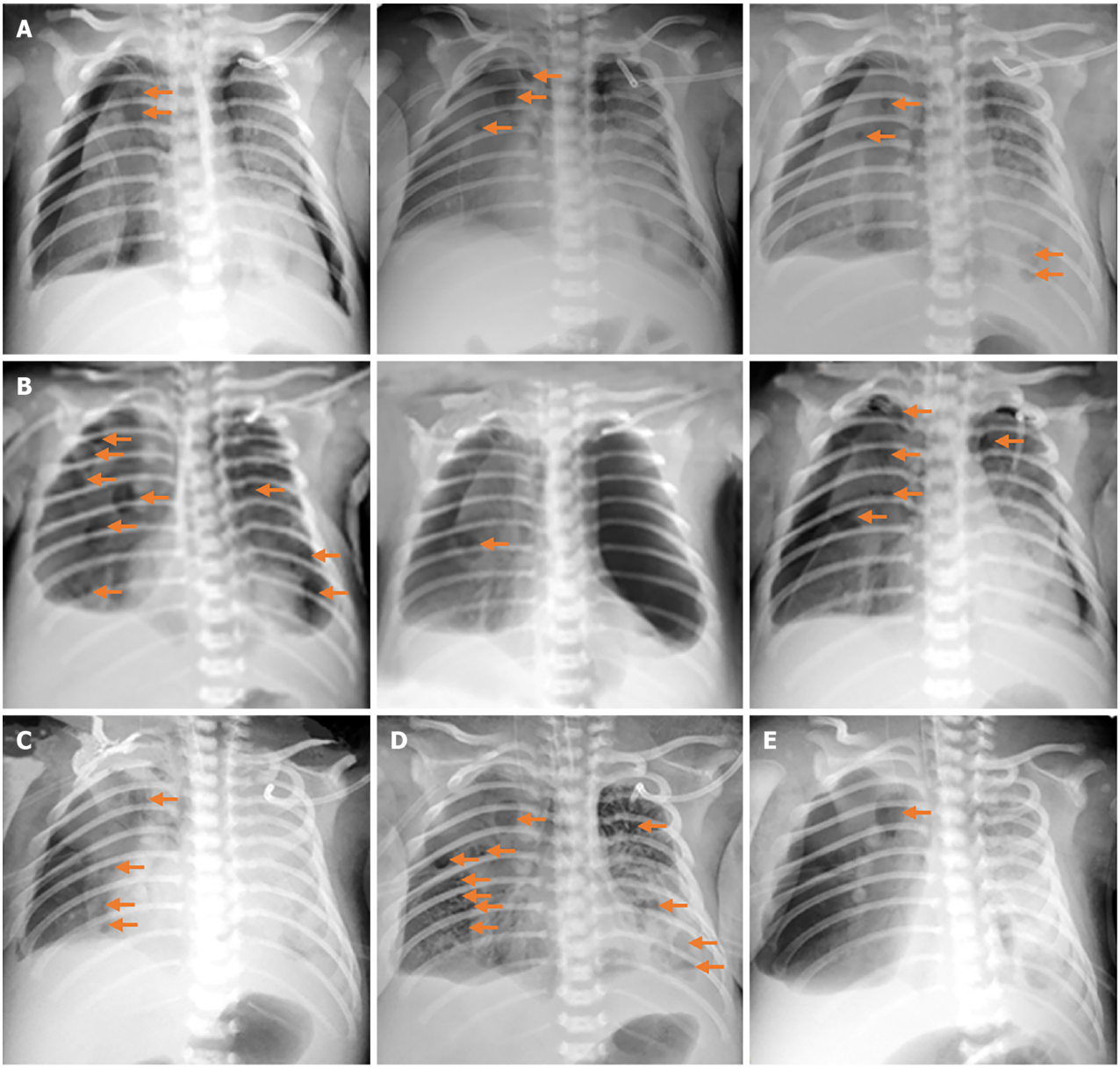

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Figure 4 Chest radiographs on the sixth, seventh, eighth, ninth, and eleventh days of hospitalization. A: Recurrent bilateral pyopneumothorax, with multiple high-density shadows and pneumatoceles (orange arrows) in both lungs (on the sixth day of hospitalization, DOH 6); B: Recurrent bilateral pyopneumothorax, with multiple high-density shadows and pneumatoceles (orange arrows) in both lungs (on DOH 7); C: Multiple pneumatoceles (orange arrows) in the right lung and high-density shadows in both lungs (on DOH 8); D: Multiple high-density shadows and pneumatoceles (orange arrows) in both lungs (on DOH 9); E: Recurrent pyopneumothorax and pneumatocele (orange arrow) in the right lung and high-density shadows in both lungs (on DOH 11).

(ECPR) could be attempted[40].

