Validation of treatment strategies for enterohaemorrhagic *Escherichia coli* O104:H4 induced haemolytic uraemic syndrome: case-control study

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Objective To evaluate the effect of different treatment strategies on enterohaemorrhagic *Escherichia coli* O104:H4 induced haemolytic uraemic syndrome.

Design Multicentre retrospective case-control study.

Setting 23 hospitals in northern Germany.

Participants 298 adults with enterohaemorrhagic *E coli* induced haemolytic uraemic syndrome.

Main outcome measures Dialysis, seizures, mechanical ventilation, abdominal surgery owing to perforation of the bowel or bowel necrosis, and death.

Results 160 of the 298 patients (54%) temporarily required dialysis, with only three needing treatment long term. 37 patients (12%) had seizures, 54 (18%) required mechanical ventilation, and 12 (4%) died. No clear benefit was found from use of plasmapheresis or plasmapheresis with glucocorticoids. 67 of the patients were treated with eculizumab, a monoclonal antibody directed against the complement cascade. No short term benefit was detected that could be attributed to this treatment. 52 patients in one centre that used a strategy of aggressive treatment with combined antibiotics had fewer seizures (2% v 15%, $P=0.03$), fewer deaths (0% v 5%, $p=0.029$), required no abdominal surgery, and excreted *E coli* for a shorter duration.

Conclusions Enterohaemorrhagic *E coli* induced haemolytic uraemic syndrome is a severe self limiting acute condition. Our findings question the benefit of eculizumab and of plasmapheresis with or without glucocorticoids. Patients with established haemolytic uraemic syndrome seemed to benefit from antibiotic treatment and this should be investigated in a controlled trial.

Introduction

The recent outbreak of enterohaemorrhagic *Escherichia coli* associated haemolytic uraemic syndrome in northern Germany, 2011, the largest to date, underscored the threat to public health of such pathogens.¹ Diarrhoea associated haemolytic uraemic syndrome is characterised by the triad of microangiopathic haemolytic anaemia, thrombocytopenia, and acute kidney injury. In the outbreak in Germany, 855 of 3842 people infected with enterohaemorrhagic *E coli* developed haemolytic uraemic syndrome.² Adults, especially healthy middle aged women, were predominantly affected (90%), probably because of the source of the infection (fenu-greek sprouts). The second largest outbreak was considerably smaller and occurred in Scotland, when 34 of 512 (279 confirmed) people infected with enterohaemorrhagic *E coli*

WHAT IS ALREADY KNOWN ON THIS TOPIC

Recommendations for the treatment of patients with haemolytic uraemic syndrome are based on small cases series and include plasmapheresis with or without glucocorticoids
Antibiotics are believed to be harmful and to induce the development of haemolytic uraemic syndrome and are therefore withheld in patients with enterohaemorrhagic *Escherichia coli* related infection
In few reported cases eculizumab was helpful in the treatment of patients with shiga toxin induced haemolytic uraemic syndrome

WHAT THIS STUDY ADDS

No benefit of plasmapheresis or glucocorticoid treatment was found for patients with enterohaemorrhagic *E coli* O104:H4 induced haemolytic uraemic syndrome, and prolonged treatment may even do more harm than good
An aggressive antibiotic treatment strategy was not harmful in patients with established haemolytic uraemic syndrome and might even be beneficial
No benefit of eculizumab could be found when short term outcome was compared with a patient group with similar severity of disease

O157:H7 developed haemolytic uraemic syndrome; 28 were adults.^{3,4} The 22% incidence rate of haemolytic uraemic syndrome was higher than the 1-15% typically reported in other outbreaks of enterohaemorrhagic *E. coli*.^{3,5,6} This is probably because the outbreak in Germany was caused by an unusual strain: enterohaemorrhagic *E. coli* O104:H4. Further analysis by several teams, including use of third generation sequencing methods, revealed that the strain carried properties of a shiga 2 toxin producing *E. coli* and an enteroaggregative *E. coli* as well as multidrug resistant plasmids.⁷⁻¹⁰ This new combination of genes seemed to enhance the occurrence of haemolytic uraemic syndrome in comparison with the O157:H7 strain encountered in most previous outbreaks.^{8,11} Importantly, data gathered by German paediatricians suggested that the clinical course and outcome of the O104:H4 induced disease was similar to that of infections with O157:H7.¹² Data generated from the 2011 outbreak could therefore add valuable information to the treatment of patients with haemolytic uraemic syndrome.

Over the years different treatments comprising plasmapheresis, glucocorticoids, antibiotics, and eculizumab have been developed to treat enterohaemorrhagic *E. coli* associated haemolytic uraemic syndrome.^{5,13,14} Owing to the sporadic nature of the disease, most of the published studies examining the efficacy of treatments only analysed small groups and lacked a comparison group. Currently used active interventions are therefore not based on formal evidence. The large number of patients affected and differences in treatment strategies between the hospitals enabled us to compare and analyse treatment options in an exploratory fashion. We were mainly interested in the outcomes after treatment with plasmapheresis, glucocorticoids, antibiotics, and eculizumab (for terminal complement blockade). In some hospitals patients received no more than 3-5 sessions of plasmapheresis (limited plasmapheresis) followed by alternative treatments if required. In contrast, in most hospitals plasmapheresis was continued until platelet counts increased

to at least 100/nL. Furthermore, several hospitals did not use glucocorticoids, whereas the others administered at least 50 mg with plasmapheresis. Twenty two hospitals followed the recommendation not to use antibiotics and administered them only if medically required. One hospital, however, used double or triple antibiotic treatment with meropenem, ciprofloxacin, and rifaximin with the aim of speedy eradication. Eculizumab is a monoclonal antibody directed against the complement protein C5. It has been successfully used to treat patients with paroxysmal nocturnal haemoglobinuria¹⁵ and atypical haemolytic uraemic syndrome.¹⁶ In May 2011, just at the beginning of the Germany outbreak, it was reported that eculizumab seemed to be beneficial in three infants with severe shiga toxin associated haemolytic uraemic syndrome.¹⁴ In these cases eculizumab was given to block dysregulated complement activation, which is thought to play a part in the development of haemolytic uraemic syndrome.^{17,18} In light of this report, eculizumab was extensively used (>300 patients) as a therapeutic option during the Germany outbreak. The recommended treatment schedule was 900 mg at days 0, 7, 14, and 21, and 1200 mg at days 28, 42, and 56. Additionally, azithromycin was prescribed for 14 days to prevent meningococcal infections.

