Clinical analysis of 7 cases of cryptogenic new-onset refractory status epilepticus

Haiyan Diao
Under postgraduate, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University

Yanhong Wang (✉️ 13834676852@163.com)
Third Hospital of Shanxi Medical University, Shanxi Academy of Medical Sciences Tongji Shanxi Hospital Taiyuan

Haixia QU
Under postgraduate, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University

Gang Ren
Third Hospital of Shanxi Medical University, Shanxi Academy of Medical Sciences Tongji Shanxi Hospital Taiyuan

Zhijun Wang
Third Hospital of Shanxi Medical University, Shanxi Academy of Medical Sciences Tongji Shanxi Hospital Taiyuan

Hailong Wang
Third Hospital of Shanxi Medical University, Shanxi Academy of Medical Sciences Tongji Shanxi Hospital Taiyuan

Qian Pang
Third Hospital of Shanxi Medical University, Shanxi Academy of Medical Sciences Tongji Shanxi Hospital Taiyuan

Naibing Xiang
Third Hospital of Shanxi Medical University, Shanxi Academy of Medical Sciences Tongji Shanxi Hospital Taiyuan

Research Article

Keywords: New-onset refractory status epilepsy, Phenobarbital, Ketogenic diet

Posted Date: June 7th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2848648/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background

There are relatively few studies related to new-onset refractory status epilepticus (NORSE), in which patients with cryptogenic NORSE have more frequent and longer duration seizures than patients with a clear etiology, are more likely to develop drug-refractory epilepsy and have a more likely prognosis of severe cognitive impairment. We have conducted a series of case studies to investigate the treatment options and prognosis of NORSE.

Methods

Seven adult patients with cryptogenic NORSE who were treated at the Third Hospital of Shanxi Medical University from June 2016 to April 2022 were reviewed. We collected basic information and clinical data of the study subjects, including demographic characteristics, clinical manifestations, laboratory tests and imaging data, medication use, and prognostic regression; the prognosis was assessed by a modified Rankin Scale score (MRS).

Results

The median age of the 7 patients with cryptogenic NORSE was 32 years (interquartile range 25.00–39.00), and 4 patients (57.1%) were male. 6 patients (85.7%) had a history of prodromal fever; 2 (28.6%) patients received high-dose propofol and midazolam and 5 (71.4%) patients received high-dose phenobarbital, of which 4 patients (57.1%) were treated with a ketogenic diet KD. The overall mortality rate was 28.6% (2/7), with 2 patients dying during hospitalization (both treated with high-dose propofol and midazolam). Of all surviving patients at discharge, 3 patients (60%) had an mRS score of 2, and 2 patients (40%) had an mRS score of 4. In the 3-month post-discharge follow-up data, all surviving patients had an mRS score of 2.

Conclusion

In a retrospective description of our cohort high-dose phenobarbital and a ketogenic diet were found to be probably safe and effective in the treatment of cryptogenic NORSE.

Introduction

New onset refractory status epilepticus (NORSE) is a rare and devastating disorder characterized by new onset refractory status epilepticus (RSE) in the absence of a clear acute or active structural, toxic, or metabolic cause. A diagnosis of Febrile infection-related epilepsy syndrome (FIRES), a subclass of NORSE, is made if febrile illness (with or without fever at the onset of persistent epilepsy) is present within 2 weeks to 24 hours before the onset of RSE. NORSE is a clinical presentation in which many NORSE is a clinical presentation in which many progress to super-refractory status epilepticus, called neo-onset super-refractory status epilepticus (new-onset super-refractory status epilepticus NO-SRSE), with a mortality rate of 61% and a poor prognosis[1]. Cryptogenic NORSE has a higher seizure burden, tends to have higher seizure frequency, longer duration, more difficult to control seizures, and is more likely to have severe and permanent cognitive impairment in the prognosis. This study summarizes and reports on seven patients with cryptogenic NORSE admitted to our hospital.

