6. Wong CS, *et al.* Risk factors for the hemolytic uremic syndrome in children infected with *Escherichia coli* O157:H7: a multivariable analysis. Clin Infect Dis 2012; 55: 33-41. (level 4)
7. Dundas S, *et al.* The central Scotland *Escherichia coli* O157:H7 outbreak: risk factors for the hemolytic uremic syndrome and death among hospitalized patients. Clin Infect Dis 2001; 33: 923-931. (level 4)
8. Shiomi M, *et al.* Effect of early oral fluoroquinolones in hemorrhagic colitis due to *Escherichia coli* O157:H7. Pediatr Int 1999; 41: 228-232. (level 4)
9. Ikeda K, *et al.* Effect of early fosfomycin treatment on prevention of hemolytic uremic syndrome accompanying *Escherichia coli* O157:H7 infection. Clin Nephrol 1999; 52: 357-362. (level 4)
10. Bell BP, *et al.* Predictors of hemolytic uremic syndrome in children during a large outbreak of *Escherichia coli* O157:H7 infections. Pediatrics 1997; 100:E12. (level 4)
11. Cimolai N, *et al.* A continuing assessment of risk factors for the development of *Escherichia coli* O157:H7-associated hemolytic uremic syndrome. Clin Nephrol 1994; 42: 85-89. (level 4)
12. Cimolai N, *et al.* Risk factors for the central nervous system manifestations of gastroenteritis-associated hemolytic-uremic syndrome. Pediatrics 1992; 90: 616-621. (level 4)

II. Diagnosis of HUS

II.1 Diagnosis procedure

STEC causes HUS characterized by thrombotic microangiopathy. Definitive diagnosis of STEC-HUS should be based on the following tests. **[Grade of Recommendation: Not Graded]**

A. Diagnostic tests

1. Hemolytic anemia (Hb <10 g/dL, positive for schistocytes, Figure 1)
2. Thrombocytopenia (platelet count $<15\times10^4/\mu L$)
3. Acute kidney injury (AKI; serum creatinine ≥1.5 times that of age- and gender-matched standard values, according to the Japanese Pediatric Nephrology Society; Table 1)

B. Concomitant symptoms

1. Central nervous system (CNS) involvement: conscious disturbance, seizure, headache, and hemorrhagic infarction
2. Gastrointestinal involvement: diarrhea, bloody stool, abdominal pain, intestinal perforation, intestinal stenosis, rectal prolapse and intussusceptions
3. Cardiac involvement: cardiac infarction and cardiac failure due to myocardial injury
4. Pancreatic involvement: pancreatitis
5. Disseminated intravascular coagulation (DIC)

Notes

1: The following markers in serum may support diagnosis: marked elevation of lactate dehydrogenase (LDH), decreased haptoglobin and negative Coombs test despite hyperbilirubinemia

2: Serum O157 lipopolysaccharide (LPS) antibody, rapid diagnostic test for stool O157 antigen or Shiga toxin, and isolation of STEC by stool culture help definitive diagnosis.

[Comments]

1. Clinical manifestations and diagnosis of HUS

Up to 10% of patients infected with STEC developed HUS 4-10 days after the onset of diarrhea. Patients who developed HUS within three days after the onset of diarrhea may take a rapid and severe clinical course. 20-60% of patients with HUS need dialysis due to AKI, and between 25-33% of patients have CNS involvement. Mortality in the acute phase may reach to 2-5%, mainly caused by CNS involvement or intestinal perforation.

Diagnosis of HUS should be based on the summary described above. Age- and gender-matched standard values should be referred to in order to monitor the increase of serum creatinine in children (Table 1).

Isolation of STEC from stool culture, positivity of stool O157 antigen or STX test, and positivity of serum anti O157 LPS antibody, can help definitive diagnosis. However, some patients do not show gastrointestinal involvement, together with negative STEC results.

Decreased level of platelets in the blood and elevated serum LDH are initial abnormal findings observed in patients with HUS. In particular, a marked increase in LDH of more than 1000 IU/mL is characteristic of HUS, and is helpful for diagnosis. Subsequently, hemolytic anemia and elevated serum creatinine (leading to AKI) occurs. Additionally, marked thickening of the large intestinal wall on abdominal CT and increased echogenicity of the kidney on abdominal ultrasound are characteristic findings that are detectable even in the early phase of HUS (Fig 2. See also Chapter II.4, Concomitant Symptoms: Gastrointestinal involvement).

STEC-HUS accounts for 90% of HUS. Non-STEC HUS is defined as atypical HUS (aHUS). To confirm STEC-HUS, both aHUS and von Willebrand factor–cleaving protease (ADAMTS13)–related thrombotic thrombocytopenic purpura (TTP) should be excluded. Plasma therapy or plasma exchange is the first line treatment against aHUS and TTP, and differs from the treatment for STEC-HUS. It is noteworthy that patients with aHUS are also frequently complicated by gastrointestinal manifestations.

(1) Risk factors for developing HUS from STEC infection

According to the survey of the largest outbreak of STEC in 1996 in Sakai city, Japan, risk factors for developing HUS are increased white blood cell (WBC) count in blood (HUS group vs non HUS group: WBC 13,900 vs 8300 /μL, $p< 0.001$) and increased serum C-reactive protein (CRP; HUS group vs non HUS group: CRP 1.3 vs 0.5 mg/dL, $p< 0.001$) [1].

(2) Risk factors for progression to severe HUS

According to a Japanese nationwide survey of childhood STEC-HUS conducted between January 2001 and December 2002, the risk factors for AKI requiring dialysis are low serum sodium (≤130 mEq/L, odds ratio 8.1) and increased serum aspartate transaminase (AST; ≥80 mg/dL, odds ratio 8.9) at the onset of HUS. In total, 64% of patients with serum sodium ≤130 mEq/L and 73% of those with AST ≥70 IU/dL received dialysis [2]. The risk factors for CNS involvement are the need for dialysis (odds ratio 6.6) or CRP ≥5.0 mg/dL (odds ratio 6.3). In total, 75% of patients with CRP ≥5.0 mg/dL and 51% of patients requiring dialysis have CNS involvement [2].