We evaluated the effectiveness of these various therapeutic strategies in 298 patients with enterohaemorrhagic *E. coli* associated haemolytic uraemic syndrome (35% of the population affected). These patients were similar for age, sex distribution, and mortality as the 855 patients with the disease reported to the Robert Koch Institute² and in line with data collected by the relevant German registry (JT Kielstein, personal communication, 2012).

Methods

During the first three weeks of the outbreak of enterohaemorrhagic *E. coli* associated haemolytic uraemic syndrome in northern Germany a group of clinicians involved in the clinical care of patients with this condition assembled to learn as

Fig 1 | Therapeutic strategies used by hospitals during outbreak of enterohaemorrhagic *Escherichia coli* associated haemolytic uraemic syndrome in northern Germany, 2011. Percentage of patients available for present analysis are in brackets

Table 1 Characteristics of patients within participating centres. Usage of eculizumab is shown to highlight how participation in the industry sponsored trial of the drug affected the number of patients available for analysis. Values are numbers (percentages) of participants

Participating centres	All patients			After exclusion of participants in sponsored trial										Mean minimum platelet count (nL)
	No with HUS	Ecuzumab treatment	Ecuzumab treatment	Patients in present analysis	Patient outcomes (% of study patients affected)						Days from start of diarrhoea to admission	Mean maximum LDH level (U/L)		
					Dialysis	Seizures	Death	Plasmapheresis	Ventilation					
1	55	35 (64)	1 (3)	31 (100)	21 (38)	3 (14)	1 (5)	1 (5)	18 (85.7)	2 (10)	4.1	764.7	58.7	
2	52	31 (60)	31 (100)	52 (100)	33 (64)	1 (2)	0 (0)	47 (90)	9 (17)	5.6	1267.9	44.4		
3	48	25 (52)	2 (8)	25 (52)	12 (48)	3 (12)	1 (4.0)	19 (76)	3 (12)	2.8	1151.8	39.6		
4	33	7 (21)	7 (100)	33 (100)	17 (52)	6 (18)	2 (6)	31 (94)	14 (42)	2.8	1330.7	43.6		
5	31	9 (29)	0 (0)	22 (71)	9 (41)	0 (0)	1 (5)	20 (91)	3 (14)	3.7	1046.2	34.8		
6	24	15 (63)	15 (100)	24 (100)	13 (54)	5 (21)	2 (8)	17 (71)	1 (4)	3.1	1388.7	40.5		
7	22	5 (23)	0 (0)	17 (77)	7 (41)	3 (18)	2 (12)	12 (71)	3 (18)	3.2	1329.8	51.3		
8	17	8 (47)	0 (0)	10 (59)	6 (60)	0 (0)	1 (10)	8 (80)	1 (10)	3.4	1227	44		
9	15	5 (33)	0 (0)	10 (67)	5 (50)	1 (10)	0 (0)	10 (100)	1 (10)	4.4	1204.7	49.1		
10	15	2 (13)	2 (100)	15 (100)	10 (67)	7 (47)	0 (0)	12 (80)	3 (20)	3.6	1032.5	89.8		
11	14	8 (57)	0 (0)	6 (43)	0 (0)	0 (0)	0 (0)	6 (100)	0 (0)	5.7	544.2	62.2		
12	13	0 (0)	NA	13 (100)	6 (46)	4 (31)	1 (8)	9 (69)	3 (23)	2.8	1024.8	54.8		
13	8	1 (13)	0 (0)	7 (88)	6 (86)	1 (14)	0 (0)	6 (86)	1 (14)	3.2	801	65.6		
14	7	4 (57)	4 (100)	7 (100)	6 (86)	2 (29)	0 (0)	6 (86)	1 (14)	5.1	1142.1	42		
15	6	1 (17)	1 (100)	6 (100)	6 (100)	0 (0)	0 (0)	6 (100)	1 (17)	1.7	912.2	36.3		
16	6	3 (50)	3 (100)	6 (100)	5 (83)	4 (67)	0 (0)	6 (100)	6 (100)	2.3	1294.8	34.5		
17	6	3 (50)	0 (0)	3 (50)	3 (100)	0 (0)	0 (0)	3 (100)	0 (0)	5.3	1282.3	41		
18	6	1 (17)	0 (0)	5 (83)	2 (40)	0 (0)	0 (0)	3 (60)	1 (20)	5.6	943.5	66.8		
19	5	1 (20)	1 (100)	5 (100)	5 (100)	1 (20)	1 (20)	5 (100)	1 (20)	3	1059	32.8		
20	5	0 (0)	NA	5 (100)	1 (20)	1 (20)	0 (0)	5 (100)	0 (0)	6	594.6	45.6		
21	3	0 (0)	NA	3 (100)	3 (100)	0 (0)	0 (0)	3 (100)	0 (0)	4.3	1973.7	29.3		
22	3	1 (33)	0 (0)	2 (67)	2 (100)	0 (0)	0 (0)	2 (100)	0 (0)	4	1709	47		
23	1	0 (0)	NA	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	3	1127	49		
Total	395	165 (42)	—	298 (75)	—	—	—	—	—	—	—	—	—	

HUS=haemolytic uraemic syndrome; LDH=lactate dehydrogenase; NA=not applicable.

Fig 2 Onset of symptoms and complications in 298 patients, laboratory results, and diagnosis of haemolytic uraemic syndrome

much as possible from the outbreak as it evolved. The group initially comprised nephrologists, gastroenterologists, neurologists, and others from three university hospitals (Hanover, Lübeck, and Kiel). Other hospitals then joined. The participating centres prospectively agreed on the data to be collected. These data were entered into a database that was available to all members of the consortium to ensure correct data entry. As the outbreak evolved, more centres joined the consortium. A dedicated study team used a standardised

case history form to collect the data retrospectively from patients' charts. To minimise the number of mistakes, two study team members in most cases entered the data on each patient. In 20 hospitals it was possible to export all laboratory values into an Excel file, significantly reducing the number of possible mistakes. In the other centres the laboratory values were entered manually into the database. We carried out several checks of the database and we reviewed the patients' charts for a second time if data seemed to be incorrect or important data were missing.

Patient population

This report is on the patients treated in these centres who fulfilled the criteria for haemolytic uraemic syndrome. Some of the centres were participating in an industry sponsored open label trial of eculizumab in patients with haemolytic uraemic syndrome. These centres had signed a non-disclosure agreement with the manufacturer of eculizumab (Soliris; Alexion, Cheshire, CT). We included in the present study those patients who received eculizumab outside of the trial.

