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Sporadic bloody diarrhoea-associated thrombotic thrombocytopenic purpura-haemolytic uraemic syndrome: an adult and paediatric comparison

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Summary

Although diarrhoea-associated haemolytic uremic syndrome (HUS) in children is well described, the clinical features of bloody diarrhoea-associated thrombotic thrombocytopenic purpura (TTP)-HUS in adults are not documented. Twenty-one adults, 6·5% of the 322 adults in The Oklahoma TTP–HUS Registry, 1989–2006, have presented with bloody diarrhoea. There were no case clusters. *Escherichia coli* O157:H7 was identified in five patients, but many patients did not have appropriate studies. The annual incidence was $0{\cdot}68/10^6$, 10-fold less than the incidence of diarrhoea-associated HUS in children in Oklahoma. Two (13%) of 16 patients in whom ADAMTS13 (A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13) was measured had <10% activity. Severe neurological abnormalities (67%) and renal failure (62%) were common; seven patients (33%) died; no survivors have relapsed. Compared to the 38 other Oklahoma Registry patients with ADAMTS13 <10%, frequency of severe neurological abnormalities and death was not different; frequency of renal failure was greater; frequency of relapse was less. Compared to 5999 children with sporadic diarrhoea-associated HUS in published reports, frequency of renal failure and relapse was not different; frequency of severe neurological abnormalities and death was greater ($P < 0{\cdot}05$ for all differences). Awareness of the continuous occurrence of sporadic bloody diarrhoea-associated TTP–HUS in adults is important for prompt diagnosis and appropriate management.

Keywords: thrombotic thrombocytopenic purpura, haemolytic uremic syndrome, *Escherichia coli* O157:H7, ADAMTS13, plasma exchange treatment.

Infection with *Escherichia coli* O157:H7 and the resulting diarrhoea-associated haemolytic-uremic syndrome (HUS), manifested by thrombocytopenia, microangiopathic haemolytic anaemia, and renal failure, are important public health problems that primarily affect children (Bell *et al*, 1994; Boyce *et al*, 1995; Mead & Griffin, 1998; Besser *et al*, 1999; Tarr *et al*, 2005; Maki, 2006). Diarrhoea-associated HUS is most familiar from reports of outbreaks related to a documented source of *E. coli* O157:H7 infection (Bell *et al*, 1994; Maki, 2006), but sporadic cases may be more common (Tarr *et al*, 2005; Maki, 2006). Although sporadic diarrhoea-associated HUS in children is well known from many studies, and outbreaks involving adults have been reported (Carter *et al*, 1987; Dundas *et al*, 1999; Reiss *et al*, 2006), the frequency, demographics, presenting features, management, and clinical outcomes of adults with sporadic HUS [described here as thrombotic thrombocytopenic purpura (TTP)–HUS] have not been documented.

The Oklahoma TTP–HUS Registry has documented the occurrence of bloody diarrhoea-associated TTP–HUS in 21 adults from 1989 to 2006. We describe these patients and compare their frequency, demographics, presenting features, management and clinical outcomes to adults with TTP and severe ADAMTS13 (A Disintegrin And Metalloproteinase with

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a ThromboSpondin type 1 motif, member 13) deficiency and to children with sporadic diarrhoea-associated HUS.

Methods

The Oklahoma TTP–HUS Registry

The Registry includes all consecutive patients for whom the Oklahoma Blood Institute (OBI) is requested to provide plasma exchange treatment for patients with a diagnosis of TTP or HUS (Vesely *et al*, 2003; George *et al*, 2004; Johnson *et al*, 2007). The OBI is the sole provider of plasma exchange services for all hospitals in 58 of the 77 Oklahoma counties. As the standard practice in this region is to treat all adult patients who are diagnosed with either TTP or HUS with plasma exchange, the Registry is an inception cohort of consecutive patients in whom the diagnosis of TTP or HUS was established and a decision to initiate plasma exchange treatment was made. Plasma exchange procedures used replacement with one plasma volume of fresh frozen plasma (frozen <8 h after donation), 24 h plasma (frozen >8 but <24 h after donation), or cryoprecipitate-poor plasma; plasma selection was based only on product availability. The Registry has enroled and followed prospectively all 348 consecutive patients who had their first episode of clinically diagnosed TTP–HUS between 1 January 1989 and 31 December 2006. Because these syndromes in adults, with or without renal failure or neurological abnormalities, are commonly known as TTP (George, 2006) and because children with a diarrhoea prodrome are known as HUS, we describe adults with a prodrome of bloody diarrhoea as TTP–HUS. To focus our study on adults, 21 patients age 18 years old or less were excluded. To focus our study within a defined geographic region to estimate incidence, five additional patients who did not live in the counties served by the OBI were excluded; none of these five patients presented with bloody diarrhoea. The Oklahoma TTP–HUS Registry is approved by the institutional review boards of the University of Oklahoma Health Sciences Center and each participating hospital.

Patients were assigned in a hierarchical order to one of six predefined clinical categories related to associated conditions and potential aetiologies (Vesely *et al*, 2003): [1] following haematopoietic stem cell transplantation, [2] pregnant/postpartum, [3] drug association, [4] a prodrome of overt, severe bloody (bright red) diarrhoea, [5] presence of an additional or alternative disorder that may have caused the presenting features, and [6] idiopathic, if none of the criteria for the previous five clinical categories were fulfilled. Therefore, patients in the first three clinical categories may have presented with bloody diarrhoea but it was not considered to be the principal condition related to the onset of TTP–HUS. In addition, patients who presented with bloody diarrhoea and were assigned to category [4] could have had an additional disorder, such as systemic lupus erythematosus, or could have been subsequently diagnosed with an alternative disorder, such as sepsis or malignancy. For patients who had more than one episode of TTP–HUS, the first episode defined the clinical category and only data from the first episode are reported in this study.

Demographic, clinical and laboratory data were collected prospectively and systematically on standardized forms and entered into a Microsoft Access® database (Vesely *et al*, 2003). Obesity was defined as a body mass index (BMI) ≥30 kg/m^2. Exacerbations was defined as recurrent thrombocytopenia following recovery to a normal platelet count that required resumption of daily plasma exchange treatment and was assumed to represent continuation of a single acute episode. Remission was defined as no plasma exchange treatment for at least 30 d. Relapse was defined as recurrence of TTP–HUS following a remission and was assumed to represent a subsequent, distinct acute episode (Vesely *et al*, 2003). Acute and chronic renal failure, minor and severe neurological abnormalities, and outcome measures were previously defined (Kojouri *et al*, 2001; Vesely *et al*, 2003; George *et al*, 2004). For this study, sporadic cases of patients with a prodrome of overt bloody diarrhoea were defined as cases that were separated by time or distance and had no apparent contact or common exposures.

Follow-up to the present time is complete on all 14 surviving patients who presented with bloody diarrhoea and 32 of 33 surviving patients with severe ADAMTS13 deficiency. To calculate incidence, we used census data from 2000 that provided age specific populations for each county in Oklahoma (U.S. Census, 2000).

Adults with severe ADAMTS13 deficiency

Serum for ADAMTS13 assays was collected immediately before the first plasma exchange procedure in 215 (92%) of the 234 patients who presented since 13 November 1995. ADAMTS13 activity was measured as previously described by immunoblot assay of von Willebrand factor multimers (Furlan *et al*, 1998; Bianchi *et al*, 2002). Severe ADAMTS13 deficiency was defined as <10% activity. Patients with severe deficiency were tested for ADAMTS13 inhibitory activity by measuring ADAMTS13 activity in mixtures of patient and normal sera (Furlan *et al*, 1998; Bianchi *et al*, 2002).