A registry of 352 children with post-diarrheal HUS in the USA showed that risk factors for

death are increased blood WBC count (>20,000 /μL, P=0.025) and hematocrit >23% (P=0.00045). A hematocrit of >23% seems paradoxical, but the authors provided an argument that the patients took a very rapid and progressive course, and expired before the emergence of decreased hematocrit [3]. CNS involvement was the highest cause of death (n=8).

HUS patients with a serum creatinine level double that of the age- and gender-matched standard value have a higher chance of requiring dialysis. Such patients should be promptly transferred to a hospital for renal replacement therapy.

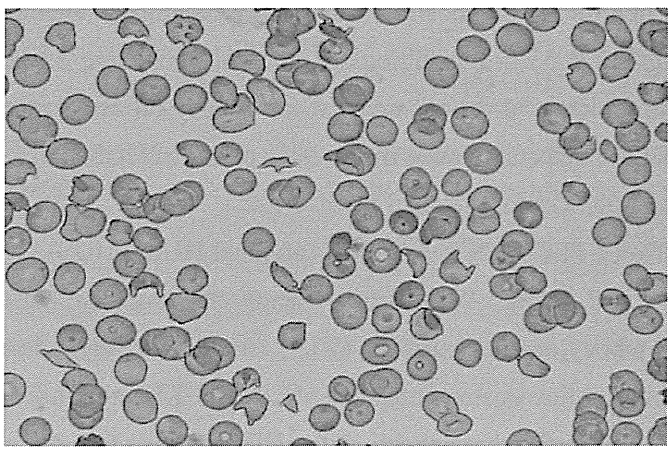

Fig. 1. Poikilocytes in a patient with HUS (x 400).

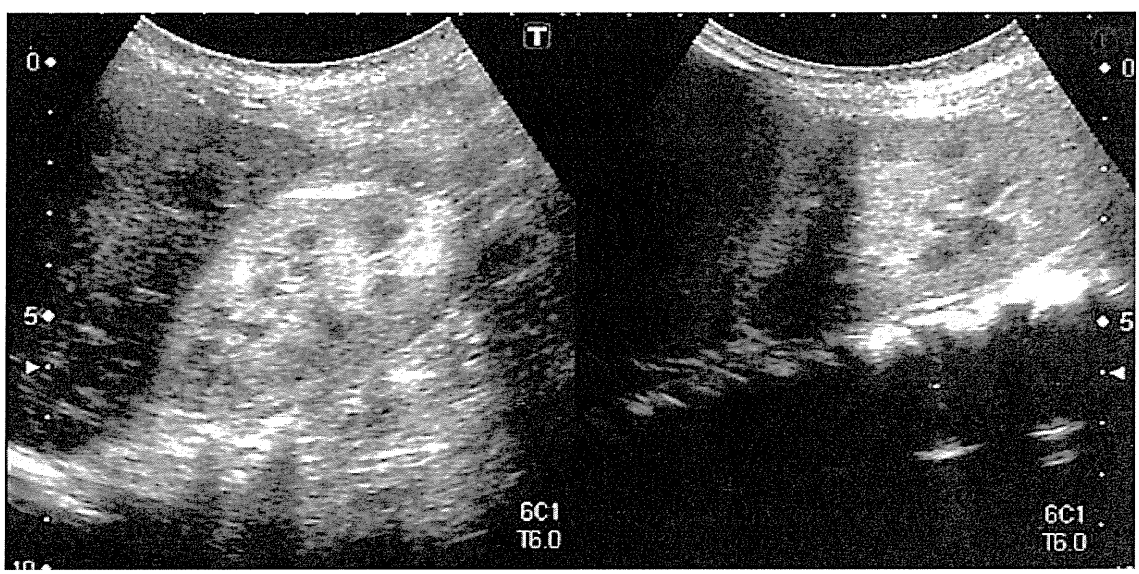

Fig. 2. Increased echogenicity of renal ultrasound in a patient with HUS.

Table 1. Standard serum creatinine values by age and gender in Japanese children (f)

age	2.50%	50%	97.5%
3-5m	0.14	0.2	0.26
6-8m	0.14	0.22	0.31
9-11m	0.14	0.22	0.34
1y	0.16	0.23	0.32
2 y	0.21	0.24	0.37
3 y	0.21	0.27	0.37
4 y	0.2	0.3	0.4
5 y	0.25	0.34	0.45
6 y	0.25	0.34	0.48
7 y	0.28	0.37	0.49
8 y	0.29	0.4	0.53
9 y	0.34	0.41	0.51
10 y	0.3	0.41	0.57
11 y	0.35	0.45	0.58
12 y boy	0.4	0.53	0.61
13 y boy	0.42	0.59	0.8
14 y boy	0.54	0.65	0.96
15 y boy	0.48	0.68	0.93
16 y boy	0.62	0.73	0.96
12 y girl	0.4	0.52	0.66
13 y girl	0.41	0.53	0.69
14 y girl	0.46	0.58	0.71
15 y girl	0.47	0.59	0.72
16 y girl	0.51	0.59	0.74

[Supplementary articles]

a. UpToDate: Clinical manifestations and diagnosis of Shiga toxin associated (typical) hemolytic uremic syndrome in children. http://www.uptodate.com/contents/search

b. Frank C, *et al.* Epidemic profile of Shiga-Toxin-Producing Escherichia coli O104:H4 outbreak in Germany. N Engl J Med 2011; 365: 1771-1780.

c. Loos S, *et al.* An outbreak of Shiga toxin-producing Escherichia coli O104:H4 hemolytic uremic syndrome in Germany: Presentation and short-term outcome in children. Clin Infect

Dis 2012; 55: 753-759.

d. Trachtman H, *et al.* Renal and neurological involvement in typical Shiga toxin-associated HUS. Nat Rev. Nephrol; 8: 658-669.

e. Kagami S, *et al.* Diagnostic criteria of atypical hemolytic uremic syndrome. Nihon Jinzo Gakkai Shi 2013; 55:91-93.

f. Uemura O, *et al.* Age, gender, and body length effects on reference serum creatinine levels determined by an enzymatic method in Japanese children: a multicenter study. Clin Exp Nephrol 2011; 15: 694-699.

g. Kidney Disease| Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int. Suppl. 2012; 2: 1–138.