The consortium has treated a total of 395 adults with enterohaemorrhagic *E coli* associated haemolytic uraemic syndrome at 23 centres: six university hospitals and 17 district hospitals. Ninety seven patients receiving eculizumab were excluded from analysis as they were part of the industry sponsored trial (tables 1 and 2, fig 1). The remaining 298 (75%) patients were included in the present analysis. Part of the clinical data on 33 of those patients has been published previously.^{19 20}

Definition of haemolytic uraemic syndrome

We defined haemolytic uraemic syndrome as a diagnosis of enterohaemorrhagic *E coli* associated haemolytic uraemic syndrome between May and July 2011. Patients with stools positive for enterohaemorrhagic *E coli* or shiga toxin 2 or a history of bloody diarrhoea needed to fulfill the following three diagnostic criteria for haemolytic uraemic syndrome: platelet count $<150 \times 10^9/L$, haemolytic anaemia with haemoglobin level less than lower limit of normal range, and serum creatinine level greater than upper limit of normal range. Overall, 283 out of the 298 patients fulfilled these criteria. The remaining 15 patients did not fulfill the criterion for increased creatinine levels but haemolytic uraemic syndrome was diagnosed by the treating doctor and eight of the patients underwent plasmapheresis. We included these patients in our analysis.

Outcome variables

We chose the following as outcome variables as they were the most severe complications observed during the outbreak: requirement for dialysis, mechanical ventilation, abdominal surgery due to perforation or bowel necrosis, documented seizures, and death.

Statistical analysis

As treatment strategies varied between the centres (fig 1 and table 2) we compared the outcomes of the different approaches. The analysis was done using R, Prism5, or SPSS. We compared the two treatment groups using an unpaired two sided Student's *t* test and categorical variables using a χ^2 test. Multivariate analysis was done by logistic regression. The independent variables and covariables

Table 2 | Effect of eculizumab trial on number of patients available to analyse from hospitals using different treatment strategies. Values are numbers (percentages) of patients unless stated otherwise

Variables	Eculizumab trial		Total No
	Participants	Non-participants	
Patients	97 (25)	298 (75)	395
Pre-emptive antibiotics	0 (0)	52 (100)	52
Limited plasmapheresis*	56 (51)	54 (49)	110
Platelet guided plasmapheresis	38 (16)	199 (84)	237
Plasmapheresis with glucocorticoids	57 (27)	174 (75)	231

*3-5 sessions.

Table 3 | Baseline characteristics of 298 patients at time haemolytic uraemic syndrome was diagnosed, in relation to receipt of plasmapheresis and antibiotic treatment. Values are means (standard deviations) unless stated otherwise

Characteristics	All patients (n=298)	No plasmapheresis (n=47)	Plasmapheresis (n=251)	No pre-emptive antibiotics (n=246)	Pre-emptive antibiotics (n=52)
No (%) women	212 (71)	34 (72)	178 (71)	170 (69)	42 (81)
Age (years)	47.7 (18.4)	51.8 (18.9)	46.7 (18.3)	46.6 (18.6)	51.5 (17.2)
Temperature (°C)	37.2 (4.8)	36.9 (0.6)	37.3 (5.2)	37.3 (5.4)	36.8 (0.6)
Duration of diarrhoea (days)	6.3 (4.5)	7 (4.2)	6 (3)	6.2 (3.2)	5.9 (3.1)
Laboratory data:					
Lactate dehydrogenase (U/L)	932.1 (575.9)	580.8 (410.2)	980 (574.7)**	904.4 (575.6)	977.4 (548.3)
Platelet count (/nL)	70.6 (46.0)	96.5 (47.6)	66.5 (43.3)**	71.3 (42.2)	70.2 (57.5)
Haemoglobin (g/L)	113 (20)	118 (13)	113 (20)	114 (20)	113 (18)
Creatinine (μmol/L)	202.9 (157.9)	146.4 (138.4)	207.9 (155.8)*	195.3 (157.2)	211.8 (142.7)
Leucocytes (×10 ⁹ /L)	13 (7.3)	10.8 (5.2)	13.4 (7.5)*	13.1 (7.4)	12.7 (6.8)
No (%) with comorbidities:					
Hypertension	61 (21)	8 (17)	53 (21)	51 (21)	10 (19)
Chronic renal insufficiency	5 (2)	1 (2)	4 (2)	3 (1)	2 (4)
Diabetes mellitus	14 (5)	2 (4)	12 (5)	12 (5)	2 (4)
Neurological or psychiatric disease	21 (7)	1 (2)	20 (8)	8 (3)	13 (25)**
Coronary heart disease	13 (4)	1 (2)	12 (5)	11 (5)	2 (4)

*P<0.05; **P<0.01 versus respective control groups.

(platelet count, creatinine level, leucocyte count, age, and sex) were defined a priori, and in univariate analysis all of these variables were predictors for a worse outcome. We also used a linear model to analyse if differences in the mean laboratory values over time differed between the treatment strategies. We did not adjust for multiple testing as the intention of our analysis was exploratory. Data are presented as means (standard deviations) and medians (ranges).

Results

Tables 3 and 4 summarise the characteristics of the patients at the time haemolytic uraemic syndrome was diagnosed. Overall, 212 (71%) were women and the median age was 45.5 (range 18-86) years. In total, 99% of cases had diarrhoea that usually turned sanguineous within one day (fig 2). The earliest date diarrhoea started was 10 May 2011 and the latest 19 June, with 75% of cases occurring before 24 May. Diarrhoea lasted a mean 9.3 (SD 6.7) days (median 6.0 days). Most patients were admitted

Thick lines represent means
Thin lines represent standard deviations

Fig 3 | Effect of plasmapheresis on platelet counts and levels of lactate dehydrogenase, creatinine, and haemoglobin

to hospital within seven days after the onset of diarrhoea (fig 2), with a mean of 4.1 (SD 4.4) days (median 3.0 days). The mean length of hospital stay was 22.6 (SD 14.3) days (median 19 days). A formal diagnosis of haemolytic uraemic syndrome was established after a median of 6 (range 4-8) days after the onset of diarrhoea (fig 2).

Haemolysis and thrombocytopenia

At the onset of diarrhoea the levels of lactate dehydrogenase were slightly raised and platelet counts were in normal range but both variables quickly reached parallel levels that were indicative of disease, peaking at days 6-8 (fig 2). On average the platelet counts normalised within one week. In contrast, lactate dehydrogenase levels declined only slowly and remained out of normal range for several weeks. At diarrhoea onset, the results for haemoglobin levels were still within normal range but dropped progressively and reached a nadir at day 12 (fig 2). One hundred and sixty seven (56%) patients underwent transfusion, with a mean 4.9 (SD 3.6) blood units used (fig 2).