Materials and Methods

Patient selection We conducted a retrospective descriptive study of 7 adult patients with cryptogenic NO-SR admitted to the Department of Neurology at the Third Hospital of Shanxi Medical University from June 2016 to April 2022, and the inclusion criteria were adopted from the 2018 International NORSE and FIRES workshop: new-onset refractory persistent epilepsy in patients with no previous history of epilepsy or other related neurological disorders without a clear structural, toxic or metabolic etiology, but the etiology remains unknown after adequate examination[2].

Data collection Electronic medical record data were collected retrospectively, including demographics (age, gender, underlying disease), clinical presentation (aura symptoms, baseline modified Rankin score (mRS) score, history), laboratory tests, and imaging data (laboratory, EEG, imaging) and treatment (antiepileptic drugs, narcotics, immunomodulatory therapy, ketogenic diet, etc.). The primary outcome observed was the patient's mRS score at discharge: an mRS score of 0–3 was considered better; an mRS score of 4–6 was considered worse; the secondary outcomes observed were the mRS score at the most recent follow-up (3 months after discharge), the neurological intensive care unit (NICU) and total length of stay, and the long-term antiepileptic drugs used. Results are shown as medians (interquartile range [IQR]) or numbers (percentages). Statistical analysis was performed using SPSS version 25.

Results

Clinical features Single-center review of 7 adult patients with cryptogenic NORSE, median age 32 years (interquartile range 25.00–39.00), 4 (57.1%) males and 3 (42.9%) females, none of the 7 patients had a previous history of epilepsy, 6 patients (85.7%) had a history of prodromal fever before the seizure, all patients (100%) had an mRS score of 4 on admission (Table 1). 7 patients were admitted to the hospital and their laboratory tests and examinations such
as routine blood, biochemistry, rheumatic series, cerebrospinal fluid routine, biochemistry, pathogenesis, autoimmune encephalitis antibodies, and imaging were generally normal.

**Treatment data** All 7 patients received standard antiepileptic medication (Table 2), and all failed to terminate the seizures and subsequently developed super-refractory status epilepticus (super-RSE), with 2 (28.6%) patients receiving only high-dose propofol and midazolam for intravenous anesthetic medication to control the seizures. Two patients (28.6%) received only high-dose propofol and midazolam for seizure control, and both patients died in the hospital, with a mortality rate of 28.6% (2/7). The remaining 5 patients (71.4%) received intravenous propofol and midazolam in addition to a safe dose of intravenous phenobarbital for seizure control. The median dose of phenobarbital used was 46.68 mg/kg/d (interquartile range 46.61-50.00); four (57.1%) of these patients received a ketogenic diet in conjunction with high-dose phenobarbital antiepileptic therapy (Table 3). The median time to start the ketogenic diet was 41.5 days (interquartile range 15.75–62.75), the median time to reach ketosis was 2 days (interquartile range 1.25–2.75), the median time to onset of the ketogenic diet was 3 days (interquartile range 2.25–4.5), and the median total duration of ketogenic diet treatment was 76.5 days (interquartile range 30.00–129.75). The median duration of intravenous narcotics was 34 days (interquartile range 14–117). The median length of hospitalization was 86 days (interquartile range 14.00-135.00) and the median length of stay in the neurological care unit was 60 days (interquartile range 14.00–91.00). Patients 5 and 6 were discharged from our hospital and transferred to a rehabilitation hospital for further rehabilitation.

**Results Prognosis and follow-up** Patients were followed up on neurological deficits by mRS score at admission, at discharge, and 3 months after discharge; all 7 patients (100%) had an mRS score of 4 at admission; 2 (28.6%) patients eventually died, both from persistent seizures and respiratory and circulatory failure. All survivors were discharged with a better mRS score of 2 in 3 (60%) patients (numbers 3, 4, and 7) and a worse mRS score of 4 in 2 (40%) patients. All survivors received post-discharge follow-up, and all 5 (100%) survivors had a better mRS score of 2 at 3 months after discharge.