[References]

1. Kawamura N, *et al.* Risk factors for the development of *Escherichia coli* O157: H7 associated with hemolytic uremic syndrome. Pediatr Int 1999; 41: 218-222. (level 4)

2. Kamioka I, *et al.* Japanese Society for Pediatric Nephrology: Risk factors for developing severe clinical course in HUS patients: a national survey in Japan. Pediatr Int 2008; 50: 441-446. (level 4)

3. Oakes RS, *et al.* Predictors of fatality in postdiarrheal hemolytic uremic syndrome. Pediatrics 2006; 117: 1656-1662. (level 4)

II.2 Assessment of acute kidney injury (AKI)

AKI is a severe complication in HUS patients. 50% of HUS patients manifest oliguria or anuria. Patients with oliguria or anuria require renal replacement therapy (acute blood purification). **[Grade of Recommendation: Not Graded]**

Risk factors of oliguria, anuria or hemodialysis are: dehydration, lack of isotonic fluid administration before development of HUS, hyponatremia (≦ 130 mEq/L), increase of serum ALT (≧ 70 IU/L) and infection by STEC O157:H7. **[Grade of Recommendation: Not Graded]**

When serum creatinine level is two times higher than age-sex standard, we suggest transferring the patient to a hospital where renal replacement therapy (acute blood purification) can be performed. **[Grade of Recommendation: B]**

[Comments]

1. AKI in HUS - epidemiology and pathophysiology

Over half of the patients with HUS manifested AKI. A Japanese survey reported that 47% of the 132 patients with HUS manifested oliguria or anuria, and 27% of the 132 patients had received renal replacement therapy [1]. In a European survey, 60% of 394 patients with HUS received renal replacement therapy. Renal replacement therapy started usually on the 10th day in the USA [2] and on the 12th day in Japan [1] in average after STEC gastrointestinal infection manifested. HUS patients develop oliguria, anuria, edema, proteinuria, hematuria (including macrohematuria) and urinary casts. They also manifest an increase of serum creatinine, hyperkalemia, and hyponatremia. There are two main pathophysiology of AKI due to HUS, prerenal failure and intrinsic renal failure. The cause of intrinsic renal failure is STX which mainly affects the endotherial cells. STX is composed of an A subunit with toxic activity, and five B subunits with cell binding activity. The B subunits bind to Gb3 receptor (globotriosylceramide 3 receptor) of target cells. Upon binding, only A subunit is transported to cytoplasm. RNA N-glycosidase activity of A subunit inhibits 60S ribosome. Finally, the A subunit irreversibly inhibits protein production, leading to cell death. Gb3 receptors are expressed on red blood cells, white blood cells and endotherial cells. Renal interstitium is also a frequent target, as renal tubules also express Gb3 receptors.

Ultrasound findings of kidneys in HUS patients (in oliguric or anuric period disclose) include normal or enlarged kidney, hyperechoic renal cortex (higher than liver) and hypoechoic medulla (pyramides renales) [b]. Ultrasonography also revealed the absence of peripheral arterial diastolic blood flow or significant decrease of peripheral arterial diastolic blood flow in the kidneys. In the recovery period, peripheral arterial diastolic blood flow gradually increased.

Pathologic findings revealed narrowed lumen of glomerular capillary due to the endothelial edema and thrombus formation in the glomerular capillaries. Swollen and degenerated mesangial cells leadin to mesangiolysis were also observed. Glomerulus was collapsed by thrombus of interlobular artery and arteriole, leading to fibrinoid necrosis. When thrombus formation in the interlobular artery woul be widespread, cortical necrosis could ensue [c]. Inflammatory cytokines and chemokines such as TNF-α, IL-1β, IL-6 and IL-8, complement system and coagulation system including Von Wilbrand factor are involved in endotherial cell injury. Hypovolemia is an exacerbating factor of AKI in HUS.

2. Risk factors of AKI

Prerenal failure can contribute to cause AKI in patients with HUS. Renal replacement therapy was frequently needed in patients with HUS who manifested hypovolemia on admission [3, 4]. HUS patients who received insufficient fluid (water and sodium) therapy often manifest oliguria

or anuria. Such patients frequently receive renal replacement therapy (refer to Chapter III.1) [3, 4]. When patients with STEC infection or potential HUS patients first present themselves to the doctor, it is important to assess the dehydration level and to confirm how much of which kind of fluid is to be administrated in anticipation of AKI. In a nationwide survey conducted in Japan, indication of renal replacement therapy is 64% (odds ratio 8:1) for patients who manifest hyponatremia (under 130 mEq/L) at onset of HUS, and 73% (odds ratio 8:1) for patients who manifest elevated serum ALT over 70 IU/L [1]. Hospital induced hyponatremia is often introduced when hypotonic fluid was administered to STEC patients. Iatrogenic hyponatremia can cause brain edema leading to acute encephalopathy. Therefore, it is mandatory to evaluate serum electrolytes and water balance in patients with possible STEC infection. Specific serotype in STEC can cause severe form of HUS. Patients with O157:H7 infection are more likely to receive renal replacement therapy and manifest bloody stool (with elevated serum LDH) than patients with O157:non-H7 infection.