Acute kidney injury

A sharp increase in serum creatinine levels was noted during the first days of diarrhoea onset, and by day 8 the mean values had reached peak levels (fig 2). One hundred and sixty (54%) patients required renal replacement therapy and in 50% of these treatment was started within the first eight days (fig 2). Dialysis was required for a mean 10.3 (SD 11.5) days, with a mean 7.7 (SD 8.1) sessions provided. In most patients renal function normalised within 4-6 weeks. Long term (>6 months) data are available for 238 patients. At discharge 13 of these patients were receiving dialysis; only three required long term renal replacement therapy.

Table 4 | Baseline characteristics at day of first plasmapheresis in 251 patients treated in centres that used platelet guided plasmapheresis (until platelet counts were >100/nL), re-evaluated plasmapheresis after 3-5 sessions (limited), or used glucocorticoids with plasmapheresis. Patients receiving eculizumab were compared with a matched control group with similar severity of haemolytic uraemic syndrome. Values are means (standard deviations) unless stated otherwise

Characteristics	Plasmapheresis strategy				No eculizumab treatment (n=65)	Eculizumab treatment (n=67)
	Limited (n=54)	Platelet guided (n=197)	Without glucocorticoids (n=77)	With glucocorticoids (n=174)		
No (%) women	37 (69)	141 (72)	49 (64)	129 (74)	43 (66)	56 (84)*
Age (years)	43.9 (19.2)	47.3 (18.1)	45.2 (18.1)	47.2 (18.3)	42.3 (17.7)	50.6 (18.3)*
Temperature (°C)	36.7 (1.8)	37.4 (5.7)	38.2 (9.7)	36.9 (0.5)	38.3 (10.5)	36.9 (0.6)
Duration of diarrhoea (days)	6.1 (3)	6 (3)	6.2 (2.6)	5.9 (3.2)	5.6 (2.9)	5.3 (2.8)
Laboratory data:						
Lactate dehydrogenase (U/L)	1036.7 (658.7)	960 (543.2)	759.2 (457.4)	1061.6 (593.3)**	1392.7 (573.8)	1160.2 (596.8)*
Platelet counts (/nL)	68.9 (50.1)	65.8 (40.9)	77.2 (46.1)	62.8 (41.8)*	47.5 (35.7)	57.6 (40.2)
Haemoglobin (g/L)	111 (21)	114 (20)	113 (22)	113 (20)	112 (24)	116 (17)
Creatinine (μmol/L)	202 (156.3)	209.9 (156)	159.5 (104)	224.4 (166.9)*	267.3 (196.8)	225.2 (139.6)
Leucocytes (×10 ⁹ /L)	14.6 (9.9)	13 (6.6)	13.4 (8.8)	13.4 (7.1)	14.3 (6.7)	14.1 (8)
No (%) with comorbidities:	18 (33.3)	77 (39.1)	26 (33.8)	69 (39.7)	24 (36.9)	31 (46.3)
Hypertension	11 (20.4)	42 (21.3)	18 (23.4)	35 (20.1)	14 (21.5)	13 (19.4)
Chronic renal insufficiency	1 (1.9)	3 (1.5)	1 (1.3)	3 (1.7)	1 (1.5)	0 (0)
Diabetes mellitus	1 (1.9)	11 (5.6)	3 (3.9)	9 (5.2)	6 (9.2)	1 (1.5)
Neurological or psychiatric disease	2 (3.7)	18 (9.1)	3 (3.9)	17 (9.8)	1 (1.5)*	11 (16.4)
Coronary heart disease	2 (3.7)	10 (5.1)	3 (3.9)	9 (5.2)	3 (4.6)	2 (3)

*P<0.05; **P<0.01 versus respective control groups.

Thick lines represent means
Thin lines represent standard deviations

Fig 4 | Clinical data in patients with enterohaemorrhagic *Escherichia coli* induced haemolytic uraemia syndrome treated with or without limited plasmapheresis (3-5 sessions) versus platelet guided plasmapheresis, with plasmapheresis with or without glucocorticoid therapy, and with or without antibiotics

Table 5 | Complications and outcomes in patients treated with or without plasmapheresis stratified by treatment strategies and in patients treated with eculizumab compared with control group with similar severity of haemolytic uraemic syndrome. Values are numbers (percentages) of patients unless stated otherwise

Outcomes	None† (n=47)	Plasmapheresis (n=251)†	Plasmapheresis strategy						Antibiotics (n=52)	Odds ratio (95% CI)	No eculizumab (n=65)	Eculizumab (n=67)	Odds ratio (95% CI)
			Limited‡ (n=54)	Platelet guided§ (n=197)	Without glucocorticoids# (n=77)	With glucocorticoids# (n=174)	Odds ratio (95% CI)	No antibiotics (n=246)					
Dialysis	6 (13)	154 (61)	8 (15)	64 (33)	19 (24.7)	53 (30.5)	3.30 (1.40 to 7.94)**	127 (51.6)	33 (63.5)	0.54 (0.18 to 1.63)	53 (81.5)	51 (76.1)	1.00 (0.22 to 4.60)
Ventilation	4 (9)	50 (20)	2 (4)	31 (15.7)	14 (18.2)	19 (10.9)	12.05 (1.21 to 120)*	45 (18.3)	9 (17.3)	0.38 (0.10 to 1.37)	27 (41.5)	23 (34.3)	0.58 (0.15 to 2.23)
Seizures	3 (6)	34 (14)	5 (9)	19 (9.6)	9 (11.7)	15 (8.6)	1.70 (0.37 to 7.77)	36 (14.6)	1 (1.9)	0.03 (0.003 to 0.29)**	19 (29.2)	16 (23.9)	2.28 (0.62 to 8.47)
Death	4 (9)	8 (3)	3 (6)	5 (2.5)	3 (3.9)	5 (2.9)	0.10 (0.004 to 2.77)	12 (4.9)	0 (0)	Not estimable§	5 (7.7)	3 (4.5)	0.28 (0.009 to 8.83)

Multivariate logistic regression analyses were done with adjustments for creatinine, leucocytes, and platelets at time of haemolytic uraemic syndrome diagnosis and age and sex as well as adjustments for three of four treatment strategies (platelet guided plasmapheresis, plasmapheresis with glucocorticoids, early antibiotics, or eculizumab) depending on analysed treatment variables.

