者には、血漿交換療法、血漿輸注等の血漿治療を速やかに導入する。
【推奨グレードC1 】

日本小児科学会及び日本腎臓学会の診断基準等に基づきaHUSと診断された患者に対してはエクリズマブでの治療を行う。【推奨グレードC1 】

aHUSが原因の末期腎不全患者の場合は、血縁者からの生体腎移植を行うべきではない。【推奨グレードC2 】

aHUSが原因の末期腎不全患者に献腎移植を行う場合は、周術期に予防的血漿治療を行う。【推奨グレードC1 】

aHUSが原因の末期腎不全患者に献腎移植を行う場合は、周術期の予防的なエクリズマブ治療を考慮する。【推奨グレードC1 】

【解説】

aHUSは診断の項でも述べたようにaHUSの発症に関連する基礎疾患が多数存在することが明らかとなり、基礎疾患に対する治療は様々となっている。しかし、aHUSに対する治療もEHEC関連のHUSと同様に支持療法を中心とした全身管理なくしては基礎疾患に対する特殊治療は成立しないと考え、本ガイドイドラインでは支持療法を中心とした全身管理の重要性をステートメントの最初に記載した。

(1)　侵襲的肺炎球菌感染症に関連するaHUS

aHUSの中で、侵襲的肺炎球菌感染症に関連して発症するaHUSは、EHEC感染に続発するHUSに比し年少児に多く、症状は重篤であり (c)、死亡率は12.5% (c)、26% (1)、末期腎不全率も10.1% (c)、8% (1)と、EHEC感染症に続発するHUSに比し2 - 3倍の発症率と報告されている。病態生理は、肺炎球菌が産生するneuraminidaseによる赤血球、血小板、腎糸球体内皮細胞表面からのN-acetyl neuraminic acidの解離、細胞表面へのThomsen-Friedenreich抗原の露出によるとされる。この細胞表面上に露出したThomsen-Friedenreich抗原は、血漿中の抗Thomsen-Friedenreich IgM抗体と反応し、赤血球凝集と溶血を生じHUSの発症に至る (c)。したがって抗Thomsen-Friedenreich IgM抗体が含まれる血漿成分の投与は病状を一層悪化させると考えられ、血漿輸注や血液製剤の輸注により急速に症状の悪化をきたした例が報告されている (2, 3)。また、侵襲的肺炎球菌感染症に関連したaHUS 患者38名の文献的考察では、非洗浄血液製剤の使用患者の慢性的腎後遺症や末期腎不全の発症率が、洗浄血液製剤のみを使用した患者に比し有意に高かったと報告されている (1)。これらのことから新鮮凍結血漿を用いた血漿輸

注、血漿交換療法等の血漿療法は行わない。加えて輸血に関しても洗浄血液製剤を使用すべきであり、乳幼児への透析における透析回路への充填剤として洗浄血液製剤を用いる。

(2)　補体制御因子等の異常に関連するaHUS

補体制御因子等の異常に関連するaHUSに対する治療は、ビタミンB12補充という治療法が確立しているコバラミンC異常症等を除き、速やかに循環血漿量の1-2倍量の連日の血漿交換療法または血漿輸注を行う事が推奨される (d,h)。特に補体制御因子異常症に関連する血漿交換療法は大量の新鮮凍結血漿の輸注による正常な補体制御因子の補充を可能とし、さらに原因となる物質（異常CFH、C3、抗CFH抗体等）、炎症性サイトカイン、血小板過凝集物を除去できることから、血漿輸注よりも効果的と考えられる (f, i)。しかし、Case seriesの解析 (j, k, 4, 5) では遺伝子異常を有する補体制御因子の種類によっては血漿治療の効果（短期予後）は同一ではなく、CFH異常の予後が最も不良である。一方、MCP異常症の短期予後は非常に良好で血漿治療の有無にかかわらず90%以上が寛解し、血漿治療の有無で分けた両群間に有意な差がなかった (4)。この結果から、膜結合型因子であるMCP異常症に対する血漿治療の利点はないと考えられる。