The 38 patients (age over 18 years) who had ADAMTS13 activity <10% and did not present with bloody diarrhoea were selected as a comparison group. These 38 patients are all patients in the Oklahoma TTP–HUS Registry who had ADAMTS13 activity <10%, except for the two patients included in the group who presented with bloody diarrhoea and two other patients who were subsequently diagnosed with sepsis as the aetiology of their disease and were therefore excluded from this analysis. Among these 38 patients who had ADAMTS13 activity <10%, three were postpartum, three also had systemic lupus erythematosus or Sjögren's syndrome, 32 were idiopathic. ADAMTS13 inhibitory activity was identified in 35 of the 38 patients.

Children with diarrhoea-associated HUS: systematic literature review

Search strategy. Ovid software was used to search the Medline database from 1970 to 20 April 2007. The key words and MeSH terms searched for HUS were 'hemolytic uremic syndrome', 'hemolytic-uremic syndrome' and 'HUS'. The key words and MeSH terms searched for diarrhoea-associated HUS were '*Escherichia coli* O157', '*Escherichia coli* O157:H7', '*Escherichia coli*', '*Escherichia coli* infection', 'Shiga toxin', 'diarrhea' and 'bloody diarrhea'. The search was limited to English language and children. All articles identified by both one of the HUS terms and one of the *E. coli* or diarrhoea terms were retrieved. The bibliographies of all articles selected for review were searched to identify additional articles.

Study selection. All case series reporting 10 or more children with diarrhoea-associated HUS were identified. Articles reporting less than 10 patients were not reviewed to avoid reports of exceptional patients. Articles reporting patients accrued before 1970 were excluded to avoid analysis of outcomes before supportive care with dialysis was commonly available. Articles were selected for review if they reported original patient data and the HUS did not result only from an outbreak, but rather presented all children from a defined region and time.

Data extraction. Children with sporadic HUS were selected because they were comparable to the adults reported in this study. Articles reporting both sporadic and outbreak data, or both diarrhoea-associated and atypical HUS, were excluded unless the data were reported separately. Articles that had both children, age 18 years or less, and adult patients were not reviewed unless data for children were reported separately.

Children with diarrhoea-associated HUS: The Children's Hospital of Oklahoma

Records with a discharge diagnosis of HUS [International Classification of Diseases (ICD)-9 code, 283·11] at The Children's Hospital of Oklahoma from 2002–2006 were reviewed. Records for children hospitalized prior to 2002 were incomplete. It was postulated that most children with HUS in Oklahoma were hospitalized at The Children's Hospital of Oklahoma since it is the major paediatric referral center and the only paediatric nephrology service in the state.

Statistical methods

We used the non-parametric Wilcoxon Mann–Whitney test for continuous data and the chi-square test or Fisher exact test for categorical data to compare the demographics, clinical features, and outcomes among different groups. Statistical analyses were performed by using SAS, version 9·1 (SAS Institute, Inc., Cary, NC, USA). An alpha of 0·05 was used.

Results

Adults with bloody-diarrhoea-associated TTP–HUS

Over a period of 18 years (Table I), 1989–2006, 21 adult patients had overt, severe bloody diarrhoea as a dominant presenting feature of their TTP–HUS. These 21 patients represented 6·5% of all 322 adult patients in the Oklahoma Registry region who had their first episode of clinically diagnosed TTP–HUS during this time. Three other patients also presented with acute bloody diarrhoea but were not included because their TTP–HUS followed allogeneic stem cell transplantation (one patient) or quinine ingestion (two patients). None of the 21 patients had an alternative diagnosis as the cause of the clinical features of TTP–HUS. Patients who presented with overt, severe bloody diarrhoea were distinct; non-bloody diarrhoea was more common, occurring in 73 (24%) of the 298 adult patients who did not present with overt bloody diarrhoea.

The 21 patients with bloody diarrhoea-associated TTP–HUS were 21–82 years old (median, 59 years); 17 (81%) were women; 20 (95%) were white, one patient was black; five (24%) were obese (BMI $\geq$30 kg/m^2). Fifteen patients had routine stool cultures; 14 were normal; one patient had *Shigella sonnei* infection. Stool was cultured for *E. coli* O157:H7 in 12 patients and was identified in five. In some patients stool cultures were only obtained after antibiotic treatment was begun or after diarrhoea had resolved. No source of *E. coli* O157:H7 infection was identified. The 21 patients presented in 11 of the 18 years of the Registry; there was no increased frequency during summer months (five of 21 patients presented between June and August). Patients 14 and 15 both lived in Oklahoma County and presented 1 week apart, but there was no apparent connection between them. No other patients presented within a month of each other.

In addition to bloody diarrhoea, abdominal pain was a major presenting symptom. Most patients saw a physician promptly after the onset of bloody diarrhoea (median, 1 d; range 0–18 d). Three patients were initially diagnosed with conditions that required urgent surgery. Patients 2 and 12 were diagnosed with ischaemic colitis; patient 2 had a right hemicolectomy and patient 12 had a total colectomy and ileostomy. Patient 8 had an appendectomy followed 6 d later by a right hemicolectomy. The interval between the onset of bloody diarrhoea and the onset of thrombocytopenia (platelet count $<100 \times 10^9$/l), indicating the onset of TTP–HUS, was 0–18 d (median, 4 d); the interval between the onset of thrombocytopenia and the diagnosis of TTP–HUS was 0–19 d (median, 2 d).

Fourteen patients (67%) had severe neurological abnormalities at presentation or during the course of their TTP–HUS; 13 (62%) had seizures, eight (38%) were comatose. Three other patients had minor neurological abnormalities (transient confusion, disorientation); four patients (19%) had no neurological abnormalities.

Table I. Demographics, clinical features, and outcomes of adults with bloody diarrhoea-associated TTP–HUS.

No.	Age (years)	Race	Sex	Days from onset of bloody diarrhoea to diagnosis of TTP–HUS	Presenting symptoms (in addition to bloody diarrhoea)	Neurological abnormalities	Presenting laboratory data							Days from diagnosis to death
							Plt ($\times 10^9$/l)	Hct (%)	LDH (U/l)	Cr (μmol/l)	ADAMTS13 (% activity)	Routine Stool Culture	Stool Culture for *Escherichia coli* O157:H7	
1	63	W	M	9	Abdominal pain, nausea, vomiting	Seizure	15	25	1393	592	NA	Not done	Not done	NA
2	45	W	F	6	Abdominal pain, nausea, vomiting	Confusion	26	24	1282	327	NA	Normal	Not done	NA
3	79	W	F	7	Fever	Seizure, coma	12	18	2575	583	NA	Normal	Not done	1
4	58	W	F	6	Abdominal pain, weakness	Focal seizure, coma	33	19	2059	504	NA	Normal	Not done	NA
5	71	W	F	3	Chest pain	Seizure, coma	15	21	1249	716	NA	Normal	Not done	12
6	50	W	F	3	Abdominal pain, nausea, vomiting	Seizure, coma	16	22	3109	619	50	Not done	Not done	10
7	68	W	M	4	Abdominal pain	Confusion	27	22	1095	239	100	*Shigella sonnei*	Positive	NA
8	24	W	F	11	Abdominal pain, nausea, vomiting	Diplopia, seizure	23	22	6660	575	100	Normal	Negative	NA
9	39	W	F	1	Confusion, nausea, vomiting	Right-side numbness, seizure	18	22	1976	97	<5	Not done	Not done	NA
10	82	W	F	5	Abdominal pain, weakness	Seizure, coma	11	24	2040	566	40	Not done	Not done	6
11	69	W	F	10	Abdominal pain	Normal	77	15	1026	389	40	Normal	Positive	8
12	69	W	F	10	Abdominal pain, nausea, vomiting	Focal facial seizure	28	22	1325	203	40	Normal	Negative	NA
13	59	W	F	5	Abdominal pain, nausea, vomiting	Normal	36	20	657	97	50	Normal	Positive	NA
14	67	W	F	10	Abdominal pain, nausea, vomiting, dyspnea	Confusion, seizure	15	20	1908	345	50	Normal	Positive	NA
15	53	B	F	21	Abdominal pain, nausea, vomiting, dyspnea	Confusion	21	24	3232	88	5	Not done	Not done	NA
16	79	W	F	1	Abdominal pain, nausea, vomiting,	Seizure, coma	28	28	5022	309	50	Normal	Negative	1
17	40	W	F	9	Abdominal pain, nausea, vomiting	Seizure, coma	25	20	7687	230	90	Normal	Negative	NA
18	21	W	M	7	Abdominal pain, nausea, vomiting,	Normal	44	23	1387	1945	85	Normal	Positive	NA

Table I. (Continued).