* $P<0.05$, ** $P<0.01$, *** $P<0.001$ versus respective controls.

†Events after first plasmapheresis.

‡Analyses restricted to patients receiving plasmapheresis.

§Owing to 0% in one group.

Neurological and other complications

One hundred and forty three (48%) patients had neurological symptoms (fig 2). Symptoms included cerebellar dysfunction, myoclonus, memory disorders, focal neurological deficits, and seizures.

Overall, 156 (52%) of the patients were treated in the intensive care unit and 54 (18%) required mechanical ventilation a mean 9.1 (SD 5.3) days after disease onset (fig 2). Patients were ventilated for a mean 11.4 (SD 10.1) days (median 8 (range 6–13) days). Twelve (4%) patients died (mean age 68.7 (range 24–86, fig 2). More than 50% of the deaths were due to infective complications. Laparotomy was required in seven patients who developed an acute abdomen due to perforation or severe colitis, often within the first days of the disease.

Effect of plasmapheresis

Plasmapheresis was carried out in 251 (84%) patients. Treatment was started after a mean 6.8 (SD 3.0) days of disease onset (table 3 and fig 2). The treatment was continued for a mean 7.6 (SD 7.4) days (median 5 (range 3–9) days) and the patients received a mean 7.3 (SD 6.7) sessions (median 5 (range 4–9) sessions). Mean lactate dehydrogenase levels declined and platelet counts increased after the start of plasmapheresis (fig 3). However, similar patterns for lactate dehydrogenase and creatinine levels were observed in 47 patients who did not undergo plasmapheresis (fig 4). These patients had a milder form of haemolytic uraemic syndrome (tables 3–6 and fig 4). Mortality seemed to be higher in the group that did not undergo plasmapheresis (table 4), but all four cases had complications due to infection that were unlikely to have been influenced by plasmapheresis. The cause of death in two patients was severe colitis with perforation of the bowel within the first three days after onset of diarrhoea. A third patient had severe colitis and refused invasive therapy. These three patients died within the first nine days after diarrhoea onset. A fourth patient (aged 83 years) recovered from the haemolytic uraemic episode but developed an aspiration pneumonia and died on day 38.

Three of the centres (total 54 patients) carried out limited plasmapheresis (3–5 sessions) and then re-evaluated the treatment, whereas the other 20 centres continued with plasmapheresis until the platelet count had increased to at least 100/nL (table 3). We therefore analysed whether a more intensive plasmapheresis regimen would change the main outcome variables. At the start of treatment the patient groups were well matched (table 3). Patients in the platelet guided arm required dialysis more often after the start of plasmapheresis than patients in the limited plasmapheresis arm (tables 5 and 6). Platelet counts and the levels of lactate dehydrogenase and creatinine were comparable (fig 4)

Effect of plasmapheresis associated glucocorticoid therapy

For plasmapheresis most of the centres used high dose (≥ 50 mg) prednisone (or prednisolone) as premedication before fresh frozen plasma was administered. However, seven centres (total 80 patients) did not administer glucocorticoids (table 4). No benefit of glucocorticoid treatment was observed and the time course suggested a delay in platelet recovery and normalisation of lactate

Fig 5 | Platelet counts and levels of lactate dehydrogenase, creatinine, and haemoglobin in 67 patients who were treated with eculizumab and 65 control patients with a similar severity of haemolytic uraemic syndrome

dehydrogenase levels (table 5 and fig 4). No significant differences could be detected using a linear model.

Effect of treatment with antibiotics

One university hospital administered a combination of at least two antibiotics. In particular, meropenem and ciprofloxacin were given intravenously in dosages adapted to glomerular filtration rates to prevent complications such as intestinal damage and sepsis. Rifaximin 600 mg daily was given orally to patients on the intensive care unit. Both groups (with or without antibiotics) had comparable baseline variables at diagnosis of haemolytic uraemic syndrome (table 3). With antibiotic treatment the duration of enterohaemorrhagic *E coli* excretion in stools was significantly shortened, from a mean 22.6 (SD 11.3) days to 14.8 (10.6) days ($P<0.001$). The incidence of seizures was significantly ($P=0.03$) lower in the antibiotic treatment group (tables 3 and 6). Furthermore, death was lower (0% v 5.2%, $P=0.029$), the need for intestinal surgery was not significant (0 v 2.8%), and there were no signs of toxic shock (table 5).

Effect of treatment with eculizumab

In the present cohort 67 patients received eculizumab outside the industry sponsored trial (table 4), with treatment started a mean 10.2 (SD 4.6) days after the onset of diarrhoea and a mean total of 2700 mg administered. Twenty three (34%) of these 67 patients required ventilation, 51 (76%) required dialysis, and 16 (24%) had seizures (table 7). The severity of haemolytic uraemic syndrome was therefore worse than in the rest of the study population. Despite treatment with eculizumab, 27 (40%) patients needed further plasmapheresis (table 6). After the start of treatment seven patients (10%) required ventilation, 12 (18%) required dialysis, and four (6%) had seizures (table 6).

To analyse the therapeutic effect of eculizumab a con-

trol group with a similar severity of haemolytic uraemic syndrome was formed who did not receive eculizumab but did undergo plasmapheresis and fulfilled the following criteria: lactate dehydrogenase concentrations >700 U/L at diagnosis of haemolytic uraemic syndrome, with maximal concentrations >1500 U/L or seizure or ventilation or death. These criteria were fulfilled by 65 out of 184 patients who underwent plasmapheresis. These patients had similar baseline characteristics and rates of complications to the group treated with eculizumab (table 4). No significant difference was noted between the groups for platelet recovery and levels of lactate dehydrogenase, creatinine, or haemoglobin (fig 5). The rate of complications was also similar between the groups (tables 6 and 7).

Discussion

Current treatment recommendations for adults with haemolytic uraemic syndrome might need to be modified in light of the findings in this large cohort of patients from the outbreak of enterohaemorrhagic *Escherichia coli* associated haemolytic uraemic syndrome in northern German, 2011. Evidence of the benefits from plasmapheresis was not clear. Contrary to current notions, antibiotic treatment of established haemolytic uraemic syndrome is not harmful and might even improve the outcome.