3. Staging and timing of renal replacement therapy in AKI

It is necessary to access serum creatinine and urine volume in patients with HUS who manifest AKI in order to determine the necessity of renal replacement therapy. Kidney Disease Improving Global Outcomes (KDIGO) disclosed clinical diagnostic criteria for AKI (Table 1) [d]. AKI stage is categorized by elevated value of serum creatinine and urine volume. Standard serum creatinine values for age and gender may vary as these values depend on the quantity of muscle (See Chapter II. 1).

Renal replacement therapy is indicated when signs of fluid overload (including pulmonary edema, cardiac failure, hypertension, electrolyte abnormality, hyperkalemia, hyponatremia and acidemia, nausea, vomiting, consciousness disorder and convulsion) are seen. The list of signs, however, is by no means exhaustive. Renal replacement therapy should be prepared before patients progress to AKI, which is potentially life-threatening. The KDIGO guidelines for AKI recommend that patients with Stage 2 AKI (and over two times of normal serum creatinine level, or urine volume less than 0.5 mL/kg/hr for 12 hours) should be transferred to medical institutions where renal replacement therapy and critical care medicine are available.

Table 1. Staging of AKI [d]

stage	Serum Creatinine	Urine output
Stage 1	1.5-1.9 times baseline* or ≧0.3 mg/dL (≧26.5 μmol/L) increase	< 0.5 mL/kg/hr for 6-12hours
Stage 2	2-2.9 times baseline*	< 0.5 mL/kg/hr for 12 hours
Stage 3	3 times baseline* or increase in serum creatinine to ≧4.0 mg/dL (≧ 353.6 μmol/L) or inhibition of renal replacement therapy or <18years, decrease in eGFR to <35 mL/1.73m^2	< 0.3 mL/kg/hr for ≧24hours or Anuria for ≧12hours

* : Assess within 7 days

[Supplementary articles]

a. UpToDate: Clinical manifestations and diagnosis of Shiga toxin associated (typical) hemolytic uremic syndrome in children. http://www.uptodate.com/contents/search
b. Siegel MJ: Urinary tract. In: Siegel MJ. (ed), Pediatric Sonography. Lippincott Williams & Wilkins, Philadelphia, pp.385-473, 2002.
c. Johnson S, *et al.* Hemolytic uremic syndrome. In: Avner E, Harmon WE, Niaudet P, Yoshikawa N. (eds), Pediatric Nephrology 6th ed. Springer-Verlag, Berlin Heidelberg, pp.1155-1181, 2009.
d. Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int. Suppl 2012; 2: 1–138.
e. Laszik ZG, *et al.* Hemolytic uremic syndrome, Thrombotic thrombocytopenic purpura and other Thrombotic microangiopathies. In: Jennette JC, Olson JL, Schwartz MM, Silva FG. (eds), Heptinstall's Pathology of the Kidney 6th ed, Wolters Kluwer, Lippincott Williams and Wilkins, Philadelphia, pp.701-764, 2007.

[References]

1. Kamioka I, *et al.* Japanese Society for Pediatric Nephrology. Risk factors for developing severe clinical course in HUS patients: a national survey in Japan. Pediatr Int 2008; 50: 441-446. (level 4)
2. Gerber A, *et al.* Clinical course and the role of shiga toxin-producing *Escherichia coli* infection in the hemolytic-uremic syndrome in pediatric patients, 1997-2000, in Germany and Austria: a prospective study. J Infect Dis 2002; 15: 493-500. (level 4)

3. Balestracci A, *et al.* Dehydration at admission increased the need for dialysis in hemolytic uremic syndrome children. Pediatr Nephrol 2012; 27: 1407-1410. (level 4)
4. Hickey CA, *et al.* Early volume expansion during diarrhea and relative nephroprotection during subsequent hemolytic uremic syndrome. Arch Pediatr Adolesc Med 2011; 165: 884-889. (level 4)

II.3 Diagnosis of encephalopathy

It is not uncommon for STEC infection to be complicated by acute encephalopathy, immediately before or after the onset of HUS. Common clinical symptoms include convulsion and impairment of consciousness. On suspicion of encephalopathy (when probable diagnostic criteria are met), cranial imaging studies (CT or MRI) and electroencephalography (EEG) should be performed.**[Grade of Recommendation: Not Graded]**

Diagnostic criteria

Definite:

Presence of one of the following findings during the course of STEC infection.

1) Clinical signs of convulsion and/or impairment of consciousness. Abnormal imaging findings (bilateral deep gray matter lesions or diffuse brain edema) on cranial CT or MRI.
2) Impairment of consciousness (equal to or above II-10 on Japan Coma Scale, or equal to or below 13 on Glasgow Coma Scale) lasting for more than 24 hours.

Probable:

Clinical signs of convulsion and/or impairment of consciousness during the course of STEC infection.

[Comments]

1. Central nervous system (CNS) involvement and HUS in STEC infection

STEC infection is often complicated by CNS involvement as well as HUS. In the paper describing HUS for the first time in 1955 [1], CNS involvement was regarded as a part of HUS; whereas many papers after 1970 dealt with CNS involvement as an extrarenal complication independent of HUS. However, the vast majority of patients with CNS involvement also have severe HUS. Patients who developed CNS involvement and expired before meeting the diagnostic criteria of HUS have been reported, but are only exceptional [1]. Signs of CNS involvement often appear just after the onset of HUS (between 24 to 48 hours). Approximately 10% of HUS cases have CNS involvement, although the ratio ranges from 5% to more than 30% according to the studies [3 - 5].

