Case Report

Antibiotic treatment for infection with Shiga toxin producing Escherichia coli infection inducing a hemolytic uremic syndrome

Lars Lindberg

Institution of Clinical Science, Faculty of Medicine, Lund University, Sweden

*Correspondence: Lars Lindberg (lars.lindberg@med.lu.se)

Abstract: Background: Shiga toxin producing Escherichia coli (STEC) inducing hemolytic uremic syndrome (HUS) with multiple organ involvement is associated with significant morbidity and mortality. The treatment has mostly been focused on kidney, respiratory and cardiovascular supports and not against the bacteria that cause STEC-HUS. The use of bactericidal therapy has been shown to be antibiotic dependent and certain antibiotics inhibit the production and release of Shiga toxin, eradicate STEC without harmful effects, and improve outcome. **Methods:** A previously healthy 18-months-old girl with STEC causing severe colitis, kidney failure and multi-organ dysfunction was treated with antibiotics that were known to inhibit the release of Shiga toxin as a supplement to supportive care. **Results**: The antibiotic regime stopped the pathophysiological process with prompt clinical improvement in association with the disappearance of the Shiga toxins. **Conclusions:** The present case report fortifies and recommends appropriate antibiotic treatment during STEC-HUS, suggesting clinicians to consider the use of these in severe STEC-HUS as early as possible.

Keywords: Shiga toxin; Hemolytic uremic syndrome; Shiga toxin-producing Escherichia coli antibiotics; Continuous kidney replacement therapy; CKRT; Treatment

1. Introduction

Shiga toxin producing Escherichia coli (STEC) strains are pathogenic in humans. Twelve percent of paediatric patients with STEC-HUS developed complications, such as septic shock, neurologic dysfunction, left ventricular systolic dysfunction, transmural colonic necrosis, and need of intensive care. The mortality rate was 27 % and death occurred on average 10 days after admission, despite supportive care with mechanical ventilation, kidney replacement therapy, and inotropic treatment [1].

The STEC infection is related to the cell death caused by Shiga toxin, which consists of an A-subunit and a B-subunit (AB_5) [2]. The B-subunit binds to globotriaosyl ceramide, which acts as a receptor localized on the surface of target cells, primarily endothelial cells [3]. After the toxin enters the cell through endocytosis, the A-subunit is released and binds to the ribosome in the cytosol, disrupts protein synthesis, and induces apoptosis and cell death [2].

A microangiopathy develops, disrupts the intestinal barrier, and enables the bacterial toxin to enter the circulation. The amount of Shiga toxin in the stool is related to the amount released to the circulation [4]. In the circulation, the toxin binds to organs rich in globotriaosyl ceramide, e.g. kidney cells, causing HUS [5].

Treatment with antibiotics has been questioned due to publications supporting the view that antibiotics should not be given in STEC-HUS [6-9]. An editorial commented that the reason for this is, among other things, a selection bias of studies that use antibiotics, which increase the production and release of Shiga toxin, and that studies that use antibiotics, which inhibit the production have been discarded [10]. Concurrently, several publications have presented data that show that certain antibiotics have good effect on the clinical course [11, 12]. A global overview has also showed that the release of Shiga toxin and the outcome in STEC-HUS are antibiotic dependent [13]. However, the treatment of STEC-HUS with antibiotics seems to remain controversial even today [7] making an update important.

This case with several predictive factors for poor kidney outcome and multi-organ failure promptly improved after the administration of antibiotics. The rationale for the use of specific antibiotic treatment in severe STEC-HUS is discussed.

2. Results

A girl (12 kg) came to the emergency department with epileptic seizures after three days of bloody diarrhoea. She was anuric, thrombocytopenic, and hypertensive. Peritoneal dialysis (PD) started in the PICU. She was colonized with STEC producing both Shiga toxin type 1 and type 2. After 3 days in the PICU she was transferred to the paediatric ward with ongoing PD. No antibiotics were given.