Strengths and limitations of the study

The major strength of this study was the large number of patients and the extensive data available by database to describe the population. Another advantage was that not all the centres used the same treatment strategy. These differences allowed a retrospective analysis of treatment strategies. This non-randomised group assignment was also the major weakness of our study. Our comparisons involved imperfect controls and thus bias was introduced by indication. Such bias is obvious in the analysis of

Table 6 | Outcomes in 298 patients with haemolytic uraemic syndrome according to treatment strategies. Values are means (standard deviations) unless stated otherwise

Variables	All patients (n=298)	No plasmapheresis (n=47)	Plasmapheresis (n=251)	No pre-emptive antibiotics (n=246)	Pre-emptive antibiotics (n=52)
Plasmapheresis:					
No (%) treated	251 (84)	0 (0)	251 (100)	204 (83)	47 (90)
Day treatment started	6.8 (3)	NA	6.8 (3)	6.9 (2.7)	6.8 (4.2)
No of treatments	7.3 (6.7)	0 (0)	7.4 (6.7)	7.1 (6.8)	8.4 (6.3)
Eculizumab:					
No (%) treated	67 (23)	1 (2)	66 (26)	36 (15)	31 (60)***
Day of first dose	10.2 (4.6)	NA	NA	10.4 (5)	10.1 (4.3)
Total dose (mg)	2646 (1620)	2700 (0)	2601 (1627)	3225 (1290)	2497 (1680)
No (%) requiring further plasmapheresis after first dose	27 (40)	NA	27 (41)	12 (33)	15 (48)***
Day of last plasmapheresis after first eculizumab dose	16 (9.5)	NA	16 (9.5)	15.1 (10.7)	16.8 (8.6)
No of days in hospital	22.6 (14.3)	13.2 (8.6)	24.3 (14.4)***	22.4 (14.4)	23.6 (14)
No (%) requiring ventilation:					
Ventilated	54 (18)	4 (9)	50 (20)	45 (18)	9 (17)
After first plasmapheresis	33 (11)	0 (0)	33 (13)**	27 (11)	6 (12)
After first eculizumab dose	7 (2)	NA	7 (3)	4 (2)	3 (6)
Days ventilated	11.4 (10.9)	3.5 (3.5)	12.1 (11.1)	11.4 (11.8)	11.3 (5.1)
No (%) requiring dialysis:					
No (%) dialysed	160 (54)	6 (13)	154 (61)***	127 (52)	33 (64)
After first plasmapheresis	72 (24)	0 (0)	72 (29)***	50 (20)	22 (42)***
After first eculizumab dose	12 (4)	NA	12 (5)	4 (2)	8 (15)***
No of dialysis treatments	7.7 (8.1)	4.9 (7.5)	7.9 (8.1)	8.1 (8.4)	6.3 (6.5)
Creatinine concentration at discharge (µmol/L)	145.1 (109.8)	116.9 (87.4)	153.1 (115.3)	143.8 (105.5)	150.4 (126.4)
No (%) with neurological complications:					
Total	143 (48)	10 (21)	133 (53)***	116 (47)	27 (52)
After first plasmapheresis	76 (26)	0 (0)	76 (30)***	53 (22)	23 (44)***
After first eculizumab dose	14 (5)	NA	14 (6)	2 (1)	12 (23)***
No (%) with seizures:					
Total	37 (12)	3 (6)	34 (14)	36 (15)	1 (2)**
After first plasmapheresis	24 (8)	0 (0)	24 (10)*	23 (9)	1 (2)
After first eculizumab dose	4 (1)	NA	4 (2)	3 (1)	1 (2)
No (%) of deaths:					
Total	12 (4)	4 (9)	8 (3)	12 (5)	0 (0)
Day of death	30.4 (32.6)	16 (14.7)	34.6 (37)	30.4 (32.6)	NA
After first plasmapheresis	8 (3)	0 (0)	8 (3)	8 (3)	0 (0)
Day of death	30 (36.1)	NA	30 (36.1)	30 (36.1)	NA
After first eculizumab dose	3 (1)	NA	3 (1)	3 (1)	0 (0)
Day of death	33.7 (43.8)	NA	33.7 (43.8)	33.7 (43.8)	NA

NA=not applicable.

*P<0.05; **P<0.01; ***P<0.001 versus respective control groups (t test or χ^2 test as appropriate).

plasmapheresis, a treatment that was begun in patients with severe haemolytic uraemic syndrome but not in the less severely affected patients who served as controls. Whenever possible we used adjusted analyses to take into account the differences in baseline severity. Nevertheless, these results should be interpreted with caution. Comparisons are easier when baseline characteristics are similar, such as in patients who received limited plasmapheresis versus platelet guided plasmapheresis.

Importantly, differences in participation between the centres owing to the exclusion of patients taking part in the industry sponsored trial gives rise to bias. For example, none of the patients receiving the early antibiotic strategy were excluded, owing to participation in the eculizumab trial, but 28% were excluded in the respective control group when they received eculizumab (table 2). As patients receiving eculizumab were usually sicker than the rest of the study population this biases the analysis towards a smaller therapeutic effect of antibiotics. Limited plasmapheresis would be biased towards a more favourable outcome as only 49.1% of the patients in these centres were included in the present analysis.

Clinical picture of haemolytic uraemic syndrome in adults

The 298 patients with haemolytic uraemic syndrome in the present study had a similar sex and age distribution to the adults with haemolytic uraemic syndrome reported by the Robert Koch Institute.^{1 2} Our figures for mortality were also in line with the national data (4.0% v 4.1%).³ Most of the formerly healthy patients were severely ill during the acute phase of the disease: 54% required dialysis, many had neurological problems, and more than 12% had seizures. Over half of the patients (n=156, 52%) were treated on an intensive care ward and more than 18% (n=54) required ventilation for an average of 10 days. Despite the severity of the disease during the acute phase, most of the patients recovered completely and only five were still receiving renal replacement therapy after nine months. A previous study reported that the neurological symptoms resolved completely in most patients.²¹

Plasmapheresis

At the beginning of this outbreak the German Society of Nephrology recommended use of plasmapheresis, especially for cases of enterohaemorrhagic *E coli* associated

Table 7 | Baseline characteristics of 251 patients with haemolytic uraemia syndrome in centres that used plasmapheresis until normalisation of platelets >100/nL (platelet guided), that re-evaluated plasmapheresis after 3-5 sessions (limited), or did or did not use glucocorticoids with plasmapheresis. Values are means (standard deviations) unless stated otherwise