補体制御因子異常症に関連するaHUS患者の腎移植後の再発は総じて50%程度で、再発症例の80-90%は移植腎機能の廃絶をきたす (l-n, 6)。この移植後再発率も異常因子の種類により様々で、CFH、CFI、C3異常症は特に移植後再発が発生しやすい。一方、MCP異常症は移植後の再発率も低く、移植腎上に発現するMCPが非変異体であることによると考えられている (6)。移植後の原病再発を抑止することを目的に周術期からの積極的な血漿療法を併用することで移植腎機能を保持しているとの報告も散見される (l-n)。補体制御因子異常症に関連するaHUS患者に腎移植を行う際には、これらを併用することも考慮する必要がある。このように高率な移植後再発を考えると、特に再発率の高いCFH、CFI、CFB、C3等の遺伝子変異を有する患者に対して生体腎移植は施行されるべきではない。特に血縁者からの生体腎移植では、ドナーが補体制御因子異常を保有している可能性があり、移植後にaHUSを発症した報告 (l)もあり現段階では禁忌と考えるべきである。

補体制御因子異常症に関連するaHUSの根本的治療として、補体関連因子のCFH、CFI、CFBとC3は主に肝臓で合成されることから肝移植が理論的には考えられる。現在まで10名以上で肝腎複合移植が施行され (o, p, 7-12)、周術期の予防的な大量血漿療法を併用した成功例も散見される (10-12)。しかし現段階においては施行患者数も非常に少なく、術後成績を正確に評価できる段階にはない。

aHUSの多くの患者にCFH、CFI、MCPをはじめとする補体制御因子の遺伝子異常が発見され、補体活性化第二経路を介した過度の補体活性化が本疾患の中心的な病因と考

えられている。C5 に対するヒト化モノクローナル抗体であるエクリズマブは、C5 に結合し C5a と C5b への開裂を阻止し補体の最終産物である膜侵襲複合体(membrane attack complex: MAC）の形成をも阻止することから、補体活性を制御する薬剤として開発された。成人を対象とした 2 つの前向き単群試験と小児を対象とした後ろ向き研究が施行され、アメリカおよびヨーロッパで 2011 年秋に aHUS に対する治療薬として承認された (q)。血漿治療に抵抗性を示した患者への有効性 (13 - 15)を示した報告や、aHUS 患者の腎移植に際しての長期にわたる再発予防に有効であったとする報告 (16 - 20) 等が多数存在する。これらのことからエクリズマブは aHUS の治療手段として、また、aHUS 患者への移植後再発の予防治療手段として、aHUS 患者に大きな福音をもたらす可能性がある。しかし、本薬剤が補体活性化カスケードの最終段階を阻害する薬剤であることから、被包化細菌の感染リスクが上昇すると考えられ、特に髄膜炎菌感染は死亡リスクもあり、本薬剤使用 2 週間以上前に髄膜炎菌ワクチンを接種する。本薬剤投与までに 2 週間の期間が取れない場合にはシプロフロキサシン等適切な抗菌薬を併用し感染を予防する (r)。さらに小児においては同じ被包化細菌に分類される肺炎球菌、インフルエンザ菌 b 型に関してもワクチンの接種状況を確認し、未接種の場合にはワクチン接種を検討することが必要である(s)。わが国でも 2013 年 9 月に aHUS における血栓性微小血管障害の抑制への適応拡大が承認されたところである。エクリズマブ(ソリリス®)の添付文書には使用上の注意として「本剤の有効性及び安全性を十分に理解した上で、本剤投与の是非を慎重に検討し、適切な対象患者に対し投与を開始すること。」、「本剤の適用にあたっては、日本小児科学会及び日本腎臓学会の診断基準等に基づいて非典型溶血性尿毒症症候群と診断された患者を対象とすること。」と記載されており(s), aHUS と適切に診断することが重要である。また本添付文書に記載されている aHUS に対する用法・用量を表 2、3 に記載した (s)。