On the ward, fever, anuria, and bloody diarrhoea continued. A profound thrombocytopenia, anaemia, leucocytosis, hypoalbuminemia, pleural effusion, and general oedema developed (Table 1). A leak occurred around the PD catheter which was removed. She received a platelet transfusion without any adverse effects and a venous dialysis catheter was inserted. Mechanical ventilation was commenced with a FIO_2 of 0.8 for acceptable oxygenation. Continuous kidney replacement therapy (CKRT) was started due to her anuria.

Table 1. Course of events and laboratory variables.

Parameter	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18
Shiga toxins	+/+				+/+			+/+				-/-			-/-			-/-
Antibiotics								M/A	M/A	M/A	M/A	M/A	M/A	M/A	M/A	M/A	M/A	M/A
PICU/W	PICU	PICU	PICU	W	W	W	W	PICU	PICU	PICU	PICU	PICU	PICU	PICU	W	W	W	W
P-CRP	38	45	78	72	70	50	65	52	47	79	40	16	9.5	6.9	9.2	3		
B-WBC	29.6	24.1	22.5	23.5	22.6	20.1		37	26.1	29.1	32	24.8	15.8	9.1				
B-Platelescount	76	83	105	101	93	49	20	15	56	107	237	347	470	373				
B-Hemoglobin	115	91	121	84	81	80	113	74	102	104	95	95	99	88	92	96	92	89
B-Hematocrit	35	28	37	26	25	25	35	23	32	32	30	30	31	27	29	30	29	28
P-Na	124	126	134	139	139	137	135	137	137	138	134	134	136	135	136	136	138	138
S-LDH	52		50	38					18		11	10			6,5			
P-K	3.7	3.5	4.1	4.4	4.1	4.3	5.4	4.1	3.7	4.3	5.2	4.4	5.0	4.9	4.3	4.7	4.2	4.1
Platelets								X										
P-Creatinine	334	374	397	425	490	469	502	499	170	89	74	160	238	170	249	181		
P-Urea	39.8	41.1	37.6	37.1	39.8	38.7	43.8	47.9	18.3	9	6.8	13.9	21.8	13.2	20.6	12.3		
Diuresis	0	0	0	7	2	5	0	0	12	0	0	0	0	0	0	74	195	291
SAG		X					X		X							X		
Ventilator								X	X	X	X							

D – Day: starting D1 at admittance to the hospital, three days after onset of diarrhea; PICU – Pediatric intensive care unit; W – treatment at the hospital ward, P-CRP – C-reactive protein (mg/L; ref <3 mg/L); B-WBC – white blood count (x10$^{9/L}$); B-Hemoglobin (g/L; ref 100-150 g/L) ; B-Hematocrit (%; 37-41 %); P-Na (Sodium) (mmol/L; ref 137-145 mmol/L); P-K (potassium)(mmol/L ; ref 3.7-4.6 mmol/L; S-LDH- lactate dehydrogenase (µkat/L; ref 2.2 – 5.3 µkat/L) ; P-Creatinine (µmol/L; ref 17-42 µmol/L) ; P-Urea (mmol/l; ref 3.1 – 7.8 mmol/L), SAG - packed red cells diluted with saline-adenine-glucose-mannitol solution, (P – plasma, B - blood, S - serum).

Inflammatory parameters were increased (Table 2). Four consecutive blood, urine, and tracheal tube cultures were all negative. PCR tests for detection of viruses in blood and airways were negative. Combur-Test® Roche diagnostics for leucocytes and bacteria in the PD fluid was tested two times a day and were negative. Culture for bacteria and fungus of the removed PD catheter was negative.

Table 2. Inflammatory markers.

Parameter	Value	Normal values
P-Procalcitonin	36 µg/L	< 0.05 µg/L
P-Ferritin	2160 µg/L	13 - 148 µg/L
S-Calprotectin	>24.0 µg/mL	<2.9 µg/mL
S-Soluble interleukin 2 receptor	4740 kE/L	< 700 kE/L
S-TNFα	44 ng/L	< 15 ng/L
S-IL-6	60 ng/L	< 8 ng/L
S-IL-1β	48 ng/L	< 5 ng/L

TNFα – Tumor necrosis factor alpha; IL-6 – Interleukin-6; IL-1β – Interleukin 1 beta. (P – plasma, S - serum).