**Discussion**

In this study, seven adult patients with a diagnosis of cryptogenic NORSE were described retrospectively, six of whom (86%) had a history of prodromal fever, five of whom (71%) received high-dose phenobarbital to induce prolonged burst suppression coma to terminate persistent epilepsy, and four of whom (57%) were treated with a ketogenic diet in combination with rapid decompensation of anesthetic drugs. The mortality rate was 28.6% (2/7), all of whom received high doses of intravenous propofol and midazolam for seizure control, with propofol doses as high as 4–10 mg/kg/h. Both patients developed propofol infusion syndrome followed by respiratory and circulatory failure and died. Three patients had a good prognosis at discharge with an mRS score of 2. At long-term follow-up, all surviving patients had an mRS score of 0–3 and all had residual cognitive and memory impairment and required long-term oral antiepileptic medication. 2020 Elizabeth Matthews et al. reported a case series reviewing 26 cases of adult NOSRSE[1]. 73% were cryptogenic and 7 patients (27%) died; at discharge, 6 patients (23%) had a good prognosis (mRS score 0–3) and 12 patients (71%) had an mRS of 0–3 at long-term follow-up, suggesting that patients with cryptogenic NORSE may be more highly resistant to antiepileptic drugs. The majority of patients in the acute phase of NORSE progress to super-refractory status epilepticus (super-refractory status epilepticus,super-RSE), and the chronic phase mainly presents with drug-refractory epilepsy and varying degrees of neurological deficit symptoms[2]. According to the 2022 NORSE and FRIES international consensus for its acute treatment, the use of antiepileptic drugs should be similar to the acute treatment of seizures in other situations[3]. However, treatment options for terminating seizures in SRSE are still in an active phase of exploration and research. We found high-dose phenobarbital and the ketogenic diet to be safe and effective in the treatment of cryptogenic NORSE.

In 2015 Jung-Ick Byun et al. reported a study of 10 adults with high-dose phenobarbital applied to control SRSE with a median duration of 17.5 days (range 6–60) for persistent epilepsy and 14.0 days (range 2–54) for anesthesia. SRSE was successfully controlled in half of the patients. The median duration of high-dose phenobarbital was 45.5 days and the maximum serum phenobarbital level reached a median of 151.5 ug/ml (range 6–60) for persistent epilepsy and 14.0 days (range 2–54) for anesthesia. SRSE was successfully controlled in half of the patients. The median mRS score of 2 at 3 months after discharge. Both barbiturates and benzodiazepines bind to GABA receptors to induce inhibitory postsynaptic signaling and it exerts its neuroprotective effects by decreasing cerebral metabolism and oxygen consumption[4–6]. Classical benzodiazepines act by binding to benzodiazepine sites containing the α1, α2, α3 or α5 subunits of GABA receptors to induce inhibitory postsynaptic signaling[7]. An animal study showed that GABA receptors may change after short-term benzodiazepine treatment and that these changes affect the action of the drug at different regulatory sites[8]. So patients who are resistant to midazolam respond to high doses of phenobarbital[9].

There is increasing evidence that several adverse effects develop with the continued use of large amounts of intravenous anesthetic drugs; the most common side effect of intravenous anesthetic use is respiratory depression; all seven patients in this article received tracheal intubation ventilator-assisted respiratory therapy[10]. The majority of infections resulting from intravenous anesthetic use were respiratory infections and ventilator-associated pneumonia, with all 7 (100%) patients in this article developing pulmonary infections; there was also an increased incidence of bacteremia and urinary tract infections, leading to increased mortality[11]. Propofol infusion doses above 5 mg/kg/h for > 48 h are associated with the risk of propofol infusion syndrome[12], which is characterized by metabolic acidosis, hyperlipidemia, hepatic fatty infiltration, rhabdomyolysis, cardiac arrhythmias and refractory heart failure or even death. The two patients who died for this paper both received high doses of propofol intravenously at doses as high as 4–10
mg/kg/h and both developed propofol infusion syndrome followed by respiratory and circulatory failure and death. Phenobarbital can increase the risk of immunosuppression by inhibiting leukocyte phagocytosis and lymphocyte activation, leading to an increased risk of infection,[5] and patients with maximum serum levels of phenobarbital up to 353.7 μg/ml die of sepsis in the 2015 study by Jung-ilc Byun et al.[5] Due to redistribution of circulating blood volume and possible reduction in cardiac output due to myocardial dysfunction has also been considered as an adverse effect of barbiturates[13], two (40%) patients out of five patients on high dose phenobarbital in this study were on antihypertensive drugs. After EEG burst suppression coma induced by the use of high dose phenobarbital in this study, patients tend to experience focal seizures again when intravenous antiepileptic drugs are tapered, which inevitably leads to long-term high dose intravenous phenobarbital use, along with a progressively increasing risk of various complications, affecting patient prognosis and seriously leading to patient death. In this study, four patients were treated with high-dose phenobarbital in combination with a ketogenic diet for seizure control, and after induction of coma suppression, the use of phenobarbital was gradually discontinued to avoid prolonged intravenous use.