No.	Age (years)	Race	Sex	Days from onset of bloody diarrhoea to diagnosis of TTP–HUS	Presenting symptoms (in addition to bloody diarrhoea)	Neurological abnormalities	Presenting laboratory data					Routine Stool Culture	Stool Culture for *Escherichia coli* O157:H7	Days from diagnosis to death
							Plt ($\times 10^9$/l)	Hct (%)	LDH (U/l)	Cr (μmol/l)	ADAMTS13 (% activity)			
19	57	W	M	8	Abdominal pain, nausea, vomiting,	Confusion, dysarthria, seizure	48	22	1292	274	90	Normal	Negative	NA
20	69	W	F	20	Nausea, vomiting, dyspnea	Confusion, coma	20	32	762	194	75	Normal	Negative	3
21	47	W	F	6	Abdominal pain, nausea, vomiting	Normal	15	21	1530	203	60	Not done	Negative	NA

Individual data are presented for the 21 adult patients who presented with bloody diarrhoea between 1 January 1989 and 31 December 2006. Lactate dehydrogenase (LDH) values were normalized across hospital laboratories to an upper limit of normal of 200 U/l. The upper limit of normal for serum creatinine (Cr) was 106 μmol/l. The normal range for ADAMTS13 activity was 50–150%.
W, White; B, Black; NA, not available or not applicable.

At presentation with TTP–HUS, all patients were thrombocytopenic (platelet counts 11–77 $\times$ 10^9/l; median, 23 $\times$ 10^9/l) and anaemic (haematocrits 15–32%; median, 22%); all patients had fragmented red cells and increased levels of lactate dehydrogenase (LDH, 657–7687 U/l; median, 1530 U/l). Thirteen patients (62%) had acute renal failure; nine required dialysis. ADAMTS13 activity was measured in 16 patients; two (13%) had severe deficiency (<10%) with inhibitors of ADAMTS13 activity; in the remaining 14 patients ADAMTS13 activity was 40–100%. Although 50% ADAMTS13 activity is the lower limit in normal subjects, mildly reduced activity levels of 26–50% are common among hospitalized patients with many different illnesses (Mannucci *et al*, 2001). In three patients (14%) the serum creatinine never exceeded 97 μmol/l; stool culture identified *E. coli* O157:H7 in one; the other two had severe ADAMTS13 deficiency (one had her stool cultured for *E. coli* O157:H7 and it was negative).

Seven (33%) patients died; six were comatose prior to death; one patient had pre-existing congestive heart failure and chronic obstructive pulmonary disease as major causes of death. Three patients had responded to plasma exchange treatment before they died: (i) Two were comatose on admission and remained comatose; treatments were stopped when it was judged that there was no chance of recovery. (ii) The third responding patient died from complications of preexisting congestive heart failure and chronic obstructive pulmonary disease. The median number of plasma exchange treatments required to achieve a response in these three patients and the 14 surviving patients was six (range, 3–40). The median total number of plasma exchanges for the 14 surviving patients was 11 (range, 5–65). Patients 4 and 15 had exacerbations after 2–11 d of no plasma exchange treatment requiring repeated courses of daily plasma exchange; they required 65 and 54 plasma exchange treatments respectively. These two patients and nine others were also treated with glucocorticoids; one patient was treated with vincristine. The 14 patients continue to survive (follow-up 2·4–15·5 years; median, 7·7 years); one patient has residual neurological abnormalities, none have chronic renal failure and none have relapsed.

Comparison of adults with bloody diarrhoea-associated TTP–HUS to adults with TTP and severe ADAMTS13 deficiency

The 21 patients who presented with bloody diarrhoea were compared to the 38 patients with severe ADAMTS13 deficiency who did not have bloody diarrhoea (Table II). The patients who presented with bloody diarrhoea were older, more frequently white, and less frequently obese; women predominated in both groups. Patients who presented with bloody diarrhoea had more frequent acute renal failure and less severe thrombocytopenia. The frequency of severe neurological abnormalities, severity of anaemia, frequency of

Table II. Comparison of adults with bloody diarrhoea-associated TTP–HUS to adults with severe ADAMTS13 deficiency.

Patients	Bloody diarrhoea	Severe ADAMTS13 deficiency (<10%)	*P*-value
Patients (no.)	16	38	
Demographics			
Age (years, median, range)	58 (21–82)	40 (19–71)	0·003
Race (white)	15 (94%)	20 (53%)	0·004
Sex (female)	13 (81%)	31 (82%)	1·000
BMI (≥30 kg/m^2)	4 (25%)	22 (58%)	0·027
Presenting clinical features [*n* (%)]			
Severe neurological abnormalities	10 (63)	17 (45)	0·233
Acute renal failure	8 (50)	2 (5)	<0·001
Laboratory data (median, range)			
Platelets (×10^9/l)	24 (11–77)	10 (2–63)	<0·001
Haematocrit (%)	22 (15–32)	21 (13–30)	0·122
LDH (U/l)	1410 (247–3109)	1496 (274–3909)	0·756
Cr (μmol/l)	239 (88–1945)	88 (71–442)	<0·001
Outcomes			
Response	13 (81%)	34 (89%)	0·411
Exacerbation	1 (6%)	18 (47%)	0·004
Plasma exchange (no.)	10 (11 pts, 5–54)	20 (33 pts, 3–79)	0·037
Dialysis	5 (31%)	0 (0%)	0·001
Death	5 (31%)	5 (13%)	0·141
Relapse	0/11 (0%)	13/33 (39%)	0·019

Demographics, clinical features, and outcomes of the 16 adult patients who presented with bloody diarrhoea between 13 November 1995, the day when routine serum samples were first collected for measurements of ADAMTS13 activity, and 31 December 2006, are compared to the 38 adult patients without bloody diarrhoea who had severe ADAMTS13 deficiency (<10% activity). Severe neurological abnormalities were defined as coma, stroke, seizure, or focal abnormalities (Vesely *et al*, 2003). Lactate dehydrogenase (LDH) values were normalized across hospital laboratories to an upper limit of normal of 200 U/l. Acute renal failure and the outcome measures of response, exacerbation, death and relapse have been previously defined (George *et al*, 2004; Vesely *et al*, 2003). The number of plasma exchange treatments is reported only for surviving patients.
BMI, body mass index.

response to plasma exchange, and mortality were not different between the two groups. Patients who presented with bloody diarrhoea required fewer plasma exchange treatments to achieve a remission, had fewer exacerbations, and none have relapsed.

