

World Journal of *Clinical Cases*

World J Clin Cases 2021 September 26; 9(27): 7963-8279



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The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for WJCC as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The WJCC's CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Ji-Hong Lin; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lai Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

September 26, 2021

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<https://www.wjgnet.com/bpg/gerinfo/204>

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<https://www.wjgnet.com/bpg/gerinfo/287>

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<https://www.wjgnet.com/bpg/gerinfo/240>

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<https://www.wjgnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Streptococcal pneumonia-associated hemolytic uremic syndrome treated by T-antibody-negative plasma exchange in children: Two case reports

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Author contributions: Du Y and Wang QS designed the new treatment; Wang XL and Zhao CG analyzed the data and co-wrote the manuscript; Wu YB, Yang N, Pei L and Wang LJ cared for the patient; All authors read and approved the final manuscript.

Informed consent statement:

Written consents were obtained from the parents of the patients for publication.

Conflict-of-interest statement: No financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

CARE Checklist (2016) statement:

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Abstract

BACKGROUND

The occurrence of *Streptococcus pneumoniae*-associated hemolytic uremic syndrome (SP-HUS) is increasing. Thomsen-Friedenreich antigen activation is highly involved in the pathogenesis of SP-HUS, and T-antibody-negative plasma exchange (PE) may be effective in the treatment of severe cases of SP-HUS.

CASE SUMMARY

We retrospectively reviewed two pediatric patients with SP-HUS. Both clinical features and laboratory examination results of the children were described. T-antibody-negative PE was performed in both cases. Both children made a full recovery after repeated PE and remained well at a 2 year follow-up.

CONCLUSION

Streptococcal pneumonia continues to be an uncommon but important cause of HUS. The successful treatment of the presented cases suggests that T-antibody-negative PE may benefit patients with SP-HUS.

Key Words: *Streptococcus pneumoniae*; Hemolytic uremic syndrome; Children; Plasma exchange; Thomsen-Friedenreich antigen exposure; Case report

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Manuscript source: Unsolicited manuscript

Specialty type: Medicine, research and experimental

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: April 26, 2021

Peer-review started: April 26, 2021

First decision: May 24, 2021

Revised: May 29, 2021

Accepted: July 28, 2021

Article in press: July 28, 2021

Published online: September 26, 2021

P-Reviewer: El Chazli Y

S-Editor: Fan JR

L-Editor: Filipodia

P-Editor: Li JH



Core Tip: We present the cases of two pediatric patients with atypical hemolytic uremic syndrome associated with *Streptococcus pneumoniae*-hemolytic uremic syndrome that was successfully treated by T-antibody-negative plasma exchange. The patients were followed up for 2 years with normalization of all laboratory parameters, normal blood pressure and normal renal function.

Citation: Wang XL, Du Y, Zhao CG, Wu YB, Yang N, Pei L, Wang LJ, Wang QS. Streptococcal pneumonia-associated hemolytic uremic syndrome treated by T-antibody-negative plasma exchange in children: Two case reports. *World J Clin Cases* 2021; 9(27): 8164-8170

URL: <https://www.wjgnet.com/2307-8960/full/v9/i27/8164.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v9.i27.8164>

INTRODUCTION

Atypical hemolytic uremic syndrome (HUS) associated with *Streptococcus pneumoniae* (SP-HUS) was first reported by Klein *et al*[1] in 1977 and Novak *et al*[2] in 1983. SP-HUS is one of the most commonly seen types of atypical HUS[3-6]. In recent years, an increase in the incidence of reported SP-HUS cases has been noted, which may be due to increased awareness of the syndrome[7].

Thomsen-Friedenreich antigens (T-antigens) of red blood cells (RBCs), platelets and glomerular endothelial cells are exposed through the action of *Streptococcus pneumoniae* neuraminidase, which triggers an antigen-antibody reaction in the plasma, leading to a cascade of thrombotic microangiopathy[7]. T-antibody is commonly seen in the plasma of blood donors. As such, the condition of patients with SP-HUS will be aggravated when treated with plasma exchange (PE) using plasma that contains T-antibody. This and other difficulties make treatment of SP-HUS challenging and contribute to the poor prognosis of SP-HUS patients. T-antibody-negative PE may be valuable for the treatment of SP-HUS based on the removal of naturally occurring antibodies, which reduces activation of T-antigen and the level of neuraminidase[8]. Herein, we present the cases of two pediatric patients with SP-HUS who were successfully treated by T-antibody-negative PE. Notably, the two cases were not linked epidemiologically.