エクリズマブ治療は、特に血漿治療に抵抗性や依存性を示す患者、血漿に対するアレルギーや血漿交換のためのブラッドアクセスの確保困難等血漿治療の危険性が非常に大きく血漿治療施行が困難と判断される患者に対する有用性は大きく、これらの患者及び補体性制御因子異常症に関連する aHUS と確定診断された患者に対しては、海外での報告と同様に(t)本剤による治療優先度は高くなると考える。しかし、日本人に対するエクリズマブの使用は、現在 3 例の治験例と個人輸入による使用経験例が数例存在するのみであり、日本人における効果や副作用に関しては今後の検討課題であることから、推奨グレードを C1 とした。今後、エクリズマブの aHUS への治療経験が蓄積されることにより、aHUS の治療プロトコールや、腎移植後の aHUS 再発予防治療のプロトコールが大きく変化する可能性がある。

2013 年、新たに劣性遺伝形式をとる aHUS の原因として DKGE 異常症が報告された(f)。本症に関連して発症する aHUS 関しては補体の異常活性化の関与は明らかでなく、血漿輸注、エクリズマブ投与にて補体活性をコントロール中の症例においても aHUS の再発を認めた

症例が確認され、血漿治療やエクリズマブの有効性に関しては不明である。一方、移植に関しては、献腎移植をうけた3例において、2例が生着（2年、4年）、1例が慢性拒絶により移植腎機能が廃絶したと報告され、aHUS再発による移植腎機能廃絶例がないことが注目すべき点に挙げられている。また、DKGE異常症は微小血管障害症を伴う膜性増殖性糸球体腎炎の原因遺伝子との報告(t)もあり、今後の症例蓄積・解析が待たれるところである。

表2　エクリズマブの用量・用法 (s)

年齢または体重	導入期	維持量
18歳以上	1回900 mg/を週1回で計4回	初回投与4週間後から1回1,200 mgを2週に1回
18歳未満		
40 kg以上	1回900 mgを週1回で計4回	初回投与4週間後から1回1,200 mgを2週に1回
30 kg以上 40 kg未満	1回600 mgを週1回で計2回	初回投与2週間後から1回900 mgを2週に1回
20 kg以上 30 kg未満	1回600 mgを週1回で計2回	初回投与2週間後から1回600 mgを2週に1回以降2週毎に600 mg
10 kg以上 20 kg未満	1回600 mgを週1回で計1回	初回投与1週間後から1回300 mgを2週に1回
5 kg以上 10 kg未満	1回300 mgを週1回で計1回	初回投与1週間後から1回300 mgを3週に1回

表3　血漿交換／血漿輸注後のエクリズマブの補充投与 (s)

	直近のエクリズマブ投与量	エクリズマブ補充用量	補充投与の時期
血漿交換	300 mg	1回につき300 mg	施行後60分以内
	600 mg以上	1回につき600 mg	
新鮮凍結血漿輸注	300 mg以上	1回につき300 mg	施行60分前

註：血漿交換により本剤の一部が除去されること、新鮮凍結血漿内には補体C5が含まれることから、本剤投与中に血漿交換または新鮮凍結血漿輸注を施行する必要がある場合には、血漿交換の施行後または新鮮凍結血漿輸注の施行前に、表3を参考に本剤の補充投与を考慮すること。なお、表3はシミュレーション結果に基づき設定されたものであることから、補充投与後は患者の状態を慎重に観察する (s)。

【検索式】

PubMed、医中誌で、1992年1月 - 2012年8月までの期間で検索した。また重要と判断した文献をハンドサーチで検索した。

PubMed

(("Hemolytic-Uremic Syndrome"[MH] AND atypical[TIAB]) OR "Atypical hemolytic uremic syndrome" [Supplementary Concept] OR (atypical*[TIAB] AND hemolytic*[TIAB])) AND English[LA] AND "1992"[EDAT]:"2012/08/31"[EDAT]=510件