Variables	Plasmapheresis strategy				No ecilizumab treatment (n=65)	Ecilizumab treatment (n=67)
	Limited (n=54)	Platelet guided (n=197)	Without glucocorticoids (n=77)	With glucocorticoids (n=174)		
Plasmapheresis:						
No (%) receiving treatment	54 (100)	197 (100)	77 (100)	174 (100)	65 (100)	66 (98.5)
Day of first session	7.0 (2.9)	6.8 (3.1)	7.1 (2.4)	6.7 (3.3)	6.5 (2.7)	5.8 (2.9)
No of sessions	4.0 (1.6)	8.3 (7.2)***	8.9 (10.1)	6.8 (4.4)*	8.2 (4.8)	10.2 (11.3)
Ecilizumab treatment:						
No (%) receiving treatment	17 (32)	49 (25)	11 (14)	55 (32)**	0 (0)	67 (100)
Day of first dose	8.9 (4.3)	10.5 (4.5)	12.7 (6.3)	9.6 (4)	NA	10.2 (4.6)
Total dose (mg)	4400 (755)	2500 (1591)*	3600 (0)	2595 (1648)	NA	2646 (1620)
No (%) requiring further plasmapheresis after first dose	3 (18)	24 (49)	6 (55)	21 (38)	NA	27 (40)
Day of last plasmapheresis after first dose	6.7 (2.9)	17.2 (9.4)	24.3 (6.6)	13.7 (8.9)*	NA	16 (9.5)
No of days in hospital	21.3 (13.6)	25.1 (14.6)	26.7 (18)	23.3 (12.6)	29.2 (15)	31.2 (16.9)
No (%) requiring ventilation:						
Total	5 (9)	45 (23)*	19 (25)	31 (18)	27 (42)	23 (34)
After first plasmapheresis	2 (4)	31 (16)*	14 (18)	19 (11)	16 (25)	17 (25)
After first ecilizumab dose	3 (6)	4 (2)	0 (0)	7 (4)	NA	7 (10)
Days ventilated	22.2 (21)	10.9 (9)*	10.9 (10.3)	12.7 (11.6)	11.3 (13.4)	12.9 (7.7)
No (%) requiring dialysis:						
Total	27 (50)	127 (64.5)	42 (54.5)	112 (64.4)	53 (81.5)	51 (76.1)
After first plasmapheresis	8 (14.8)	64 (32.5)*	19 (24.7)	53 (30.5)	26 (40)	25 (37.3)
After first ecilizumab dose	1 (1.9)	11 (5.6)	1 (1.3)	11 (6.3)	NA	12 (17.9)
No of dialysis treatments	7.0 (4.7)	8.1 (8.7)	8.1 (9.4)	7.8 (7.5)	10.3 (10.2)	7.6 (6.3)
Creatinine concentration at discharge (μmol/L)	139 (92.5)	154 (118.5)	128.6 (87.5)	157 (119)	206 (156)	153.7 (101.8)*
No (%) with neurological complications:						
Total	34 (63)	99 (50)	39 (51)	94 (54)	43 (66)	49 (73)
After first plasmapheresis	11 (20)	65 (33)	24 (31)	52 (30)	20 (31)	32 (48)*
After first ecilizumab dose	1 (2)	13 (7)	0 (0)	14 (8)*	NA	14 (21)
No (%) with seizures:						
Total	8 (15)	26 (13)	14 (18)	20 (12)	19 (29)	16 (24)
After first plasmapheresis	5 (9)	19 (10)	9 (12)	15 (9)	12 (19)	12 (18)
After first ecilizumab dose	3 (6)	1 (1)**	0 (0)	4 (2)	NA	4 (6)
No (%) of deaths:						
Total	3 (6)	5 (3)	3 (4)	5 (3)	5 (8)	3 (5)
Day of death	42.5 (34.6)	37.0 (43.2)	54.0 (51.1)	27.0 (27.4)	28.4 (25.8)	64.0 (65.1)
After first plasmapheresis	2 (4)	5 (3)	3 (4)	4 (2)	5 (8)	2 (3)
Day of death	36.0 (35.4)	32.2 (42.5)	48 (51.4)	22.3 (26.4)	23.6 (25.2)	57.5 (65.8)
After first ecilizumab dose	1 (1.9)	1 (0.5)	1 (1.3)	1 (0.6)	NA	2 (3)
Day of death	13	84	84	13	NA	48.5 (50.2)
NA=not applicable. *P<0.05; **P<0.01; ***P<0.001 versus respective control group						

NA=not applicable.

*P<0.05; **P<0.01; ***P<0.001 versus respective control group.

haemolytic uraemic syndrome with neurological or severe renal involvement. This recommendation is supported by the American Society for Apheresis, which gives a low II-3 recommendation for the usage of plasmapheresis in patients with typical haemolytic uraemic syndrome.²² It is believed that plasmapheresis might remove the circulating shiga toxin or factors that damage the endothelium. Data to support such an assumption are, however, scarce. Firstly, shiga toxin has never been identified in the circulation. Secondly, the density of the infecting organism and concentration of toxin in stools diminish in the colon as haemolytic uraemic syndrome develops.²³ Thirdly, there is ample evidence of vascular injury before haemolytic uraemic syndrome ensues,²⁴ and the microvascular damage is possibly already manifested before the clinical manifestation of the disease. In addition,

injected shiga toxin in animal models has shown a short half life in the circulation. Hence the evidence for plasmapheresis is based on empirical observations.²⁵ In the Scottish outbreak overall mortality seemed better in the small number of patients treated with plasmapheresis, although statistically robust conclusions were not possible owing to lack of power.³ More recently, findings in five patients in the 2011 outbreak were published and it was suggested that plasmapheresis is beneficial.²⁶ Furthermore, the authors of an accompanying editorial mentioned that plasmapheresis remains “the cornerstone of treatment.”²⁷ We observed an improvement in the average platelet count and a drop in the levels of lactate dehydrogenase after initiation of plasmapheresis in 251 patients. However, our data also suggest that this might reflect the natural course of the disease, as plasmapheresis

was usually started at the peak of disease activity, around days 6–8, misleading the observers to conclude that the improvement shortly after the start of therapy resulted from plasmapheresis. In our cohort, 47 patients were not treated with plasmapheresis. The time courses of platelet count and levels of lactate dehydrogenase, haemoglobin, and creatinine during recovery from the disease were similar to the group that received plasmapheresis. Secondly, the three centres that treated patients with limited plasmapheresis (3–5 sessions) had similar or better outcomes than centres that continued plasmapheresis until platelet counts had increased to more than 100/nL. These results question the current recommendation to use plasmapheresis as a standard treatment in adults with enterohaemorrhagic *E coli* associated haemolytic uraemic syndrome^{26–27} and are in agreement with the experience of paediatric nephrologists, who encounter shiga toxin induced haemolytic uraemic syndrome more often than doctors treating adults and use plasmapheresis only rarely. During the current epidemic, 17 of the 90 children were treated with plasmapheresis (data not shown) and the outcome was good.