Prolonged asphyxia can lead to acidosis[41-42], which not only inhibits cardiac contractility[42-43] but also reduces the sensitivity of cardiomyocytes to catecholamine[43] and can even result in death[42]. Therefore, when the effect of conventional neonatal CPR is not ideal, to antagonize the inhibition of cardiomyocytes by acidosis, sodium bicarbonate should be promptly injected to increase the blood pH[42]. In this patient, after a subsequent administration of epinephrine, short bursts of ventricular escape rhythm were observed, indicating that the myocardial inhibition had been partially relieved and that the sensitivity of cardiomyocytes to epinephrine had been partially restored after infusion of sodium bicarbonate, although sinus node function remained poor. Given the repeated administration of epinephrine, atropine was needed immediately to improve sinus node automaticity to restore sinus rhythm[43-44], and it was successful in this patient. At this time, although the sinus rhythm had been restored, the myocardial contraction was too weak to support adequate circulation. Prolonged asphyxia can not only lead to myocardial injury and depression[42] but also lead to hypocalcemia[45], which may further reduce the contractility of the already hypoxic and damaged myocardium, thereby decreasing cardiac output and resulting in persistent poor circulation. Neonatal hypocalcemia is common in neonatal asphyxia[45] and during plasma exchange[46]. Generally, intravenous calcium supplementation can quickly enhance myocardial contractility[43], thereby increasing cardiac output and stabilizing circulation, which occurred in this patient. The success of resuscitation in this case also benefited from the witnessed in-hospital cardiac arrest, the preexisting PICC,

and the close monitoring of his heart rhythm. However, the abovementioned drugs also have potential side effects that cannot be ignored. For instance, calcium may lead to myocardial damage, while sodium bicarbonate can cause hypercapnia, metabolic alkalosis, hypernatremia and hyperosmolality[43]. Therefore, during neonatal CPR, these drugs should not be used initially (unless there are indications), let alone routinely[43].

Could ECMO reverse this condition?

This is possible, but the following factors should be considered. First, the chief indications for neonatal ECMO are that the primary disease is reversible and that the patient meets certain criteria, such as the absence of lethal congenital malformations, irreversible organ damage (unless transplantation is considered), severe intracranial hemorrhage, and uncontrollable bleeding[40]. Second, ECMO can only temporarily replace cardiopulmonary function, gaining some time to allow the comprehensive treatment of primary disease[47]. In this patient, it is unclear whether the MRSA infection could ultimately be controlled and whether the recurrent pyopneumothorax could be eliminated, especially given the extensive erosion of the lung tissue. If those conditions could not be met and lung transplantation could not be performed, ECMO would certainly fail. Moreover, ECMO itself can also lead to infection and organ dysfunction[47]. In short, ECMO has its own pros and cons[47]. If ECMO is used relatively early, it may be beneficial for reversing the course of a disease, but its premature application, especially its long-term application, may also lead to many ECMO-related complications, while its delayed initiation will inevitably decrease the success rate.

Neonatal ECMO is commonly used in patients with persistent pulmonary hypertension of the newborn (ECMO survival: 73%), meconium aspiration syndrome (ECMO survival: 92%), neonatal sepsis (ECMO survival: 45%), neonatal pneumonia (ECMO survival: 60%), congenital diaphragmatic hernia (ECMO survival: < 50%), ECPR (ECMO survival: 40%-50%), *etc.*[40] This child's lungs were so severely damaged by MRSA that he experienced recurrent lethal pyopneumothorax. If the MRSA infection cannot be controlled and/or the damaged lungs cannot be repaired, the prognosis will be poor, which is not even ameliorated by ECMO. However, during the coronavirus disease 2019 (COVID-19) pandemic, lung transplantation has been performed for COVID-19 patients supported with ECMO, improving the prognosis of COVID-19 patients with irreversible infection-related lung injury[48-52]. Moreover, a 7-year-old girl recovered from severe inhalational burn injury and secondary Pseudomonas necrotizing pneumonia after 605 d of ECMO support, providing us with new insight into "irreversible" lung injury and the exciting possibility of lung tissue regeneration or recovery[53]. Regrettably, long-term ECMO support and lung transplantation in newborns are difficult, expensive and challenging.

CONCLUSION

Neonatal MRSA pneumonia can be refractory and lethal, especially in cases where necrotizing pneumonia leads to extensive lung necrosis and recurrent pneumothorax. Despite treatment with linezolid and other medical measures, it may still be ineffective. ECMO has been a remedial therapy, but if the lung tissue is too severely eroded to be repaired, it may be useless unless the infection can be controlled and lung transplantation can be performed. Regardless of whether ECMO is initiated, the key to successful treatment is to achieve control over the pneumonia caused by MRSA as soon as possible and to reverse lung injury as much as possible.

FOOTNOTES

Author contributions: All the authors contributed to conceptualization, data curation, formal analysis, investigation, and methodology of this work, and approved the final version as submitted to be published; Li XC and Sun L drafted the original manuscript; Li T organized this work and revised the manuscript critically.

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