医中誌

(溶血性尿毒症症候群/TH or 溶血性尿毒症症候群/AL) and (非典型/AL or atypical/AL) and (PT=会議録除く and CK=ヒト) and (PDAT=1992/01/01:2012/08/31)=21件

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Outline of the guidelines

1. Necessity to provide comprehensive guidelines for hemolytic uremic syndrome (HUS).

The first guidelines for the diagnosis and treatment of HUS following the Shiga toxin producing *Escherichia coli* (STEC) infection was published by The Japanese Society of Pediatric Nephrology (JSPN) in 2000. Since then, there has been considerable advancement in the understanding and treatment of acute encephalopathy - one of the most serious complications in HUS. Furthermore, the etiology, conditions and treatments of atypical HUS have been elucidated. Therefore, a set of comprehensive guidelines for HUS that reflects recent clinical evidence is necessary.

The aim of this set of guidelines is to provide a support, tool for daily medical practice and to contribute to the standardization and accessibility of HUS-related medical care, as well as to improve level of safety for HUS patients.

2. Preparation of guidelines

The present guidelines are produced according to the procedures proposed by the Medical Information Network Distribution Service (Minds) of the Japan Council for Quality Health Care.

The guideline writing committee (GWC) consists of members from these societies: JSPN, The Japanese Society of Nephrology (JSN), The Japanese Society of Child Neurology (JSCN), Japanese Society for Pediatric Infectious Diseases (JSPID) and The Japanese Association for Infectious Diseases (JAID).

The GWC members set the keywords in conjunction with the clinical question and critically reviewed relevant literatures published between January 1, 1992 and August 31, 2012, through the use of major databases (e.g., PubMed and the Japana Centra Revuo Medicina [Ichushi]) in cooperation with The Japan Medical Library Association. As there is a lack of high quality publications on HUS currently, publications with low quality evidences or without retrieval target period were still carefully reviewed.

All documents used are supported by evidence. A grade of recommendation was assigned to the statements. The grades were determined based on the level of evidence, as well as on the quality and clinical significance of the evidence. The levels of evidence and grades of recommendation are shown in Table 1 and 2.

3. Independent assessment

The present guidelines were reviewed by the assessment committee members derived from three JSPN and one Child Support Whole Country Network of Intractable Disease representatives. The final draft of the guidelines, together with a request for public comments,

was published on the websites of JPS, JSN and JSPN. The GWC then took on board the comments and suggestions by the public to revise and finalize the present set of guidelines accordingly.

Table 1. Level of evidence

Level I	Data obtained from a systematic review or a meta-analysis of randomized clinical trials.
Level II	Data obtained from at least one randomized comparative clinical trial.
Level III	Data obtained from non-randomized comparative clinical trials.
Level IV	Cohort studies, case–control studies, or cross-sectional studies.
Level V	Case reports, or case series.
Level VI	Opinions of special committees or specialists with no basis of patient data.

Table 2. Grade of recommendation

Grade A	A given treatment or procedure was recommended based on robust scientific evidence.
Grade B	A given treatment or procedure was suggested based on scientific evidence.
Grade C1	A given treatment or procedure may be considered although scientific evidence is not available.
Grade C2	A given treatment or procedure may not be considered due to missing scientific evidence.
Grade D	A given treatment or procedure is not recommended as scientific evidence indicated inefficacy or harm.

4. Cautionary notes on the use of the present guidelines

Users should be aware that the guidelines do not always equate to evidence-based medicine (EBM). The guidelines are not meant to overrule a physician's experience. Users should bear in mind that the guidelines are developed in accordance with evidence at the time of preparation and that the quantity and level of evidence may subsequently change. The guidelines serve to assist physicians and patients in making decisions about treatment. This set of guidelines does not provide any legal basis in the event of medical lawsuits.