According to the recommendation of the German Society of Nephrology, fresh frozen plasma should be used for plasmapheresis.²⁸ No plasmapheresis was carried out with albumin in the adults, whereas albumin was mainly used in the children. We cannot exclude the possibility that fresh plasma enhanced the disease process—for example, through further complement activation. This needs further research.

We believe that a randomised trial analysing supportive treatment plus limited plasmapheresis (3–5 sessions using albumin) compared with no additional treatment is necessary for clarification. However, from our experience during the outbreak in Germany and the experience of the paediatricians in the routine treatment of children with typical haemolytic uraemic syndrome, we believe that no benefit or only a marginal benefit will be found.

Glucocorticoids with plasmapheresis

Despite our finding that glucocorticoids had an effect on recovery of lactate dehydrogenase and creatinine levels and platelet counts, it was not significant and led to a higher number of patients requiring dialysis. As enterohaemorrhagic *E coli* associated haemolytic uraemic syndrome is an infectious disease, concomitant treatment with glucocorticoids might be harmful—an observation in keeping with a randomised trial from Italy, in which no benefit was found in children.²⁹

Antibiotic treatment

The use of antibiotics to treat enterohaemorrhagic *E coli* infection is controversial. In theory antibiotic treatment may lead to higher toxicity through an intestinal Jarisch-Herxheimer reaction, with a massive release of shiga toxin through bacterial death during the prodromal phase of diarrhoea.³⁰ This concept is supported by a mouse model with shiga toxin producing *E coli*, showing that treatment with fluoroquinolone resulted in a higher release of toxin and mortality.³¹ A report in 71 children with enterohaemorrhagic *E coli* O157:H7 induced diarrhoea described that five of nine children receiving antibiotics developed haemolytic uraemic syndrome compared with five of 62 children not receiving

antibiotics.³² In our patient cohort, all but one medical centre did not use antibiotic treatment. In this centre patients were treated with a combination of at least two antibiotics sensitive to enterohaemorrhagic *E coli* (meropenem and ciprofloxacin and additionally rifaximin in patients on intensive care ward) after a diagnosis of haemolytic uraemic syndrome. None of the patients treated with antibiotics developed signs of toxic shock. Enterohaemorrhagic *E coli* was eradicated about eight days earlier than in the other centres and the rates of seizures and mortality were improved. None of the patients required intestinal surgery. In this centre the lower incidence of seizures might also be explained by a more aggressive use of prophylactic antiepileptics in patients with neurological symptoms. Nevertheless, the results are encouraging as they suggest that the production and potential drug induced release of shiga toxin might be irrelevant and that pre-emptive antibiotics do not worsen the clinical course of established haemolytic uraemic syndrome. Moreover, in contrast with previous studies the antibiotic strategy was more aggressive. Patients simultaneously received at least two (many even three) antibiotics effective against enterohaemorrhagic *E coli*, which might have contributed to the beneficial outcome. As antibiotics seem to improve, but definitely do not worsen, the course of the infection we believe that they are beneficial in the later stages of the disease when the prodromal phase with diarrhoea has nearly subsided. Mice infected with different enterohaemorrhagic *E coli* O157:H7 strains have shown lower mortality and weight loss if treated with rifampicin compared with placebo.³³ Therefore it could be speculated that a suitable antibiotic combination strategy at the onset of bloody diarrhoea in (enteroaggregative) enterohaemorrhagic *E coli* infections might even prevent the development of haemolytic uraemic syndrome.

We believe that a randomised trial should be carried out to assess whether antibiotic treatment is beneficial in patients with enterohaemorrhagic *E coli* associated haemolytic uraemic syndrome.

Complement 5 inhibition

Eculizumab was used widely as a compassionate treatment (that is, outside the currently accepted indication for atypical haemolytic uraemic syndrome and paroxysmal nocturnal haematuria) during the outbreak in Germany. Evaluations of treatment effects were prone to bias by indication, as most of the centres treated the least sick patients with supportive care only, sicker patients with plasmapheresis, and the sickest with eculizumab. The treatment patterns in the different centres were not uniform; one larger hospital did not give eculizumab at all and in other hospitals it was administered only later during the outbreak. This enabled us to identify a control group of similarly sick patients to compare eculizumab treatment with plasmapheresis. This evaluation cannot be a substitute for a randomised controlled trial, but we believe that this is the only way to get an impression of the true effect of eculizumab treatment. Based on the data presented, patients treated with eculizumab did not improve significantly compared with a control group of patients with the same severity of haemolytic uraemic syndrome. Patients treated with eculizumab still developed new complications, such as seizure or requirement for ventilation, and in more than 40% of the patients plasmapheresis

was continued after eculizumab had been started. Data on long term (6–12 months) renal and neurological follow-up in all patients treated with eculizumab will be required to assess the effect of this treatment strategy. In addition, the effect of eculizumab might be confounded because more than 98% of patients who received the drug were simultaneously treated with the antibiotic azithromycin for meningococcal prophylaxis. Recently, this antibiotic has been shown to eradicate O104:H4 quickly³⁴ and does not lead to shiga toxin release in vitro.³⁵

Lessons for future outbreaks

A major shortcoming of our analysis was that we did not carry out a randomised study. The large number of patients affected would have been ideal to test some of the questions and hypotheses about treatment strategies that existed at the start of the outbreak. As the outbreak began at the end of May and had almost finished by July, it was impossible to design a randomised trial and get approval within that time.

Conclusions and policy implications

Haemolytic uraemic syndrome associated with *E coli* O104:H4 is an acute self limited disease with a high percentage of patients requiring dialysis and ventilation and having severe neurological impairment. Our retrospective analyses question the benefit of plasmapheresis and concomitant glucocorticoid treatment in adults with enterohaemorrhagic *E coli* associated haemolytic uraemic syndrome. Contrary to current belief, antibiotics do not seem to worsen the clinical course in patients with established haemolytic uraemic syndrome, but may be of clinical benefit. Further prospective, randomised investigations of antibiotic treatment and its timing in future cases of (enteroaggregative) enterohaemorrhagic *E coli* associated haemolytic uraemic syndrome and even outbreaks with the O157:H7 strain are required. We observed no significant short term benefit of eculizumab treatment.

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