Comparison of adults with bloody diarrhoea-associated TTP–HUS to children with sporadic diarrhoea-associated HUS

A systematic review of published case series identified 5999 children with sporadic diarrhoea-associated HUS in 38 articles (reporting 39 case series) from 14 countries (Table III) (Dolislager & Tune, 1978; Raghupathy *et al*, 1978; Fong & Kaplan, 1982; Karmali *et al*, 1983, 1985; Communicable Disease Surveillance Centre, 1986; Rogers *et al*, 1986; Sheth *et al*, 1986; Badami *et al*, 1987; Kinney *et al*, 1988; Novillo *et al*, 1988; Lopez *et al*, 1989; Tarr *et al*, 1989; Martin *et al*, 1990; Milford *et al*, 1990; Abu-Arafeh *et al*, 1991; Rowe *et al*, 1991, 1993; Bitzan *et al*, 1993; Gianviti *et al*, 1994; Jernigan & Waldo, 1994; Van de Kar *et al*, 1995, 1996; Douglas & Kurien, 1997; Nevard *et al*, 1997; Siegler *et al*, 1997; Rowe *et al*, 1998; Oakes *et al*, 2006; Decludt *et al*, 2000; Wong *et al*, 2000; Elliott *et al*, 2001; Chandler *et al*, 2002; Cummings *et al*, 2002; Gerber *et al*, 2002; Trachtman *et al*, 2003; Lynn *et al*, 2005; Haus-Cheymol *et al*, 2006; Bergstein *et al*, 1992). Among the 2880 children in whom diarrhoea was described as either bloody or not bloody, 1890 (66%) had bloody diarrhoea. In both adults and children, essentially all patients were white. Among the children, boys and girls were equally affected, different from the predominance of women among the adults. *E. coli* O157:H7 was identified in stool cultures more frequently in children, but the range in the 26 studies reporting these data varied greatly, from 2% (Lopez *et al*, 1989) to 100% (in two studies that used stool culture identification of *E. coli* O157:H7 as an inclusion criterion) (Kinney *et al*, 1988; Chandler *et al*, 2002). Adults had more frequent severe neurological abnormalities, more severe thrombocytopenia and anaemia, and a higher mortality.

Table III. Comparison of adults with TTP–HUS who presented with bloody diarrhoea to children with sporadic, diarrhoea-associated (diarrhoea-positive) HUS identified from a systematic review of published reports.

Patients	Adults	Children	*P*-value	References
Number	21	5999		
Age (years, median)	59	2 (4017)	<0·001	(Rogers *et al*, 1986; Lopez *et al*, 1989; Martin *et al*, 1990; Milford *et al*, 1990; Rowe *et al*, 1991; Douglas & Kurien, 1997; Siegler *et al*, 1997; Rowe *et al*, 1998; Decludt *et al*, 2000; Jernigan & Waldo, 1994; Elliott *et al*, 2001; Gerber *et al*, 2002; Trachtman *et al*, 2003) (Raghupathy *et al*, 1978; Karmali *et al*, 1983; Karmali *et al*, 1985; Communicable Disease Surveillance Centre, 1986; Sheth *et al*, 1986; Badami *et al*, 1987; Kinney *et al*, 1988; Abu-Arafeh *et al*, 1991; Bergstein *et al*, 1992; Bitzan *et al*, 1993; Rowe *et al*, 1993; Van de Kar *et al*, 1995, 1996) (Novillo *et al*, 1988; Gianviti *et al*, 1994; Chandler *et al*, 2002; Lynn *et al*, 2005)
Race (white)	95%	95% (726/767)	1·000	(Communicable Disease Surveillance Centre, 1986; Rogers *et al*, 1986; Kinney *et al*, 1988; Lopez *et al*, 1989; Martin *et al*, 1990; Milford *et al*, 1990; Jernigan & Waldo, 1994; Chandler *et al*, 2002; Trachtman *et al*, 2003)
Sex (female)	81%	52% (2314/4430)	0·009	(Dolislager & Tune, 1978; Rogers *et al*, 1986; Lopez *et al*, 1989; Martin *et al*, 1990; Milford *et al*, 1990; Rowe *et al*, 1991; Douglas & Kurien, 1997; Siegler *et al*, 1997; Rowe *et al*, 1998; Gerber *et al*, 2002; Decludt *et al*, 2000; Jernigan & Waldo, 1994; Trachtman *et al*, 2003) (Raghupathy *et al*, 1978; Karmali *et al*, 1983, 1985; Communicable Disease Surveillance Centre, 1986; Sheth *et al*, 1986; Badami *et al*, 1987; Abu-Arafeh *et al*, 1991; Bergstein *et al*, 1992; Bitzan *et al*, 1993; Rowe *et al*, 1993; Van de Kar *et al*, 1995, 1996; Chandler *et al*, 2002) (Novillo *et al*, 1988; Gianviti *et al*, 1994; Lynn *et al*, 2005; Oakes *et al*, 2006)
Identification of *Escherichia coli* O157:H7 or Shiga toxin	24%	51% (1997/3951)	0·015	(Lopez *et al*, 1989; Martin *et al*, 1990; Milford *et al*, 1990; Rowe *et al*, 1991; Van de Kar *et al*, 1996; Douglas & Kurien, 1997; Rowe *et al*, 1998; Cummings *et al*, 2002; Decludt *et al*, 2000; Elliott *et al*, 2001; Bitzan *et al*, 1993; Gerber *et al*, 2002; Trachtman *et al*, 2003) (Raghupathy *et al*, 1978; Karmali *et al*, 1983, 1985; Badami *et al*, 1987; Kinney *et al*, 1988; Abu-Arafeh *et al*, 1991; Rowe *et al*, 1993; Gianviti *et al*, 1994; Nevard *et al*, 1997; Chandler *et al*, 2002; Lynn *et al*, 2005; Haus-Cheymol *et al*, 2006)
Severe neurological abnormalities	67%	17% (341/2004)	<0·001	(Fong & Kaplan, 1982; Karmali *et al*, 1983; Communicable Disease Surveillance Centre, 1986; Rogers *et al*, 1986; Kinney *et al*, 1988; Martin *et al*, 1990; Milford *et al*, 1990; Rowe *et al*, 1991; Van de Kar *et al*, 1995; Nevard *et al*, 1997; Siegler *et al*, 1997; Elliott *et al*, 2001; Gerber *et al*, 2002) (Gianviti *et al*, 1994; Lynn *et al*, 2005)
Platelets ($\times 10^9$/l)	23	50	<0·001	(Dolislager & Tune, 1978; Raghupathy *et al*, 1978; Rogers *et al*, 1986; Badami *et al*, 1987; Tarr *et al*, 1989; Rowe *et al*, 1991, 1993; Nevard *et al*, 1997; Rowe *et al*, 1998; Gerber *et al*, 2002; Elliott *et al*, 2001; Trachtman *et al*, 2003; Van de Kar *et al*, 1995) (Kinney *et al*, 1988; Chandler *et al*, 2002)
Haematocrit (%)	22	29	<0·001	(Kinney *et al*, 1988; Tarr *et al*, 1989; Rowe *et al*, 1993; Chandler *et al*, 2002; Trachtman *et al*, 2003)
Creatinine (μmol/l)	301	365	0·976	(Raghupathy *et al*, 1978; Rogers *et al*, 1986; Sheth *et al*, 1986; Tarr *et al*, 1989; Rowe *et al*, 1991, 1993; Nevard *et al*, 1997; Rowe *et al*, 1998; Chandler *et al*, 2002; Elliott *et al*, 2001; Gerber *et al*, 2002; Trachtman *et al*, 2003; Van de Kar *et al*, 1995)

Table III. (Continued).