5. Conflict of interest

The expense for GWS meetings were provided by the Health Labor Sciences Research Grant (for the study on standardization of the pathogenic factor and the medical treatment for severe enterohemorrhagic *Escherichia coli* infection) supported by the Ministry of Health, Labor and Welfare (MHLW). Dr. Makoto Ohnishi chairs this research project. All committee members

confirmed their conflict of interest (COI) declaration based on the Acts of COI established by JPS, JSN and JSPN.

Table of Contents

I. Diagnosis and treatment of Shiga toxin producing *Escherichia coli* infection

I.1 Diagnosis of Shiga toxin producing *Escherichia coli* infection

Methods for Shiga toxin producing *Escherichia coli* (STEC) infection diagnosis defined by the Ministry of Health, Labor and Welfare, Japan **[Grade of Recommendation: Not Graded]**

STEC infection is diagnosed when a patient manifests clinical symptoms and signs suggestive of STEC infection and meets criterion 1, 2 or 3 below.

1. *E. coli* isolated from stool is confirmed to have the ability to produce Shiga toxin (STX) by one of the following criteria:
   a. Confirmation of STX being produced.
   b. Isolation of STX-producing genes by PCR or other methods.
2. Isolation of STX from stool of a patient with HUS.
3. Isolation of serum anti-O antigen of *E. coli* antibody or anti-STX antibody from a patient with HUS

[Comments]

1. What is enterohemorrhagic *Escherichia coli* infection?

According to the definition established by the MHLW under the Infectious Disease Control Law, enterohemorrhagic *Escherichia coli* (EHEC) is an infection caused by diarrheagenic *E. coli* that produces STX [a]. STX is also known as Verotoxin (VT). EHEC infects human intestine, where it produces STX and induces diarrhea. EHEC may also be referred to as Verotoxin producing *Escherichia coli* (VTEC).

2. Causative food

Humans usually contract STEC infection by ingesting food such as raw or inadequately cooked beef, sprout, vegetables, pickels or water contaminated with the organism. In many cases, however, specific causative food cannot be identified. Hence, the route of infection remains unconfirmed.

3. Symptoms and signs

Abdominal pain and watery diarrhea develop three to seven days after oral ingestion of STEC, and likely to be followed by bloody stool, which has similar consistency with blood in severe cases (hemorrhagic colitis, Fig 1). The wall of the large intestine shows edematous change (Fig 2, 3), accompanied by the erosion and bleeding. In more severe cases, the patient experiences diarrhea more than ten times per day and suffers serious abdominal pain. Bloody stool continues for seven to 14 days. According to the MHLW, abdominal pain, watery diarrhea and bloody stool are the main symptoms of STEC infection. A high body temperature of over 38℃ and

nausea are observed in some STEC patients [b]. High fever over 39℃ is a rare complication. Some patients with STEC infection develop HUS several days from the onset of diarrhea. A triad of symptoms typically appears in HUS, including hemolytic anemia, thrombocytopenia and acute kidney injury (AKI).

4. STEC as causative agent of HUS

Table 1 shows the reported cases of HUS in Japan from 2008 to 2011 (retrieved from the records of the Infectious Disease Surveillance Center under the National Institute of Infectious Diseases of Japan). The most common serotype of STEC isolated from HUS patients in Japan was O157. For patients who are O157 negative, O121, O111, O26, and O145 are identified [1 - 4].

5. Diagnosis

Final diagnosis requires the identification of STEC in stool. Therefore, stool sample should be obtained and cultured before antibiotics are administered to patients. According to the guidelines for the examination of intestinal infections by the Japanese Society of Clinical Microbiology, the presence of STX is the most reliable marker of STEC [c]. The guidelines from the Center for Disease Control and Prevention in the USA recommends the use of a culture that could identify STEC O157 and other serotypes in stool samples in addition to the confirmation of STX in the stool [d]. It remains difficult to diagnose STEC infection as other bacteria besides STEC can produce STX. It is also challenging to diagnose STEC infection based solely on the presence of STX in stool. The MHLW reported that the presence of STX in stool, serum antibody against *E. coli* O antigen or anti STX antibody in serum would be enough for the diagnosis of STEC infection only in cases with HUS. The MHLW arrived at this decision due to the fact that STEC is the leading cause of HUS in Japan, and that it is difficult to detect STEC in tool when antibiotics were administered to patients before examination of stool sample [1 - 4, 11]. Specimen, subjects, measurement principles and reaction time of commercially available rapid diagnostic methods are shown in Table 2.