2. Encephalopathy associated with STEC infection

In the acute stage of HUS, there are variable CNS signs, including convulsion (generalized or partial), impairment of consciousness (coma, stupor and hallucination), hemiparesis and decerebrate posture. Convulsion and impairment of consciousness are noted in more than 50% of HUS patients [3, 5, 6]. An early but tentative diagnosis of "suspicion of encephalopathy" can start therapy based on the clear evidence of STEC infection and on neurologic findings of convulsion and/or impairment of consciousness. Subsequently, when impairment of consciousness is severe (e. g. equal or above II-10 on Japan Coma Scale or equal or below 13 on Glasgow Coma Scale) and long in duration (more than 24 hours), a definite diagnosis of acute encephalopathy can be made.

CT or MRI, and EEG are useful for diagnosis. Although mild cases may appear normal on CT and MRI, severe cases often show diffuse brain edema and/or bilateral deep gray matter lesions (basal ganglia or thalami) [4, 7 - 9]. EEG reveals abnormal basic activity (an increase in slow wave) even in mild cases, and a more pronounced increase in slow wave and abnormal paroxysmal activity in severe cases [10].

Main pathogenesis is explained on the basis of systemic STX and inflammatory cytokines, causing dysfunction of cerebral blood vessels (in particular, increased permeability or breakdown of blood-brain barrier), together with the direct toxicity of intracerebral STX. Abnormalities in water, electrolytes and circulation due to acute renal injury (indicating hypertension), may also be present in varying significance among cases [3, 11, 12].

3. Cerebral infarction associated with STEC infection

Some HUS patients develop cerebral infarction. The timing of its onset varies greatly from the acute phase to the convalescence of HUS. There are focal neurological signs, such as hemiparesis, ataxia and involuntary movements. Diagnosis is made on the basis of cranial CT and MRI, which visualize lesions varying from tiny lacunar infarcts to large hemorrhagic infarcts [13 - 15]. Pathogenesis is explained mainly on the basis of thrombotic microangiopathy, with accompanying hemorrhagic diathesis due to thrombocytopenia and other factors described in the previous section.

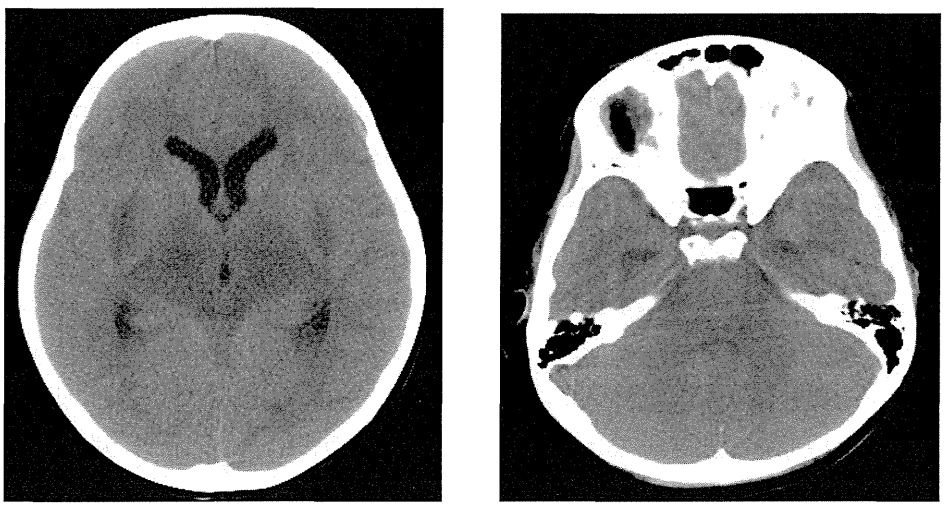

Figure 1. Acute encephalopathy in an 8-year-old girl with STEC O157 infection (Cranial CT). Diffuse brain edema, together with low density and swelling of the bilateral thalami, putamina, external capsules and pontine tegmentum, can be seen.

[References]

1. Gasser C, *et al.* Haemolytisch-uraemische syndrome: Bilaterale nierenrindennekrosen bei akuten erworbenen haemolytischen anaemien. Schweiz Med Wochenschr 1955; 85: 905-909. (level 5)
2. Akashi S, *et al.* An outbreak of *Escherichia coli* associated colitis in a kindergarten. – Committee for epidemiological study of epidemic diarrhea due to pathogenic *E. coli* in a kindergarten, Saitama, Japan. J Jpn Pediatr Soc 1991; 95: 2607-2615. [in Japanese] (level 5)
3. Siegler RL. Spectrum of extrarenal involvement in postdiarrheal hemolytic-uremic syndrome. J Pediatr 1994; 125: 511-518. (level 5)
4. Furuse A. Clinical analysis of the cases complicated with central nervous system involvement in diarrhea associated hemolytic uremic syndrome. J Jpn Pediatr Soc 2006; 110: 919-925. [in Japanese] (level 5)
5. Sheth KJ, *et al.* Neurologic involvement in hemolytic-uremic syndrome. Ann Neurol 1986; 19: 90-93. (level 5)
6. Bale CP, *et al.* CNS manifestations of the hemolytic-uremic syndrome. Am J Dis Child 1980; 134: 869-872. (level 5)
7. Theobald I, *et al.* Central nervous system involvement in hemolytic uremic syndrome (HUS)--a retrospective analysis of cerebral CT and MRI studies. Clin Nephrol 2001; 56: S3-8. (level 5)
8. Steinborn M, *et al.* CT and MRI in haemolytic uraemic syndrome with central nervous