CASE PRESENTATION

Chief complaints

Case 1 presented with fever and cough persisting for 4 d and was admitted to our hospital in April 2019. Case 2 was admitted to our hospital due to fever and cough for 7 d and anuria and feet edema for 2 d in May 2019. They were both 3-year-old boys from Shenyang and had no contact history.

History of present illness

Case 1: A 3-year-old boy presented with fever and cough persisting for 4 d and was admitted to the hospital. His peak temperature before hospitalization was 40.4 °C. He showed no response to oral azithromycin therapy, and chest X-ray showed large dense shadows in the lower lobe of the right lung, an unclear right diaphragm and costal diaphragm angle.

Case 2: A 3-year-old boy was admitted to our hospital due to fever, cough, anuria and feet edema. The fever lasted for 7 d, and the peak temperature was 39 °C with no chills or convulsions. He became anuric for 2 d. Chest X-ray indicated that the patient had bilateral pneumonia and left inferior lobe consolidation. Despite treatment with ceftriaxone, tazobartan sodium, azithromycin and intravenous liquids, symptoms persisted.

History of past illness

The two cases were both healthy in the past.

Personal and family history

Neither of the two cases were vaccinated against pneumococcal. The two cases' parents were in good health and had no family history of similar diseases.

Physical examination

Case 1: Physical examination at admission revealed a pulse rate of 120/min, a respiratory rate of 40/min, a blood pressure of 102/58 mmHg and a temperature of 38.5 °C. The liver and spleen were not palpable. The skin showed no jaundice or purpura.

Case 2: Physical examination at admission revealed a pulse rate of 96/min, a respiratory rate of 35/min, a blood pressure of 96/50 mmHg and a temperature of 36.7 °C. The liver and spleen were not palpable. The skin appeared pale but showed no purpura or jaundice.

Laboratory examinations

Case 1: Laboratory examinations revealed a hemoglobin value of 138 g/L, a white blood cell count of $2.65 \times 10^9/L$, a platelet count of $349 \times 10^9/L$, a procalcitonin level of 74 ng/mL (< 0.05 ng/mL) and a C-reactive protein concentration of 123 mg/L (0-8 mg/L). Arterial blood gas analysis showed hypoxemia (partial pressure of oxygen 36 mmHg). Two days after admission, the patient developed thrombocytopenia as well as liver and renal dysfunction. His serum creatinine value was 98 $\mu\text{mol/L}$ (22-44 $\mu\text{mol/L}$), and urea nitrogen concentration was 12.2 mmol/L. Microangiopathic hemolytic anemia and thrombocytopenia were suspected based on a platelet count of $14 \times 10^9/L$, unconjugated bilirubin level of 28 $\mu\text{mol/L}$ (3.4-11.9 $\mu\text{mol/L}$) and lactic dehydrogenase level of 1021 U/L (80-285 U/L). The direct antiglobulin test demonstrated that the patient was weakly positive for anti-C3d and anti-immunoglobulin G. Other blood chemistry results included a serum C3 concentration of 0.388 g/L (0.74-1.4 g/L) and a serum ferritin concentration of 1532 ng/mL (11-336.2 ng/mL). Urinalysis showed albuminuria and hematuria. Tests for polyagglutinability were performed by mixing the patient's RBCs with serum from an AB type adult blood donor (Table 1). Fragmented erythrocytes were found in a peripheral blood smear. The pleural fluid analysis revealed a white blood cell of $7500 \times 10^6/L$, RBC of $6000 \times 10^6/L$, neutrophil percentage of 75%, monocyte percentage of 40% and Rivalta test positive findings. Culture of the pleural effusion revealed the presence of *Streptococcus pneumoniae*.