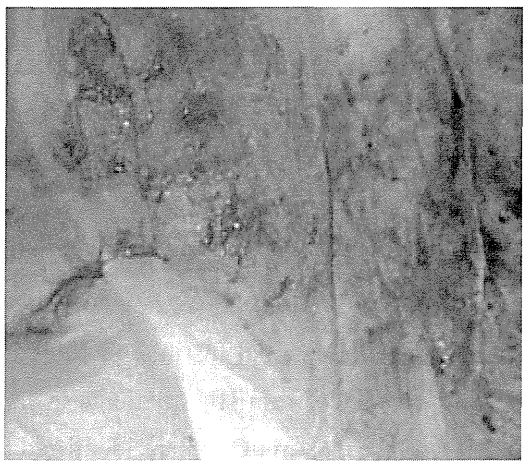

Fig 1. Bloody stool from a patient with STEC infection.

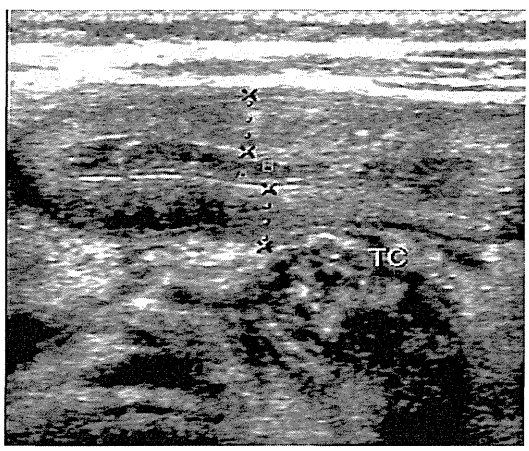

Fig 2. Edematous change of the transverse colon of a patient with STEC infection (abdominal ultrasonography).

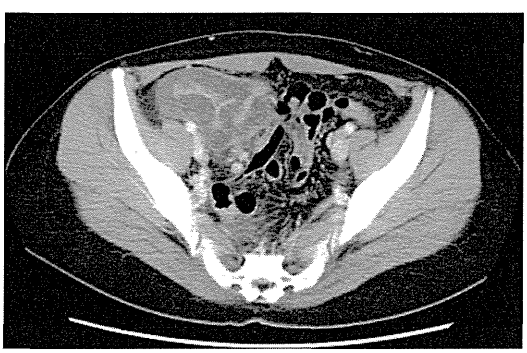

Fig 3. Edematous change of the cecum and ascending colon of a patient with STEC infection (abdominal CT scan).

Table1. Number of patients with HUS and STEC infection in Japan (2008-2011)

No. of patients with HUS	371
No. of HUS patients with detected STEC	242
No. of HUS patients with detected STEC O157	203
No. of HUS patients with detected STEC O157(producing both STX1 & STX2)	117
No. of HUS patients with detected STEC O157(producing STX2)	76
No. of HUS patients with detected STEC O157(producing unclassifiable STX)	10
No. of HUS patients with detected STEC excluding O157	39

Figures in this Table are based on data from IASR 2009, 2010, 2011 and 2012.

Table 2. Specimen, subject, measurement principle, and reaction time of commercially available rapid diagnostic methods

Specimen	Subject	Measurement principle	Reaction (required) time
Stool	Antigen of STEC O157*	Immunochromatography	10 – 15 minutes
		Latex agglutination	2 minutes
Stool	Shiga toxin	ELISA	~ 3 hours
Serum	Antibody against STEC O157 LPS	Latex agglutination	3 minutes

*Diagnosis of STEC infection should not be based on STEC antigen detected in the sttol from the patient solely.