A ketogenic diet (KD) is a special medically formulated diet with a high ratio of fat, a low ratio of carbohydrates, and the right amount of protein and other nutrients. It usually consists of a fat/(protein + carbohydrate) ratio of 4:1. Since the early 1920s, it has become an effective non-pharmacological treatment for refractory epilepsy and severe childhood encephalopathy. It is also becoming widely used in the treatment of refractory persistent epilepsy in children but is relatively less used in the treatment of super-refractory persistent epilepsy in adults.

Four patients in this study were treated with a ketogenic diet and all achieved ketosis, with a median time to ketogenic diet initiation of 41.5 days (interquartile range 15.75–62.75), a median time to ketogenic diet onset of 3 days (interquartile range 2.25–4.5), and a median total duration of ketogenic diet treatment of 76.5 days (interquartile range 30.00–129.75). Two (40%) patients had a worse mRS score of 4 at discharge, but all had an mRS score of 2 at the 3-month post-discharge follow-up. 2014 Thakur KT et al. retrospectively studied a study of 10 adult SRSE patients treated with KD at 4 medical centers, 90% achieved ketosis, and all patients who achieved ketosis stopped within a mean of 3 days had SE (IQR 8).[15] A 2018 Meta-analysis of the ketogenic diet for refractory epilepsy in adults included 16 studies with 338 cases of refractory epilepsy (all > 16 years of age), 13% were seizure-free and 53% had more than 50% reduction in seizures. Of these, the most common adverse effects were weight loss, hyperlipidemia, and hypercholesterolemia.[16] A 2020 systematic review analyzed 30 (n = 157) prior clinical studies, primarily using a 3:1 to 5:1 ratio of KD (27/30), and overall, 80% (125/157) of patients were effective, and 47% (55/117) were observed with associated of adverse events, mainly including gastrointestinal reflux, acidosis or lipid/electrolyte imbalance.[17] KD ameliorates seizures with relatively mild adverse effects, high safety profile, and manageable risk.

Guidelines published by the 2022 Chinese Antiepileptic Association Ketogenic Diet Committee state that KD is indicated for patients of any age, or gender, with a diagnosis of SRSE and no contraindications to KD. KD may have anti-inflammatory properties for those with drug-resistant epilepsy, contraindications to surgery, and drug tolerance; it may be considered if epilepsy persists after 24 hours of continuous anesthesia or to reduce the recurrence of anesthetic seizures KD; KD has a positive impact on both seizure control and cognitive outcome and therefore should be considered early in the course of treatment, even as first-line treatment.[18] The 2022 international consensus of NORSE and FRIES also states that the ketogenic diet should be started in the first week and should be considered in prolonged and severe cases if not given as treatment. If effective in the acute phase, the ketogenic diet should be continued after the acute phase, and the follow-up of the ketogenic diet after the acute phase should be at least 3 months.[18] The 2022 guidelines for the ketogenic diet indicate that the most common adverse effects of the ketogenic diet are gastrointestinal discomfort, hyperlipidemia, acidosis, and hypoglycemia; in the four patients treated with the ketogenic diet in this study, all developed hypoprothrombinaemia, and three (42.9%) patients developed anemia (severe) and fecal occult blood (+), all of whom were given blood transfusions; one patient (14.3%) developed hyperlipidemia. The side effects of KD are less harmful to patients than the complications and poorer prognosis of patients due to long-term high doses of intravenous antiepileptic drugs, and KD has an important role in decommissioning continuous infusion of anesthetics and weaning from mechanical ventilation.[11] Seizure control by combined ketogenic diet can help patients to reduce the dose of intravenous antiepileptic drugs as early as possible, shorten the duration of mechanical ventilation, restore consciousness earlier, and improve patients’ cognition and quality of life.