system involvement: distribution of lesions and prognostic value of imaging findings. Pediatr Radiol 2004; 34: 805-810. (level 5)
9. Donnerstag F, *et al.* Patterns in early diffusion-weighted MRI in children with haemolytic uraemic syndrome and CNS involvement. Eur Radiol 2012; 22: 506-513. (level 5).
10. Dhuna A, *et al.* EEG and seizures in children with hemolytic-uremic syndrome. Epilepsia 1992; 33: 482-486. (level 5)
11. Shiraishi M, *et al.* Soluble tumor necrosis factor receptor 1 and tissue inhibitor of metalloproteinase-1 in hemolytic uremic syndrome with encephalopathy. J Neuroimmunol 2008; 196: 147-152. (level 4)
12. Shimizu M, *et al.* Cytokine profiles of patients with enterohemorrhagic *Escherichia coli* O111-induced hemolytic-uremic syndrome. Cytokine 2012; 60: 694-700. (level 4)
13. Crisp DE, *et al.* Hemorrhagic cerebral infarction in the hemolytic-uremic syndrome. J Pediatr 1981; 99: 273-276. (level 5)
14. DiMario FJ, *et al.* Lacunar infarction of the basal ganglia as a complication of hemolytic-uremic syndrome. Clin Pediatr 1987; 26: 586-590. (level 5)

II.4 Acute-phase extrarenal complication (excluding encephalopathy)

1. Hypertension

Hypertension may occur during the acute phase of HUS. **[Grade of Recommendation: Not Graded]**

[Comments]

Hypertension occurs in up to 25% of patients with HUS during its acute phase, resulting from overflow, renal glomerular disorder and vascular disorder, etc [1-3] (See Chapter III. 2).

[References]

1. Spinale JM, *et al.* Long-term outcomes of Shiga toxin hemolytic uremic syndrome. Pediatr Nephrol 2013 Jan 4. [Epub ahead of print]. (level 4)
2. Habib R, *et al.* Hemolytic-uremic syndrome in children and arterial hypertension. Arch Mal Coeur Vaiss 1981; 74: 37-43. (level 5)
3. Siegler RL, *et al.* Hemolytic-uremic syndrome in adolescents. Arch Pediatr Adolesc Med 1997; 151: 165-169. (level 4)

2. Gastrointestinal complications

HUS patients infected with STEC will experience gastrointestinal complications such as marked gastrointestinal edemas, intussusception, rectal prolapse, appendicitis, intestinal necrosis and perforation, peritonitis, acute pancreatitis, and bile stasis or cholelithiasis.

[Grade of Recommendation: Not Graded]

[Comments]

Marked intestinal edema is observed in HUS patients infected with STEC. Characteristic findings in abdominal ultrasonography are marked thickening of the ascending colon and enhancement of echo brightness [a]. Thickening extends from the ileocecal region to the anus, extending over the entire large intestine in severe cases [a]. Blood flow in the large intestinal wall decreases in the early phase of the disease and increases in the recovery period [a]. Reduced blood flow in the large intestinal wall observed in the early stage of the disease is caused by ischemia arising from microvessel fibrin thrombus [1].

In the mass infection among school children in Sakai City, Japan in 1996, several patients underwent appendicitis surgery for intestinal complication associated with STEC infection and those with intussusception were also reported. Rectal prolapse was observed in 8% of the children, while 3% had concurrent intussusception [2]. However, marked large intestinal edemas sometimes occur in patients with gastrointestinal STEC infection, showing a target sign-like image in abdominal ultrasonography. Differential diagnosis from intussusception is required. Thickening of the large intestinal wall by STEC infection observed without pseudokidney sign may be used as a reference.

As patients with STEC gastrointestinal infection usually present with severe acute abdominal pain, they are sometimes misdiagnosed with acute appendicitis. However, when ultrasonography shows thicked wall of ascending colonin addition to the appendix, the diagnosis of appendicitis should be made under careful consideration [3].

Severe patients with HUS sometimes manifest necrosis, perforation, peritonitis of gastrointestinal tract and acute pancreatitis [4]. For diagnosis of acute pancreatitis, in addition to serum amylase level, its fraction and serum lipase should also be used as a reference. When renal function decreases, the level of urinary amylase secretion decreases while the level of serum amylase increases.

As a large volume of hemolysis occurs over a short period for patients with HUS, a transient retention of biliary sludge occurs in the gall bladder, which may lead to concurrent gallbladder stone [5 - 8]. Furthermore, it can cause biliary tract infection, acute pancreatitis, and liver function impairment [2, 4].

[Supplementary articles]

a. Sivit CJ, *et al.* Gastrointestinal tract. In: Siegel MJ. (ed), Pediatric Sonography. Lippincott Williams & Wilkins, Philadelphia, pp.337-385, 2002
b. Task Force on the Mass Outbreak of Diarrhea in Schoolchildren of Sakai City: 1997. Sakai City, Japan: Sakai City Medical Association; Sakai City, Japan: Sakai City Medical Association.

[References]

1. Friedland JA, *et al. Escherichia coli* O157: H7-associated hemolytic-uremic syndrome: Value of colonic color Doppler sonography. Pediatr Radiol 1995; 25: S65-S67. (level 5)
2. Bernard A, *et al.* Digestive manifestations in hemolytic uremic syndrome in children. Arch Pediatr 1996; 3: 533-540. (level 4)
3. Yoda A. Echographic significance in gastrointestinal disease. Jp J Pediatric Medicine 1999; 31: 1700-1707. [in Japanese](level 5)
4. Crabbe DCG, *et al.* Gastrointestinal complications of the haemolytic uraemic syndrome. J Roy Soc Med 1990; 83: 773-775. (level 5)
5. de Buys Roessingh AS, *et al.* Gastrointestinal complications of post-diarrheal hemolytic uremic syndrome. Eur J Pediatr Surg 2007; 17: 328-334. (level 4)
6. Brandt JR, *et al.* Cholelithiasis following *Escherichia coli* O157: H7-assosiated hemolytic uremic syndrome. Pediatr Nephrol 1998; 12:222-225. (level 4)
7. Nagita A, *et al.* [Report on nine cases of gallbladder calculus disease]. J Jpn Pediatric Society 1993; 97: 2140−2144. [in Japanese] (level 5)
8. Yamazaki T, *et al.* Case Report of Two-year-old Boy with Bile-duct Stones Associated with Hemolytic Uremic Syndrome. J Jpn Pediatric Society 1996; 103: 865-868. [in Japanese] (level 5)

3. Diabetes

Concurrent diabetes may occur in the acute phase of HUS as a result of decreased insulin secretion.**[Grade of Recommendation: Not Graded]**

[Comments]

In the acute phase of HUS, thrombosis of nutrient vessels of the pancreas may cause necrosis, inflammation, fibrosis of pancreatic artery or islet, and reduced insulin secretion, leading to the onset of diabetes. Its frequency is 1.7% [1] to 3.2% [a]. Patients requiring dialysis or patients with central neurological symptoms are prone to the onset of diabetes.