Patients	Adults	Children	*P*-value	References
Dialysis	43%	49% (1312/2663)	0·558	(Dolislager & Tune, 1978; Rogers *et al*, 1986; Martin *et al*, 1990; Milford *et al*, 1990; Rowe *et al*, 1991; Douglas & Kurien, 1997; Rowe *et al*, 1998; Elliott *et al*, 2001; Decludt *et al*, 2000; Wong *et al*, 2000; Jernigan & Waldo, 1994; Gerber *et al*, 2002; Trachtman *et al*, 2003) (Raghupathy *et al*, 1978; Fong & Kaplan, 1982; Karmali *et al*, 1983; Badami *et al*, 1987; Tarr *et al*, 1989; Bergstein *et al*, 1992; Bitzan *et al*, 1993; Rowe *et al*, 1993; Van de Kar *et al*, 1995, 1996; Nevard *et al*, 1997; Siegler *et al*, 1997; Cummings *et al*, 2002) (Karmali *et al*, 1985; Communicable Disease Surveillance Centre, 1986; Sheth *et al*, 1986; Kinney *et al*, 1988; Novillo *et al*, 1988; Abu-Arafeh *et al*, 1991; Gianviti *et al*, 1994; Chandler *et al*, 2002; Lynn *et al*, 2005; Haus-Cheymol *et al*, 2006; Oakes *et al*, 2006)
Death	33%	3% (148/4967)	<0·001	(Dolislager & Tune, 1978; Rogers *et al*, 1986; Martin *et al*, 1990; Milford *et al*, 1990; Rowe *et al*, 1991; Jernigan & Waldo, 1994; Douglas & Kurien, 1997; Decludt *et al*, 2000; Decludt *et al*, 2000; Wong *et al*, 2000; Elliott *et al*, 2001; Gerber *et al*, 2002; Trachtman *et al*, 2003) (Raghupathy *et al*, 1978; Fong & Kaplan, 1982; Karmali *et al*, 1983; Badami *et al*, 1987; Tarr *et al*, 1989; Bergstein *et al*, 1992; Bitzan *et al*, 1993; Rowe *et al*, 1993; Van de Kar *et al*, 1995, 1996; Nevard *et al*, 1997; Siegler *et al*, 1997; Cummings *et al*, 2002) (Karmali *et al*, 1985; Communicable Disease Surveillance Centre, 1986; Sheth *et al*, 1986; Kinney *et al*, 1988; Novillo *et al*, 1988; Abu-Arafeh *et al*, 1991; Gianviti *et al*, 1994; Chandler *et al*, 2002; Lynn *et al*, 2005; Haus-Cheymol *et al*, 2006; Oakes *et al*, 2006)
Relapse	0%	1% (7/759)	1·000	(Raghupathy *et al*, 1978; Rogers *et al*, 1986; Milford *et al*, 1990; Rowe *et al*, 1991; Rowe *et al*, 1993; Decludt *et al*, 2000; Van de Kar *et al*, 1996; Douglas & Kurien, 1997; Siegler *et al*, 1997; Elliott *et al*, 2001; Wong *et al*, 2000; Bitzan *et al*, 1993; Cummings *et al*, 2002) (Fong & Kaplan, 1982; Karmali *et al*, 1983; Karmali *et al*, 1985; Communicable Disease Surveillance Centre, 1986; Sheth *et al*, 1986; Badami *et al*, 1987; Kinney *et al*, 1988; Tarr *et al*, 1989; Abu-Arafeh *et al*, 1991; Bergstein *et al*, 1992; Van de Kar *et al*, 1995; Nevard *et al*, 1997; Chandler *et al*, 2002) (Novillo *et al*, 1988; Gianviti *et al*, 1994; Lynn *et al*, 2005; Haus-Cheymol *et al*, 2006)

Demographics, clinical features, and outcomes of the 21 adult patients who presented with a prodrome of bloody diarrhoea, 1 January 1989 to 31 December 2006, were compared to children with sporadic, diarrhoea-associated HUS identified by a systematic literature review. Not all variables were described in all articles; the numbers in parentheses describe the actual number of children reported with the variable and the total number of children in the articles (citations provided) that described that variable.

Comparison of the incidence of adults with bloody diarrhoea-associated TTP–HUS to the incidence of children with diarrhoea-associated HUS

The adult population included in the Oklahoma TTP–HUS Registry region was 1 720 144. Therefore the estimated annual incidence of adults with bloody diarrhoea-associated TTP–HUS in this region was 0·68 cases/10^6. There was no difference in the incidence between the eight counties designated by the U.S. Census as urban (U.S. Census, 2000) [0·83/10^6; 95% confidence interval (CI), 0·40–1·27] and the 50 counties designated as rural (0·49/10^6; 95% CI, 0·13–0·86).

During the 5 years, 2002–2006, 31 children (ages 2 months–9 years) were hospitalized at The Children's Hospital of Oklahoma with a diagnosis of HUS. Twenty-eight (90%) children had diarrhoea-associated HUS; the diarrhoea was bloody in 23. The occurrence of HUS was sporadic in 26 children; in one family two siblings were hospitalized 2 days apart. *E. coli* O157:H7 and/or Shiga toxin were identified in 19 (68%) of these 28 children; no source of infection was identified. The demographics, clinical features, and outcomes of these 28 children were not different from the 5999 children identified from our systematic review, except that the platelet counts (median, 34×10^9/l) and the frequency of white children (75%) were less ($P < 0·01$). The population of children in the State of Oklahoma was 892 360. Therefore the estimated annual incidence of children with diarrhoea-associated HUS in Oklahoma was 6·3 cases/10^6. This estimate was not different from the annual incidence described in the 15 studies reporting these data, 7·9 cases/10^6 (95% CI, 4·8–11·0/10^6) (Communicable Disease Surveillance Centre, 1986; Rogers *et al*, 1986; Kinney *et al*, 1988; Tarr *et al*, 1989; Martin *et al*, 1990; Milford *et al*, 1990; Rowe *et al*, 1991; Bitzan *et al*, 1993; Gianviti *et al*, 1994; Jernigan & Waldo, 1994; Decludt *et al*, 2000; Cummings *et al*, 2002; Gerber *et al*, 2002; Lynn *et al*, 2005; Haus-Cheymol *et al*, 2006).

Discussion

This is the first prospective cohort study of adults with bloody diarrhoea-associated TTP–HUS. Twenty-one patients were identified during the 18 years of The Oklahoma TTP–HUS Registry, 6·5% of all adult patients. The estimated annual incidence of adults with bloody diarrhoea-associated TTP–HUS in our region was 0·68 cases/10^6, 10-fold less than the estimated annual incidence of children with diarrhoea-associated HUS in Oklahoma (6·3 cases/10^6) and in 15 previously published reports from other regions (7·9 cases/10^6). Although there are no previous direct comparisons of adults and children, *E. coli* O157:H7 infections and associated HUS are often described as more common in young children; this may be related to a decreased density of Shiga toxin glycolipid receptors in glomeruli of older children and adults (Lingwood, 1994). It has also been suggested that older adults have an increased susceptibility to *E. coli* O157:H7 infections and associated HUS (Carter *et al*, 1987; Boyce *et al*, 1995; Slutsker *et al*, 1997; Besser *et al*, 1999; Dundas *et al*, 1999, 2001; Reiss *et al*, 2006). Occurrence was not related to seasons, although diarrhoea-associated HUS in children is usually reported to be more common during summer months (Boyce *et al*, 1995; Besser *et al*, 1999).

Escherichia coli O157:H7 was considered to be the possible aetiology of bloody diarrhoea-associated TTP–HUS, since it has the strongest association with diarrhoea-associated HUS in children (Tarr *et al*, 2005), but it was identified in only five patients. The lower rate of identification of *E. coli* O157:H7 among adults may be because of less awareness of sporadic *E. coli* O157:H7 infection resulting in fewer and delayed stool cultures. Prompt stool cultures are critical for the identification of *E. coli* O157:H7 since isolation rates decline rapidly during the first days of illness (Mead & Griffin, 1998). All cases were sporadic, there were no case clusters, and there were no identified sources of *E. coli* O157:H7 infection. This is consistent with other data that most cases of *E. coli* O157:H7 infection and related HUS are sporadic, not associated with outbreaks (Pai *et al*, 1984; Remis *et al*, 1984; Tarr *et al*, 2005; Maki, 2006; Karpac *et al*, 2007).