Case 2: Initial laboratory examinations revealed a hemoglobin value of 56 g/L, a white blood cell count of $13.27 \times 10^9/L$, a platelet count of $42 \times 10^9/L$, a serum creatinine concentration of 403 $\mu\text{mol/L}$ and a C-reactive protein level of 150 mg/L. After antibiotic treatment, the C-reactive protein level dropped to 34.9 mg/L. Blood chemistry values included a serum C3 level of 0.492 g/L, alanine aminotransferase concentration of 126 U/L and aspartate aminotransferase concentration of 258 U/L. The direct antiglobulin test revealed weak positive findings for anti-C3d and anti-immunoglobulin G. Arterial blood gas analysis showed hypoxemia (partial pressure of oxygen 39 mmHg). Sputum culture showed *Streptococcus pneumoniae*. T-antigen exposure was confirmed by a polyagglutinability test. Fragmented erythrocytes were found in a peripheral blood smear.

Imaging examinations

Case 1: Chest computed tomography scanning revealed lung inflammation and pleural effusion.

Case 2: Chest computed tomography scanning showed the presence of bilateral pneumonia with pleural effusion and multiple air sacs in the left lung.

FINAL DIAGNOSIS

The two cases were diagnosed with SP-HUS.

Table 1 Assessment of erythrocyte T-antigen exposure in case 1

Day of hospitalization	Adult AB type plasma	Umbilical cord AB type plasma	Plasma polycoagulant reaction	T-antigen exposure
3	4+	Negative	Negative	Yes
4	4+	Negative	Negative	Yes
5	4+	Negative	Negative	Yes
6	4+	Negative	Negative	Yes
10	4+	Negative	Negative	Yes
15	3+	Negative	Weak positive	Suspicious
18	±	Negative	Positive	Suspicious
19	Negative	Negative	Positive	No

TREATMENT

Case 1: The patient was treated with T-antibody-negative PE (COBE Spectra, Gambro BCT, Lakewood, CO, United States) four times on days 3, 4, 5 and 6 after admission. On day 6, the patient received a transfusion of a washed erythrocyte unit (100 mL). No adverse effect was observed during PE. The patient's renal function recovered slowly after the treatment. On day 9, the platelet count had increased from the lowest value of $14 \times 10^9/L$ to $254 \times 10^9/L$, while the serum creatinine concentration decreased from the highest values of $143 \mu\text{mol/L}$ to $28 \mu\text{mol/L}$ (Table 2).

Case 2: The patient was then treated with T-antibody-negative PE (COBE Spectra, Gambro BCT, Lakewood, CO, United States) two times. The patient also received washed erythrocyte transfusion and albumin infusion therapy. Continuous renal replacement therapy was also performed for 7 d. After the treatment, the platelet count increased from the lowest value of $42 \times 10^9/L$ to $194 \times 10^9/L$ within 4 d, while his serum creatinine level decreased from the highest concentration of $403 \mu\text{mol/L}$ to only $29 \mu\text{mol/L}$ (Table 3).

The method for obtaining T-antibody-negative plasma was as follows: The Brine medium micro column method was used. The erythrocyte brine medium of patients was washed three times and diluted in 1% enchylema. Then 50 μL of donor plasma and 25 μL of 1% enchylema was added to the neutral micro column for incubation for 10 min at room temperature. After that, the sample was centrifuged for 15 min at $1000 \times g$. The patient's own RBCs were prepared as a negative control. The reaction was considered positive if the cells gathered above the micro column or negative if in the bottom. Plasma with a negative reaction was suitable for use in T-antibody-negative PE.

OUTCOME AND FOLLOW-UP

The two cases were both followed up for 2 years with normalization of all laboratory parameters, normal blood pressure and normal renal function.

DISCUSSION

Among children with HUS, approximately 5% have SP-HUS, with 38%-43% of atypical HUS cases being SP-HUS[3,9]. Notably, the occurrence of SP-HUS was reported to be higher than that of typical HUS in Taiwan[10]. Early reports from the late 1980s demonstrated a mortality rate of approximately 50%[11]. An estimated 10% of patients diagnosed with SP-HUS are likely to develop end-stage renal disease, whereas 16% will experience chronic renal disease[12].