[Supplementary articles]

a. Sivit CJ, *et al.* Gastrointestinal tract. In: Siegel MJ (ed), Pediatric Sonography. Lippincott Williams & Wilkins, Philadelphia, pp.337-385, 2002

[References]

1. Spizirri FD, *et al.* Childhood hemolytic uremic syndrome in Argentina: Long-term follow-up and prognostic features. Pediatr Nephrol 1997; 11: 156-160. (level 4)

4. Cardiovascular complications

During the acute phase of HUS, myocarditis, cardiac microthrombosis, dilated cardiomyopathy, cardiac tamponade, myocardial ischemia can occur. Please note that this list of conditions is not limited to the ones stated here.**[Grade of Recommendation: Not Graded]**

[Comments]

Myocarditis, cardiac microthrombosis, dilated cardiomyopathy, cardiac tamponade, myocardial ischemia, etc., can occur during the acute phase of HUS [a, 1 - 3]. In one patient with HUS who passed away suddenly during the acute phase [4], pathological findings disclosed inflammatory cellular infiltration in the cardiac muscle and the surrounding area of the conducting path.

[Supplementary articles]

a. Siegler R. Cardiovascular involvement in the hemolytic uremic syndrome. In: Kaplan BS, Trompeter RS, Moake JL. (eds), Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. Dekker, New York, pp.143-149, 1992

[References]

1. Poulton J, *et al.* Dilated cardiomyopathy associated with haemolytic uraemic syndrome. Br Heart J 1987; 57: 181-183. (level 5)
2. Mohammed J, *et al.* Cardiac tamponade in diarrhea-positive haemolytic uraemic syndrome. Nephrol Dial Transplant 2009; 24: 679-681. (level 5)
3. Askiti V, *et al.* Troponin I levels in a hemolytic uremic syndrome patient with severe cardiac failure. Pediatr Nephrol 2004; 19: 345-348. (level 5)
4. Abu-Arafeh I, *et al.* Myocarditis and haemolytic uraemic syndrome. Arch Dis Child 1995; 72: 46-47. (level 5)

III. Treatment of HUS

III.1 Fluid therapy and blood transfusion

1. Fluid therapy

We suggest sufficient intravenous fluid therapy using isotonic solutions be used for patients with STEC infection before the development of HUS. This is effective for preventing oliguria, anuria and dialysis. **[Grade of Recommendation: C1]**

When a patient manifests oliguria or anuria, excessive fluid therapy may induce hypertension, lung edema or electrolyte abnormalities. For such patients, the volume of daily intravenous infusion should not exceed the total daily urinary output, insensible water loss and water loss from stool. **[Grade of Recommendation: B]**

[Comments]

Most patients with HUS develop AKI. Dehydration due to vomiting and diarrhea exacerbates AKI. Therefore, fluid therapy for dehydration is critical. On the other hand, patients with oliguria or anuria due to AKI are likely to develop hypertension, lung edema, electrolyte abnormalities and cardiac failure by excessive fluid therapy. For these patients, the volume of daily intravenous infusion should not exceed the total daily urinary output, insensible water loss and water loss from stool. During the acute phase of HUS, ingoing and outgoing balance of water, serum electrolytes and blood sugar should be frequently monitored.

Recent literature regarding patients with STEC infection has demonstrated that aggressive fluid therapy before the onset of HUS or in its early stages can prevent oliguria or anuria [1, 2]. A prospective cohort including 50 children with HUS showed that aggressive intravenous fluid therapy significantly reduced oliguria or anuria (fluid therapy group vs non-fluid therapy group: 13/52 (52%) vs 21/25 (84%), P=0.02, odds ratio 1.6). Meanwhile, the non-oliguric/anuric group (n=16) had received more total intravenous fluid and more total sodium than the oliguric/anuric group (n=34) during the four days from onset of diarrhea; total volume of fluid and sodium was 1.7 (0 - 7.5) L/m^2 and 189 (0 - 483) mEq/m^2in non-oliguric/anuric group and 0 (0 - 4.9) L/m^2 and 0 (0 - 755) mEq/m^2 in oliguric/anuric group, respectively (p value was 0.02 and 0.05).

Multivariable analysis demonstrated that the most significant covariate was total volume infused during the four days from onset of diarrhea. However, total volume and total sodium supplementation were also strong covariates [2].

A retrospective analysis of 137 children with HUS revealed that dehydrated patients on admission had higher risk of needing dialysis (70.6 vs 40.7%, $p = 0.0007$) [3]. In conclusion, aggressive fluid therapy using intravenous isotonic solution in the early stage of STEC infection or HUS may prevent AKI.

Anuria and dialysis in the acute phase of HUS are known to be risk factors of chronic renal damage such as albuminuria, proteinuria, hypertension and impaired renal function. Therefore, prevention of oliguria and anuria in the acute phase is significant from the viewpoint of long-term renal prognosis. Conversely, any potential protective effects against CNS involvement remained to be elucidated. Thus, for early intervention of intravenous fluid therapy, early detection of STEC infection is mandatory. Although various pathogens could cause gastroenteritis, the possibility of STEC infection should always be considered during examination of patients with gastroenteritis. If a patient has suspected STEC infection, stool culture or rapid diagnostic tests should be performed promptly.