[Supplementary articles]

a. Ministry of Health, Labour and Welfare: Report of three cases of enterohemorrhagic *Escherichia coli* infection by doctors and veterinarians (http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-03-03.html).
b. Legal act on the medical care, prevention and treatment of infectious diseases (Law 114th, October 2, 1998. Revision: Law 122nd, December 14, 2011).
c. Japanese Society of Clinical Microbiology. [Guidelines for examination of infectious enteritis]. J Jpn Soc Clin Microbiol 2010; 20: 1-138.
d. Gould LH, *et al.* Recommendations for diagnosis of Shiga toxin-producing *Escherichia coli* infections by clinical laboratories. MMWR Recomm Rep 2009 Oct 16; 58(RR-12); 1–14.

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1. Saito T, *et al.* Reported cases of hemorrhagic uremic syndrome associated with EHEC infection in 2008-NESID. IASR 2009; 30: 122-123. [in Japanese] (level 5)

2. Komiya N, *et al.* Reported cases of hemorrhagic uremic syndrome associated with EHEC infection in 2008-NESID. IASR 2010; 31: 170-172. [in Japanese] (level 5)
3. Saito T, *et al.* Reported cases of hemorrhagic uremic syndrome associated with EHEC infection in 2010-NESID. IASR 2011; 32: 141-143. [in Japanese] (level 5)
4. Saito T, *et al.* Reported cases of hemorrhagic uremic syndrome associated with EHEC infection in 2011-NESID. IASR 2012; 33: 128-130. [in Japanese] (level 5)
5. Ezawa A, *et al.* High prevalence of Enterohemorrhagic *Escherichia coli* (EHEC) O157 from cattle in selected regions of Japan. J Vet Med Sci 2004; 66: 585-587. (level 5)
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9. Suzuki Y, *et al.* Enterohemorrhagic colitis: comparison of clinical and CT findings. Nippon Acta Radiologica 1999; 59: 183-188. [in Japanese] (level 5)
10. Kataoka S, *et al.* Ultrasonographic findings in hemorrhagic colitis in child due to *Escherichia coli* O157:H7: differential diagnosis from other bacterial enterocolitis. J Med Ultrasonics 1997; 24: 1633-1640. [in Japanese] (level 4)
11. Kamioka I, *et al.* Risk factors for developing severe clinical course in HUS patients: a national survey in Japan. Pediatr Int 2008; 50: 441-446. (level 4)

I.2 Treatment of STEC infection

1. Antibiotics

No conclusion has been made regarding the association between the use of antibiotics for STEC infection and the onset of HUS. **[Grade of Recommendation: Not Graded]**

The use of antibiotics is considered for carrier of STEC (such as patient's family members) to prevent further transmission of the disease.

[Comments]

Treatment for children with STEC infection is primarily by supportive care. In the set of guidelines in the USA, the use of antibiotics is not recommended for the treatment of STEC infection as it is a risk factor for HUS. Antibiotics are essentially bacterial toxins that eliminate other species of bacteria [a, b]. However, a global meta-analysis performed between January

1981 and February 2001 demonstrated that the use of antibiotics did not influence the incidence of HUS. This indicated the need of the appropriate randomized controlled study (RCT) [1]. One RCT comparing the incidence of HUS between antibiotics-use group and antibiotics non-use group in STEC infected patients demonstrated no differences [2]. Another case-control study evaluating patients with STEC infection outbreak in Europe showed that antibiotics-use group (n=52) had lower incidence of seizure, surgical intervention, mortality and shorter duration of bacterial colonization in stool than antibiotics non-use group n=246) [3].