Two (13%) patients with bloody diarrhoea-associated TTP–HUS had severe ADAMTS13 deficiency; these two women had demographic and clinical features similar to other patients with severe ADAMTS13 deficiency and neither had serum creatinine values greater than 97 μmol/l (Vesely *et al*, 2003; Terrell *et al*, 2005). In patients with severe ADAMTS13 deficiency, bloody diarrhoea may be caused by mesenteric microthrombi resulting in haemorrhagic mucosal ischaemia and ulceration, pathologically similar to Shiga toxin-induced haemorrhagic enterocolitis (George, 2006).

The demographic and clinical features of the adult patients who presented with bloody diarrhoea had both similarities and differences when compared to adults with severe ADAMTS13 deficiency and to children with diarrhoea-associated HUS. Similarities to adults with severe ADAMTS13 deficiency included female predominance, frequent severe neurological abnormalities, and a high mortality in spite of frequent apparent responses to plasma exchange treatment; differences included older age, predominance of white race, frequent renal failure, and fewer exacerbations and relapses. Similarities to children with diarrhoea-associated HUS included predominance of white race, frequent renal failure and rare relapses. The onset of TTP–HUS, with thrombocytopenia occurring 4 d after the onset of bloody diarrhoea, was also similar to that in children (Mead & Griffin, 1998; Tarr *et al*, 2005). Differences from children included female predominance, more frequent severe neurological abnormalities and higher mortality.

The reasons for the female predominance among adults, in contrast to children, are unknown. The female predominance among our 21 patients was probably not related to increased risk for infection with *E. coli* O157:H7, as reported infection rates are the same for women and men (Slutsker *et al*, 1997). Female predominance was also apparent across other clinical

categories of TTP (Kojouri *et al*, 2001; Roy *et al*, 2001; Vesely *et al*, 2003; Terrell *et al*, 2005). The reasons for the racial disparities, with predominantly white patients among both adults who presented with bloody diarrhoea and children with diarrhoea-associated HUS, in contrast to the ninefold relative increased incidence of blacks among patients with severe ADAMTS13 deficiency (Terrell *et al*, 2005), are also unknown. The frequency of renal failure in both children and adults may be related to the presumed Shiga toxin aetiology; the absence of relapses may be related to acquired immunity (Boyce *et al*, 1995; Besser *et al*, 1999). The high rate of relapses in adults with severe ADAMTS13 deficiency is probably related to the autoimmune aetiology. The greater severity among the adults, compared to children, may be related to their greater risk for thrombotic complications (Richardson *et al*, 2002).

Our 21 patients were identified by a request for plasma exchange, the standard treatment in our region for adults who are diagnosed with TTP or HUS. Other less severe cases may have occurred without a request for plasma exchange treatment; therefore our cohort may underestimate the frequency and overestimate the severity of bloody diarrhoea-associated TTP–HUS in adults. Since diarrhoea is not bloody in one-third of children with diarrhoea-associated HUS patients, our cohort may also underestimate the frequency of *E. coli* O157:H7-associated TTP–HUS in adults by excluding patients whose diarrhoea was not overtly bloody.

The benefit of plasma exchange treatment of adults with TTP–HUS who present with bloody diarrhoea is uncertain. The potential infectious aetiology suggests that plasma exchange treatment may be unnecessary, similar to the standard management of children with diarrhoea-associated HUS (Tarr *et al*, 2005). Withholding plasma exchange treatment may be considered to avoid the potentially critical complications of plasma exchange (Howard *et al*, 2006). However, plasma exchange appeared to be effective in our patients and also in a previous report of adult patients associated with an outbreak of *E. coli* O157:H7 infection (Dundas *et al*, 1999). Our rationale for plasma exchange treatment was the severity of illness and the apparent responses. In addition, since bloody diarrhoea may be a presenting feature of patients with severe ADAMTS13 deficiency, plasma exchange treatment must be considered in these patients.

The importance of these observations is to increase awareness of the occurrence of sporadic bloody diarrhoea-associated TTP–HUS in adults. Increased awareness will promote prompt diagnosis and help to avoid inappropriate evaluation and management procedures. Presentation with overt bloody diarrhoea requires immediate stool collection for appropriate analysis to identify *E. coli* O157:H7 infection. Increased awareness will also improve community surveillance and increase recognition of *E. coli* O157:H7 as an aetiology of sporadic bloody diarrhoea-associated TTP–HUS in adults.

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Conflict of interest

The authors have no conflicts of interest for the material in this manuscript.

References

Abu-Arafeh, I., Smail, P.J., Youngson, G.G. & Auchterlonie, I.A. (1991) Haemolytic uraemic syndrome in the defined population of Northeast of Scotland. *European Journal of Pediatrics*, **150,** 279–281.

Badami, K.G., Srivastava, R.N., Kumar, R. & Saraya, A.K. (1987) Disseminated intravascular coagulation in post-dysenteric haemolytic uraemic syndrome. *Acta Paediatrica Scandinavica*, **76,** 919–922.

Bell, B.P., Goldoft, M., Griffin, P.M., Davis, M.A., Gordon, D.C., Tarr, P.I., Bartleson, C.A., Lewis, J.H., Barrett, T.J., Wells, J.G., Baron, R. & Kobayashi, J. (1994) A multistate outbreak of *Escherichia coli* O157:H7-associated bloody diarrhea and hemolytic uremic syndrome from hamburgers: the Washington experience. *Journal of the American Medical Association*, **272,** 1349–1353.

Bergstein, J.M., Riley, M. & Bang, N.U. (1992) Role of plasminogen-activator inhibitor type 1 in the pathogenesis and outcome of the hemolytic uremic syndrome. *New England Journal of Medicine*, **327,** 755–759.

Besser, R.E., Griffin, P.M. & Slutsker, L. (1999) *Escherichia coli* 0157:H7 gastroenteritis and the hemolytic uremic syndrome: an emerging infectious disease. *Annual Review of Medicine*, **50,** 355–367.

Bianchi, V., Robles, R., Alberio, L., Furlan, M. & Lämmle, B. (2002) Von Willebrand factor-cleaving protease (ADAMTS13) in thrombocytopenic disorders: a severely deficient activity is specific for thrombotic thrombocytopenic purpura. *Blood*, **100,** 710–713.

Bitzan, M., Ludwig, K., Klemt, M., König, H., Büren, J. & Müller-Wiefel, D.E. (1993) The role of *Escherichia coli* O157 infection in the classical (enteropathic) haemolytic uraemic syndrome: results of a Central European, multicentre study. *Epidemiology and Infection*, **110,** 183–196.

Boyce, T.G., Swerdlow, D.L. & Griffin, P.M. (1995) *Escherichia coli* O157:H7 and the hemolytic-uremic syndrome. *New England Journal of Medicine*, **333,** 364–368.

Carter, A.O., Borczyk, A.A., Carlson, J.A.K., Harvey, B., Hockin, J.C., Karmall, M.A., Krishnan, C., Korn, D.A. & Lior, H. (1987) A severe outbreak of *Escherichia coli* 0157:H7-associated hemorrhagic colitis in a nursing home. *New England Journal of Medicine*, **317,** 1496–1500.