The main limitations of this study were the single-center, retrospective design, and small sample size. There are currently no randomized controlled trials in relevant clinical studies, and the data are mostly from single case reports and small sample series, which are prone to bias. A prospective, multicenter NORSE study is needed to better understand its relevant properties.

**Declarations**

Ethics approval and consent to participate: This manuscript is a descriptive retrospective study. This method of the manuscript was carried out in accordance with relevant guidelines and regulations in the declaration - Ethics approval and consent to participate section. This manuscript has received ethical approval. The name of the ethics committee is Medical Ethics Committee of Shaxi Academy of Medical Sciences, Shaxi Bethune Hospital. The reference number is YKLL-2023-108. All subjects and their legal guardians have signed a written informed consent form. And the experimental protocol is approved by the institutional and licensing committee.

Consent for publication: Not applicable.

Availability of data and materials: Data sharing is not applicable to this article as no datasets were generated or analysed during the current study. The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.
Competing interests: The authors declare that they have no competing interests.

Funding: Not applicable.

Authors' contributions: Haiyan Diao and Yanhong Wang are responsible for the substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; Yanhong Wang is responsible for the drafting the article or revising it critically for important intellectual content and final approval of the version to be published;

Haixia Qu, Gang Ren, Zhijun Wang, Hailong Wang, Qian Pang, Naibing Xiang are responsible for the agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgements: Not applicable.

Statement

This manuscript is a descriptive retrospective study. This method of the manuscript was carried out in accordance with relevant guidelines and regulations in the declaration - Ethics approval and consent to participate section.

This manuscript has received ethical approval. The name of the ethics committee is Medical Ethics Committee of Shanxi Academy of Medical Sciences, Shanxi Bethune Hospital. The reference number is YXLL-2023-108. And the experimental protocol is approved by the institutional and licensing committee.

The study did not contain personal information about the study participants, but contains the disease-related information of the study participants.

All subjects and their legal guardians have signed a written informed consent form.

References


### Tables

#### Table 1
**General information**

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67</td>
<td>27</td>
<td>35</td>
<td>39</td>
<td>32</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Prodromal symptoms</td>
<td>None</td>
<td>Fever</td>
<td>Fever, impaired consciousness</td>
<td>Fever</td>
<td>Fever, headache, abnormal mental behavior</td>
<td>Fever, headache, nausea</td>
<td>Fever, nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Underlying Diseases</td>
<td>Hypertension, Hypothyroidism</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>mRS score at admission</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