Pneumonia with empyema is seen in approximately 67% of SP-HUS patients[13]. According to a PCR analysis, Blaschke *et al*[14] demonstrated that about 71% of germiculture negative empyema cases were proven to be caused by *Streptococcus pneumoniae*. The two cases reported here were diagnosed with lobar pneumonia with pleural effusion, which is consistent with previous reports in China[15]. The possibility of SP-HUS should be considered if a patient diagnosed with lobar pneumonia with

Table 2 Primary laboratory test results during hospitalization and treatment of case 1

Day of hospitalization	Platelet count, 10 ⁹ /L	Hemoglobin, g/L	Serum creatinine, μmol/L	24-h urine output, mL	24-h urine protein, g/L	T-antigen negative plasma exchange, mL	Methyl-prednisolone dosage, mg/d
3	14	114	143	340	0.05	2000	60
4	23	91	98	890	-	2000	60
5	14	75	58	730	0.12	2000	60
6	29	63	42	680	-	1000	60
7	52	83	28	760	0.15	-	60
8	92	80	-	860	-	-	60
9	254	67	28	1100	-	-	40
12	259	77	30	1200	0.07	-	20
16	248	80	25	1020	-	-	10

Table 3 Primary laboratory test results during hospitalization and treatment of case 2

Day of hospitalization	Platelet count, 10 ⁹ /L	Hemoglobin, g/L	Serum creatinine, μmol/L	24-h urine output, mL	24-h urine protein, g/L	T-antigen negative plasma exchange, mL	Methyl-prednisolone dosage, mg/d
1	42	56	403	0	-	-	60
2	82	55	374	0	-	1000	60
3	159	56	266	1020	-	800	60
4	194	58	294	900	0.22	-	60
5	201	60	209	670	-	-	40
7	230	63	109	880	0.33	-	40
9	242	60	85	400	0.44	-	40
11	274	62	74	850	-	-	20
13	354	64	54	760	-	-	10
21	586	90	29	920	0.34	-	5

pleural effusion develops signs of HUS, even without identified evidence of bacterial infection.

All types of *Streptococcus pneumoniae* can express neuraminidase, but only a small percentage of infected cases will develop HUS. Several hypotheses have attempted to explain this observation. Animal experiments confirmed that *Streptococcus pneumoniae* from biofilm formation is more likely to release neuraminidase than free floating bacteria[16], which may explain why SP-HUS is more often caused by pneumonia with empyema other than bacteremia[13]. Additionally, different serotypes of *Streptococcus pneumoniae* may have different effects on the amount of neuraminidase production. Notably, 19A was reported to be the most common serotype associated with SP-HUS [6]. Neuraminidase can destroy the binding site of factor H, and *Streptococcus pneumoniae* surface protein C may have a direct role in inhibiting the activity of factor H[17].

The RBCs of our two cases showed strong positive reactions with adult AB type plasma but no reactions with umbilical AB type plasma. Thus, T-antigen exposure was identified in both cases. Once the patients had recovered from SP-HUS, no reactions occurred with either adult or umbilical AB type plasma, and the polycoagulant reaction returned a positive result with the same type of adult plasma (Table 1).

The plasma used in the cases was confirmed to have no reactions with T-antigen-exposed RBCs. In addition to T-antibody, other possible pathogenic factors like neuraminidase, galectin-3[18], that might damage the RBCs, platelets and glomerular endothelial cells were all removed by T-antibody negative PE. The presence of

complement factor H in the donor's plasma may be beneficial too.

Anti-infection and supportive treatments are the cornerstones of SP-HUS treatment. Vancomycin with the broad-spectrum cephalosporin is the suggested strategy[19]. It is generally believed that plasma transfusion should be avoided to prevent the possibility of T-antigen exposure to T-antibody in the plasma of normal blood donors. Washed RBCs are recommended for clearing any remaining T-antibody in the plasma. However, such therapy has not been able to stop the deterioration of disease in some critical cases. Petras *et al*[20] treated one SP-HUS patient by PE with 5% albumin replacement with a good outcome. T-antibody, neuraminidase and other possible pathogenic factors were removed by T-antibody-negative PE in the present cases, which was theoretically for etiological treatment. The two cases in our report had a favorable prognosis compared with those in the previous studies[12].

CONCLUSION

T-antibody-negative PE was used to treat the two patients in our report. The platelet counts and serum creatinine levels of the two patients returned to normal in a short time, and their condition remained stable during the follow-up. Thus, T-antibody-negative PE may be an effective method for treating SP-HUS.

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