Chandler, W.L., Jelacic, S., Boster, D.R., Ciol, M.A., Williams, G.D., Watkins, S.L., Igarashi, T. & Tarr, P.I. (2002) Prothrombotic coagulation abnormalities preceding the hemolytic-uremic syndrome. *New England Journal of Medicine*, **346,** 23–32.

Communicable Disease Surveillance Centre (1986) British Paediatric Association-Communicable Disease Surveillance Centre surveillance of haemolytic uraemic syndrome 1983-1984. *British Medical Journal*, **292,** 115–117.

Cummings, K.C., Mohle-Boetani, J.C., Werner, S.B. & Vugia, D.J. (2002) Population-based trends in pediatric hemolytic uremic syndrome in California, 1994-1999: substantial underreporting and public health implications. *American Journal of Epidemiology*, **155,** 941–948.

Decludt, B., Bouvet, P., Mariani-Kurkdjian, P., Grimont, F., Grimont, P.A.D., Hubert, B. & Loirat, C. (2000) Haemolytic uraemic syndrome and Shiga toxin-producing *Escherichia coli* infection in children in France. *Epidemiology and Infection*, **124,** 215–220.

Dolislager, D. & Tune, B. (1978) The hemolytic-uremic syndrome. *American Journal of Diseases of Children*, **132,** 55–58.

Douglas, A.S. & Kurien, A. (1997) Seasonality and other epidemiological features of haemolytic uraemic syndrome and *E. coli* O157 isolates in Scotland. *Scottish Medical Journal*, **42,** 166–171.

Dundas, S., Murphy, J., Soutar, R.L., Jones, G.A., Hutchinson, S.J. & Todd, W.T. (1999) Effectiveness of therapeutic plasma exchange in the 1996 Lanarkshire Escherichia coli 0157:H7 outbreak. *Lancet*, **354,** 1327.

Dundas, S., Todd, W.T.A., Stewart, A.I., Murdoch, P.S., Chaudhuri, A.K.R. & Hutchinson, S.J. (2001) The central Scotland *Escherichia coli* O157:H7 outbreak: risk factors for the hemolytic uremic syndrome and death among hospitalized patients. *Clinical Infectious Diseases*, **33,** 923–931.

Elliott, E.J., Robins-Browne, R.M., O'Loughlin, E.V., Bennett-Wood, V., Bourke, J., Henning, P.H., Hogg, G.G., Knight, J., Powell, H. & Redmond, D. (2001) Nationwide study of haemolytic uraemic syndrome: clinical, microbiological, and epidemiological features. *Archives of Disease in Childhood*, **85,** 125–131.

Fong, J.S.C. & Kaplan, B.S. (1982) Impairment of platelet aggregation in hemolytic uremic syndrome: evidence for platelet ''exhaustion''. *Blood*, **3,** 564–570.

Furlan, M., Robles, R., Galbusera, M., Remuzzi, G., Kyrle, P.A., Brenner, B., Krause, M., Scharrer, I., Aumann, V., Mittler, U., Solenthaler, M. & Lammle, B. (1998) Von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. *New England Journal of Medicine*, **339,** 1578–1584.

George, J.N. (2006) Thrombotic thrombocytopenic purpura. *New England Journal of Medicine*, **354,** 1927–1935.

George, J.N., Vesely, S.K. & Terrell, D.R. (2004) The Oklahoma thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) registry: a community perspective of patients with clinically diagnosed TTP-HUS. *Seminars in Hematology*, **41,** 60–67.

Gerber, A., Karch, H., Allerberger, F., Verweyen, H.M. & Zimmerhackl, L.B. (2002) 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. *Journal of Infectious Diseases*, **186,** 493–500.

Gianviti, A., Rosmini, F., Caprioli, A., Corona, R., Matteucci, M.C., Principato, F., Luzzi, I. & Rizzoni, G. (1994) Haemolytic-uraemic syndrome in childhood: surveillance and case-control studies in Italy. *Pediatric Nephrology*, **8,** 705–709.

Haus-Cheymol, R., Espie, E., Che, D., Vaillant, V., DeValk, H. & Desenclos, J.C. (2006) Association between indicators of cattle density and incidence of paediatric haemolytic-uraemic syndrome (HUS) in children under 15 years of age in France between 1996 and 2001: an ecological study. *Epidemiology and Infection*, **134,** 712–718.

Howard, M.A., Williams, L.A., Terrell, D.R., Duvall, D., Vesely, S.K. & George, J.N. (2006) Complications of plasma exchange in patients treated for clinically suspected thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. III. An additional study of 57 consecutive patients, 2002–2005. *Transfusion*, **46,** 154–156.

Jernigan, S.M. & Waldo, F.B. (1994) Racial incidence of hemolytic uremic syndrome. *Pediatric Nephrology*, **8,** 545–547.

Johnson, K.K., Duvall, D., Smith, J.W., Gilcher, R.O., Terrell, D.R., Vesely, S.K. & George, J.N. (2007) The Oklahoma Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome Registry: a community service. *Journal of the Oklahoma State Medical Association*, **100,** 273–278.

Karmali, M.A., Steele, B.T., Petric, M. & Lim, C. (1983) Sporadic cases of haemolytic-uraemic syndrome associated with faecal cytotoxin and cytotoxin-producing Escherichia coli in stools. *Lancet*, **1,** 619–620.

Karmali, M.A., Petric, M., Lim, C., Fleming, P.C., Arbus, G.S. & Lior, H. (1985) The association between idiopathic hemolytic uremic syndrome and infection by verotoxin-producing *Escherichia coli*. *Journal of Infectious Diseases*, **151,** 775–782.

Karpac, C.A., Lee, A., Kunnel, B.S., Bamgbola, O.F., Vesely, S.K. & George, J.N. (2007) Endemic *Escherichia coli* O157:H7 infections and hemolytic-uremic syndrome in Oklahoma, 2002–2005. *Journal of the Oklahoma State Medical Association*, **100,** 429–433.

Kinney, J.S., Gross, T.P., Porter, C.C., Rogers, M.F., Schonberger, L.B. & Hurwitz, E.S. (1988) Hemolytic-uremic syndrome: a population-based study in Washington, DC and Baltimore, Maryland. *American Journal of Public Health*, **78,** 64–65.

Kojouri, K., Vesely, S.K. & George, J.N. (2001) Quinine-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: frequency, clinical features, and long-term outcomes. *Annals of Internal Medicine*, **135,** 1047–1051.

Lingwood, C.A. (1994) Verotoxin-binding in human renal sections. *Nephron*, **66,** 21–28.

Lopez, E.L., Diaz, M., Grinstein, S., Devoto, S., Mendilaharzu, F., Murray, B.E., Ashkenazi, S., Rubeglio, E., Woloj, M., Vasquez, M., Turco, M., Pickering, L.K. & Cleary, T.G. (1989) Hemolytic uremic syndrome and diarrhea in Argentine children: the role of Shiga-like toxins. *Journal of Infectious Diseases*, **160,** 469–475.

Lynn, R.M., O'Brien, S.J., Taylor, C.M., Adak, G.K., Chart, H., Cheasty, T., Coai, J.E., Gillespie, L.A., Locking, M.E., Reilly, W.J., Smith, H.R., Waters, A. & Willshaw, G.A. (2005) Childhood hemolytic uremic syndrome, United Kingdom and Ireland. *Emerging Infectious Diseases*, **11,** 590–596.

Maki, D.G. (2006) Don't eat the spinach - controlling foodborne infectious disease. *New England Journal of Medicine*, **355,** 1952–1955.

Mannucci, P.M., Canciani, M.T., Forza, I., Lussana, F., Lattuada, A. & Rossi, E. (2001) Changes in health and disease of the metalloprotease that cleaves von Willebrand factor. *Blood*, **98,** 2730–2735.