#### Table 2
**Antiepileptic drug use**

<table>
<thead>
<tr>
<th>Data</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Types of seizures</td>
<td>Generalized tonic-clonic seizure</td>
<td>Generalized tonic-clonic seizure</td>
<td>Generalized tonic-clonic seizure</td>
<td>Generalized tonic-clonic seizure</td>
<td>Generalized tonic-clonic seizure</td>
<td>Generalized tonic-clonic seizure</td>
<td>Generalized tonic-clonic seizure</td>
</tr>
<tr>
<td>First-line treatment</td>
<td>Diazepam</td>
<td>Diazepam</td>
<td>Diazepam</td>
<td>Diazepam</td>
<td>Diazepam</td>
<td>Diazepam</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Second-line treatment</td>
<td>Sodium valproate 1–2mg/kg/h</td>
<td>Sodium valproate 1–2mg/kg/h</td>
<td>Sodium valproate 1–2mg/kg/h</td>
<td>Phenobarbital 20mg/kg</td>
<td>Sodium valproate 1–2mg/kg/h</td>
<td>Sodium valproate 1–2mg/kg/h</td>
<td>Phenobarbital 20mg/kg</td>
</tr>
<tr>
<td>Third-line treatment</td>
<td>Midazolam: 0.2mg/kg/h</td>
<td>Midazolam: 0.125mg/kg/h</td>
<td>Midazolam: 0.4mg/kg/h</td>
<td>Midazolam: 0.4mg/kg/h</td>
<td>Midazolam: 0.4mg/kg/h</td>
<td>Midazolam: 0.4mg/kg/h</td>
<td>Midazolam: 0.4mg/kg/h</td>
</tr>
<tr>
<td>Oral antiepileptic drugs</td>
<td>Levetiracetam; Sodium valproate; Carbamazepine</td>
<td>Sodium valproate; Levetiracetam; Lamotrigine; Carbamazepine</td>
<td>Levetiracetam; sodium valproate; clonazepam; oxcarbazepine</td>
<td>Levetiracetam; Sodium valproate; Oxcarbazepine</td>
<td>Levetiracetam; Sodium valproate; Carbamazepine</td>
<td>Levetiracetam; Topiramate tablets</td>
<td>Levetiracetam; Topiramate tablets</td>
</tr>
</tbody>
</table>

### References


Table 3  
Ketogenic diet treatment

<table>
<thead>
<tr>
<th>Data</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to initiate ketogenic diet (d)</td>
<td>Onset of disease 33d</td>
<td>Onset of disease 50d</td>
<td>Onset of disease 67d</td>
<td>Onset of disease 10d</td>
</tr>
<tr>
<td>Ketogenic diet ratio</td>
<td>4:1</td>
<td>4:1</td>
<td>4:1</td>
<td>4:1</td>
</tr>
<tr>
<td>Time to ketosis (d)</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Effective time (d)</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Total duration of ketogenic diet treatment (d)</td>
<td>30</td>
<td>123</td>
<td>132</td>
<td>30</td>
</tr>
<tr>
<td>Complications</td>
<td>Lung infection, hypoproteinemia, anemia (severe), fecal occult blood (+)</td>
<td>Lung infection, hypoproteinemia, anemia (severe), fecal occult blood (+)</td>
<td>Lung infection, hypoproteinemia, anemia (severe), fecal occult blood (+)</td>
<td>Lung infection, hyperlipidemia</td>
</tr>
</tbody>
</table>

Table 4  
Data related to patient prognosis and follow-up

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of narcotic drug use (d)</td>
<td>4</td>
<td>14</td>
<td>22</td>
<td>71</td>
<td>117</td>
<td>147</td>
</tr>
<tr>
<td>Number of oral antiepileptic drugs</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Phenobarbital maximum dose (mg/kg/d)</td>
<td>-</td>
<td>-</td>
<td>48mg/kg/d</td>
<td>46.56mg/kg/d</td>
<td>46.68mg/kg/d</td>
<td>46.66mg/kg/d</td>
</tr>
<tr>
<td>Use of blood pressure-raising drugs or not</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Whether ventilator-assisted breathing</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Use of antiviral therapy or not</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Use of immunosuppressants or not</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Complications</td>
<td>Lung infection</td>
<td>Pulmonary infection, hypoproteinemia, anemia</td>
<td>Lung infection</td>
<td>Lung infection, hypoproteinemia, anemia (severe), fecal occult blood (+)</td>
<td>Lung infection, hypoproteinemia, anemia (severe), fecal occult blood (+)</td>
<td>Lung infection, hypoproteinemia, anemia (severe), fecal occult blood (+)</td>
</tr>
<tr>
<td>Length of hospitalization (d)</td>
<td>4</td>
<td>14</td>
<td>43</td>
<td>98</td>
<td>135</td>
<td>158</td>
</tr>
<tr>
<td>Length of stay in NICU (d)</td>
<td>4</td>
<td>14</td>
<td>22</td>
<td>71</td>
<td>91</td>
<td>109</td>
</tr>
<tr>
<td>mRS score at discharge</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>mRS score at 3 months after discharge</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>