Complement factors and the complement pathway were normal. Schistocytosis and elevated reticulocytes indicate a microangiopathic hemolytic anemia. The echocardiography showed left ventricle systolic dysfunction and the plasma N-terminal brain natriuretic peptide (P-NT-ProBNP) was high (> 30000 ng/L).

Azithromycin and meropenem were given and followed by prompt improvement in laboratory parameters (Table 1), clinical condition, and a simultaneous disappearance of the Shiga toxins in the stool (Table 1).

The bloody diarrhea vanished 24 hours after initiation of antibiotics. The CKRT was stopped after 72 hours and she was extubated. Intermittent hemodialysis was performed three times, over the following days. The diuresis increased daily and she was transferred back to the ward. Antibiotics were stopped after 14 days, without any signs of STEC in the stool.

She was discharged from hospital 4 weeks after symptoms started. At an out-patient follow-up after 6 months she was alert and fit. The kidney function had improved with an estimated glomerular filtration rate of 72 ml/min/1.73 m². She had a slight proteinuria and was still on anti-hypertensive medications (enalapril, amiloride, and propranolol). Her blood pressure was under control.

3. Discussion

Initial management was supportive, without the use of antibiotics, with the hope that this STEC-HUS was self-limited. However, the clinical condition deteriorated despite dialysis with signs of catabolism, a severe colitis, and kidney failure, in accordance with cell dead caused by the Shiga toxins. A secondary co-infection could initially not be excluded, but was ruled out by all possible means by negative cultures from blood, tracheal, urine, PD fluid and negative PCR detection analyses.

Shiga toxins induce cell death. The necrotic cells are known to release damage-associated molecular patterns. Damage-associated molecular patterns (DAMPs) activate Toll-like receptors (TLRs) and the procaspase-caspase pathway. The latter activates the inflammasome. This second response converts biological inactive, pro-interleukin-1β and pro-interleukin-18 to active interleukin-1β and interleukin-18, which are then released [14]. Increase in lactate dehydrogenase, cytotoxic T-cells, natural killer T-cells, and release of interleukin-1β, without signs of bacterial, viral or fungal infections, indicate that

DAMPs from necrotic cells, , may be the most plausible reason for the clinical deterioration [5].

The Shiga toxin genes are located in a prophage within the chromosome of the bacteria. They are controlled and activated by promotors simultaneously with transcription of bacterial SOS response genes, which is a set of inducible genes in bacteria that activate a DNA repair pathway as a response to DNA damage [15]. Antibiotics such as fluoroquinolones, metronidazole, ampicillin, and trimethoprim-sulfamethoxazole, most often used during HUS, are SOS-inducing antimicrobial agents and are consequently associated with Shiga toxin expression and should accordingly be contraindicated [10, 16]. Antibiotics such as azithromycin, fosfomycin, rifampicin, gentamicin, kanamycin, doxycycline, and erythromycin block gene expression and do not release Shiga toxins [17]. Carbapenems have also been shown to inhibit the production of Shiga toxins [17, 18]. The conflicting results from randomized studies and meta-analyses can therefore be explained by the class-specific ability of certain antibiotics to induce or inhibit the prophage activation. Several of these favorable and Shiga toxin blocking antibiotics could even inhibit the production of Shiga toxins in bacteria, which already had fully induced SOS and toxin gene responses [15].

We used a combined antibiotic regime to be sure of eradicating STEC effectively [12] and thereby inhibit the development of severe colitis with perforation and irreversible kidney failure. It also diminishes the risk of prolonged shedding of STEC, reactivation of Shiga toxin production, and the transmission of the Shiga toxin prophage to other potentially resistant bacteria [19, 20].

This case report fortifies the findings that appropriate antibiotic treatment may be beneficial and safe in STEC-HUS. We suggest clinicians reappraise the recommendation not to use antibiotics and consider the use of an appropriate combined antibiotic treatment regime in severe STEC-HUS as early as possible.

In future randomized controlled trials and review articles it is important to exactly define type of antibiotics used and if they are known to inhibit or induce the Shiga toxin genes.

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