Aggressive fluid therapy with isotonic solution in oliguric or anuric patients due to AKI may increase risks of hypertension, lung edema, electrolyte abnormalities and cardiac failure. Close monitoring of blood pressure, respiratory status and urination is necessary in such patients. Intravascular volume should be comprehensively evaluated by vital signs, cardiothoracic ratio on chest X-ray, aorta to inferior vena cava (IVC) ratio on ultrasound, and central venous pressure. Additionally, patients with HUS are likely to develop lung edema even with mildly increased intravascular volume as vascular endothelial injury increases vascular permeability. During the oliguric or anuric phase, supplementation of lost water and electrolytes (such as sodium and potassium) is a basic principle. In the clinical setting, many patients with STEC infection who have already progressed to HUS and AKI, developed iatrogenic hyponatremia resulting from continuation of hypotonic solution.

Some patients with HUS develop hyperkalemia due to AKI, while others develop hypokalemia as a result of severe diarrhea. In cases of severe hypokalemia, supplementation of potassium is required.

[References]

1. Ake JA, *et al.* Relative nephroprotection during *Escherichia coli* O157:H7 infections: Association with intravenous volume expansion. Pediatrics 2005; 115: e673-80. (level 4)
2. Hickey CA, *et al.* Early volume expansion during diarrhea and relative nephroprotection during subsequent hemolytic uremic syndrome. JAMA 2012; 165: 884-889. (level 4)
3. Balestracci A, *et al.* Dehydration at admission increased the need for dialysis in hemolytic uremic syndrome children. Pediatr Nephrol 2012; 27: 1407-1410. (level 4)

2. Blood transfusion

We suggest that red blood cell transfusion be performed if hemoglobin dropped to <6 g/dL. **[Grade of Recommendation: C1]**

To reduce the frequency of red blood cell transfusion, erythropoietin therapy from early phase of HUS can be considered. **[Grade of Recommendation: C1]**

Platelet transfusion is usually not recommended as it may exacerbate thrombogenesis. However, in cases of severe bleeding tendency or massive bleeding, platelet transfusion is required. **[Grade of Recommendation: C2]**

[Comments]

Hematological complications of HUS include hemolytic anemia and thrombocytopenia. Primarily, only red blood cell (RBC) transfusion is allowed. However, this procedure should be used minimally because it accelerates generation of bilirubin and gallstones. Platelet transfusion is limited to cases of severe bleeding tendency, massive bleeding and invasive medical procedure, as it may accelerate thrombogenesis and exacerbate the clinical condition.

(1) RBC transfusion

We suggest that RBC transfusion to be considered when the hemoglobin level is <6 g/dL. In the acute phase of HUS, transfused RBC could promptly result in hemolysis. Therefore, normalization of hemoglobin is unnecessary. Excessive RBC transfusion should be avoided as it may induce cardiac failure, lung edema and gallstones [a]. RBC transfusion should be performed slowly and carefully since blood transfusion may increase intravascular volume rapidly resulting in hyperkalemia. In cases of hyperkalemia, washed RBC transfusion or use of a potassium removal filter may be necessary.

Target corrected value of hemoglobin is 8 to 10 g/dL. A small, randomized controlled trial revealed that erythropoietin therapy initiated from the early phase of HUS reduced the frequency of RBC transfusion [1]. Evaluation with a larger sized trial is expected in the future.

(2) Platelet transfusion

A retrospective cohort survey revealed the possibility that central venous (CV) and peritoneal catheters can be safely inserted without platelet transfusion. There was no significant difference in bleeding-related complications at insertion of a peritoneal dialysis catheter between patients who received platelet transfusion (n=22; $3.76\pm2.19\times10^4$ /μL, p=0.005) and those who did not

(n=51; platelet before transfusion 6.48±3.88×10^4 /μL). Simultaneously, partial omentectomy and insertion of a CV catheter were performed in both platelet-transfused group (omentectomy 45.5%, CV catheter 90.0%) and non-transfused group (omentectomy 43.1%, CV catheter 91.50%). This result suggests that some minor surgical procedures such as insertion of peritoneal dialysis or CV catheters, and omentectomy can be performed to eliminate the need for platelet transfusion [2].

[Supplementary articles]

a. UptoDate: Treatment and prognosis of Shiga toxin associated (typical) hemolytic uremic syndrome in children.

[References]

1. Pape L, *et al.* Early erythropoietin reduced the need for red blood cell transfusion in childhood hemolytic uremic syndrome: a randomized prospective pilot trial. Pediatr Nephrol 2009; 24: 1061-1064. (level 2)
2. Weil BR, *et al.* Bleeding risk for surgical dialysis procedures in children with hemolytic uremic syndrome. Pediatr Nephrol 2010; 25: 1693-1698. (level 4)

III.2 Antihypertensive therapy

Hypertension commonly occurs in HUS during acute phase. An amount of circulating blood (intravascular volume) should be evaluated correctly, and rationalization of blood pressure can be promptly attained with proper infusion, diuretic drug or antihypertensive agent, etc.
[Grade of Recommendation: C1]

Calcium channel blockers can be employed as first line therapy against acute hypertension.
[Grade of Recommendation: C1]

[Comments]

Hypertension is common in HUS during the acute phase and can cause acute heart failure and posterior reversible encephalopathy syndrome. As such, prompt antihypertensive therapy is required. In evaluating blood pressure, normal values of blood pressure are set up for every gender and age group in children (Tables 1 and 2) [a].

The causes of hypertension in HUS are excess of intravascular volume and/or activation of RAS (renin angiotensin system) associated with renal ischemia [b].