In contrast, several cohort studies evaluating STEC O157 patients demonstrated that antibiotics -use group had higher incidence of HUS than antibiotics non-use group, and concluded that the use of antibiotics is indeed a risk factor for HUS [4 - 7]. In the studies, antibiotics such as β—lactams (penicillins and cephalosporins), fluoroquinolones, and sulfamethoxazole/trimethoprim were used. Furthermore, recent *in vivo* data revealed that fluoroquinolones facilitated STX production while azithromycin did not induce STX production [c, d]. Hence, in cases where antibiotics are administered, it is crucial to consider the type being used.

During an outbreak of STEC in Japan, antibiotics - particularly fosfomycin - was used [8]. A retrospective analysis demonstrated that patients who used fosfomycin in the early onset of diarrhea (within 2 days) had lower incidence of HUS than those who did not [9].

As the indication of antibiotics differs between Japan and other countries, it is difficult to draw comparisons. To date, there has been no conclusion on whether the use of antibiotics is effective in preventing HUS. A recommendation grade is not provided as further investigation is necessary for this treatment option.

For carriers of STEC (such as patient's family members), the use antibiotics should be considered to prevent further transmission of the disease.

2. Anti-diarrheal drug

We do not recommend the use of anti-diarrheal drug for pediatric patients with STEC as it is a risk factor for HUS. **[Grade of Recommendation: D]**

[Comments]

It was previously reported that anti-diarrheal drug is a risk factor for HUS in patients with STEC infection [10-12]. Current foreign guidelines do not recommend the use of anti-diarrheal drugs [a, b]. The use of such drugs should therefore be avoided.

To date, there is no available data on the efficacy or risk of probiotics in patients with STEC infection.

3. Infection control for patients with STEC infection

In addition to standard precaution, we recommend adopting contact precaution for hospitalized patients with acute diarrhea caused by STEC until two consecutive negative stool cultures. **[Grade of Recommendation: B]**

[Comments]

In addition to standard precaution, the wearing of apron and gloves is recommended when coming into contact with patients with acute diarrhea caused by STEC [e]. Contact precaution can be lifted when two consecutive stool cultures proved negative [e].

[Supplementary articles]

a. Guerrant RL, *et al.* Infectious Diseases Society of America: Practice guidelines for the management of infectious diarrhea. Clin Infect Dis 2001; 32: 331-351.
b. Thielman NM, *et al.* Clinical practice: Acute infectious diarrhea. N Engl J Med 2004; 350: 38-47.
c. Zhang X, *et al.* Quinolone antibiotics induce Shiga toxin-encoding bacteriophages, toxin production, and death in mice. J Infect Dis 2000; 181: 664-670.
d. Zhang Q, *et al.* Gnotobiotic piglet infection model for evaluating the safe use of antibiotics against Escherichia coli O157:H7 infection. J Infect Dis 2009; 199: 486-493.
e. American Academy of Pediatrics. Committee on Infectious Diseases. Report of the Committee on Infectious Diseases. In. Evanston, Ill.: American Academy of Pediatrics; 2011

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1. Safdar N, *et al.* Risk of hemolytic uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 enteritis: a meta-analysis. JAMA 2002; 288: 996-1001. (level 2)
2. Proulx F, *et al.* Randomized, controlled trial of antibiotic therapy for *Escherichia coli* O157:H7 enteritis. J Pediatr 1992; 121:299-303. (level 2)
3. Menne J, *et al.* EHEC-HUS consortium: Validation of treatment strategies for enterohaemorrhagic *Escherichia coli* O104:H4 induced haemolytic uraemic syndrome: case-control study. BMJ 2012; 345: e4565. (level 4)
4. Smith KE, *et al.* Antibiotic treatment of Escherichia coli O157 infection and the risk of hemolytic uremic syndrome, Minnesota. Pediatr Infect Dis J 2012; 31: 37-41. (level 4)
5. Wong CS, *et al.* The risk of the hemolytic-uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. N Engl J Med 2000; 342: 1930-1936. (level 4)