Martin, D.L., MacDonald, K.L., White, K.E., Soler, J.T. & Osterholm, M.T. (1990) The epidemiology and clinical aspects of the hemolytic uremic syndrome in Minnesota. *New England Journal of Medicine*, **323,** 1161–1167.

Mead, P.S. & Griffin, P.M. (1998) *Escherichia coli* O157:H7. *Lancet*, **352,** 1207–1212.

Milford, D.V., Taylor, C.M., Guttridge, B., Hall, S.M., Rowe, B. & Kleanthous, H. (1990) Haemolytic uraemic syndromes in the British Isles 1985-8: association with Verocytotoxin producing Escherichia coli. Part 1: clinical and epidemiological aspects. *Archives of Disease in Childhood*, **65,** 716–721.

Nevard, C.H.F., Jurd, K.M., Lane, D.A., Philippou, H., Haycock, G.B. & Hunt, B.J. (1997) Activation of coagulation and fibrinolysis in childhood diarrhoea-associated haemolytic uraemic syndrome. *Thrombosis and Haemostasis*, **78,** 1450–1455.

Novillo, A.A., Voyer, L.E., Cravioto, R., Freire, M.C., Castano, G., Wainstein, R. & Binztein, N. (1988) Haemolytic uraemic syndrome associated with faecal cytotoxin and verotoxin neutralizing antibodies. *Pediatric Nephrology*, **2,** 288–291.

Oakes, R.S., Siegler, R.L., McReynolds, M.A., Pysher, T. & Pavia, A.T. (2006) Predictors of fatality in postdiarrheal hemolytic uremic syndrome. *Pediatrics*, **117,** 1656–1662.

Pai, C.H., Gordon, R., Sims, H.V. & Bryan, L.E. (1984) Sporadic cases of hemorrhagic colitis associated with *Escherichia coli* 0157:H7. *Annals of Internal Medicine*, **101,** 738–742.

Raghupathy, P., Date, A., Shastry, J.C., Sudarsanam, A. & Jadhav, M. (1978) Haemolytic-uraemic syndrome complicating shigella dysentery in south Indian children. *British Medical Journal*, **1,** 1518–1521.

Reiss, G., Kunz, P., Koin, D. & Keeffe, E.B. (2006) *Escherichia coli* O157:H7 infection in nursing homes: review of literature and report of recent outbreak. *Journal of the American Geriatrics Society*, **54,** 680–684.

Remis, R.S., MacDonald, K.L., Riley, L.W., Puhr, N.D., Wells, J.G., Davis, B.R., Blake, P.A. & Cohen, M.L. (1984) Sporadic cases of hemorrhagic colitis associated with *Escherichia coli* O157:H7. *Annals of Internal Medicine*, **101,** 624–626.

Richardson, M.W., Allen, G.A. & Monahan, P.E. (2002) Thrombosis in children: current perspective and distinct challenges. *Thrombosis and Haemostasis*, **88,** 900–911.

Rogers, M.F., Rutherford, G.W., Alexander, S.R., DiLiberti, J.H., Foster, L., Schonberger, L.B. & Hurwitz, E.S. (1986) A population-based study of hemolytic-uremic syndrome in Oregon, 1979-1982. *American Journal of Epidemiology*, **123,** 137–142.

Rowe, P.C., Orrbine, E., Wells, G.A. & McLaine, P.N. (1991) Epidemiology of hemolytic-uremic syndrome in Canadian children from 1986 to 1988. *Journal of Pediatrics*, **119,** 218–224.

Rowe, P.C., Orrbine, E., Lior, H., Wells, G.A. & McLaine, P.N. (1993) A prospective study of exposure to verotoxin-producing *Escherichia coli* among Canadian children with haemolytic uraemic syndrome. *Epidemiology and Infection*, **110,** 1–7.

Rowe, P.C., Orrbine, E., Lior, H., Wells, G.A., Yetisir, E., Clulow, M., McLaine, P.N. & Invest Canadian Pediat Kidney Dis, (1998) Risk of hemolytic uremic syndrome after sporadic *Escherichia coli* O157:H7 infection: results of a Canadian collaborative study. *Journal of Pediatrics*, **132,** 777–782.

Roy, V., Rizvi, M.A., Vesely, S.K. & George, J.N. (2001) Thrombotic thrombocytopenic purpura-like syndromes following bone marrow transplantation: an analysis of associated conditions and clinical outcomes. *Bone Marrow Transplantation*, **27,** 641–646.

Sheth, K.J., Swick, H.M. & Haworth, N. (1986) Neurological involvement in hemolytic-uremic syndrome. *Annals of Neurology*, **19,** 90–93.

Siegler, R.L., Pavia, A.T. & Cook, J.B. (1997) Hemolytic-uremic syndrome in adolescents. *Archives of Pediatrics & Adolescent Medicine*, **151,** 165–169.

Slutsker, L., Ries, A.A., Greene, K.D., Wells, J.G., Hutwagner, L. & Griffin, P.M. (1997) *Escherichia coli* O157:H7 diarrhea in the United States: clinical and epidemiologic features. *Annals of Internal Medicine*, **126,** 505–513.

Tarr, P.I., Neill, M.A., Allen, J., Siccardi, C.J., Watkins, S.L. & Hickman, R.O. (1989) The increasing incidence of the hemolytic-uremic syndrome in King County, Washington: lack of evidence for ascertainment bias. *American Journal of Epidemiology*, **129,** 582–586.

Tarr, P.I., Gordon, C.A. & Chandler, W.L. (2005) Shiga-toxin-producing *Escherichia coli* and haemolytic uraemic syndrome. *Lancet*, **365,** 1073–1086.

Terrell, D.R., Williams, L.A., Vesely, S.K., Lammle, B., Kremer Hovinga, J.A. & George, J.N. (2005) The incidence of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: all patients, idiopathic patients, and patients with severe ADAMTS13 deficiency. *Journal of Thrombosis and Haemostasis*, **3,** 1432–1436.

Trachtman, H., Cnaan, A., Christen, E., Gibbs, K., Zhao, S., Acheson, D.W.K., Weiss, R., Kaskel, F.J., Spitzer, A. & Hirschman, G.H. (2003) Effect of an oral Shiga toxin-binding agent on diarrhea-associated hemolytic uremic syndrome in children. A randomized controlled trial. *Journal of the American Medical Association*, **290,** 1337–1344.

U.S. Census (2000) Summary File 1, P12. Sex By Age (Total Population). http://factfinder.census.gov/servlet/DTSubjectShowTablesServlet?_ts=223209569900 (accessed 10 March 2008).

Van de Kar, N.C.A.J., Sauerwein, R.W., Demacker, P.N.M., Grau, G.E., Van Hinsbergh, V.W.M. & Monnens, L.A.H. (1995) Plasma cytokine levels in hemolytic uremic syndrome. *Nephron*, **71,** 309–313.

Van de Kar, N., Roelofs, H., Muytjens, H.L., Tolboom, J., Roth, B., Proesmans, W., Reitsma-Bierens, W.C., Wolff, E.D., Karmali, M.A., Chart, H. & Monnens, L.A. (1996) Verocytotoxin-producing *Escherichia coli* infection in hemolytic uremic syndrome in part of Western Europe. *European Journal of Pediatrics*, **155,** 592–595.

Vesely, S.K., George, J.N., Lämmle, B., Studt, J.-D., Alberio, L., El-Harake, M.A. & Raskob, G.E. (2003) ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. *Blood*, **101,** 60–68.

Wong, C.S., Jelacic, S., Habeeb, R.L., Watkins, S.L. & Tarr, P.I. (2000) The risk of the hemolytic-uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. *New England Journal of Medicine*, **342,** 1930–1936.

