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## ORIGINAL ARTICLES

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### Haemolytic uraemic syndrome following *Shigella dysenteriae* type 1 outbreak in Zimbabwe: a clinical experience

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#### SUMMARY

*Shigella dysenteriae* type 1 related dysentery outbreak in Zimbabwe at the end of 1992 has been associated with an increase in the frequency of haemolytic uraemic syndrome (HUS). In order to document this new clinical experience a retrospective study was undertaken to document clinical and laboratory features, treatment and outcome of children with HUS.

During the period January 1993 to June 1994, 96 children with HUS were seen at the referral hospitals in Harare. Severe and prolonged anaemia was a common feature and 80 pc of the children were given blood transfusions. Severe anaemia (HB < 6g/dl) was however, present in 50 pc of the children prior to death. Leucocytosis (white blood cell count > 20 x 10<sup>9</sup>/L) was present in 87 pc of the children on admission and there was no association between the level of leucocytosis and anuria. Anuria was present in 37 (39 pc) and was associated with a mortality of 68 pc. Peritoneal dialysis

was performed in 26 (27 pc) patients. Major neurological complications were seen in a third of the children. Thirty eight children died, an overall case fatality rate (CFR) of 40 pc.

Earlier recognition, prompt and comprehensive supportive therapy may improve the immediate survival in children with HUS in Zimbabwe.

#### INTRODUCTION

The haemolytic uraemic syndrome (HUS) characterized by the triad of microangiopathic haemolytic anaemia, thrombocytopenia and acute renal failure has been reported from various parts of the world.<sup>1</sup> Although HUS results from a variety of disease processes, two principal subgroups have been defined in children.<sup>2</sup> Diarrhoea associated HUS is the most common group and is often related to infection with cytotoxin producing organisms such as verotoxin producing *Escherichia coli* or shigatoxin-producing *Shigella dysenteriae*.<sup>3</sup> The second group consists of non diarrhoea related HUS which has been associated with many different aetiologies.<sup>4</sup>

The reported prevalence of HUS varies in different countries.<sup>3</sup> A previous survey from Southern Africa recorded that HUS was relatively common in White children but was rare in Black children. In these children there was no relationship between epidemics of gastro-enteritis and the prevalence of HUS.<sup>5</sup>

Haemolytic uraemic syndrome has been an uncommon problem in Black Zimbabwean children in the past. Hospital records at the two major referral hospitals in Harare show that only 11 children were admitted with HUS during the period 1980 to 1991.

Towards the end of 1992 outbreaks of dysentery were reported from various parts of Zimbabwe which were later confirmed to be due to *Shigella dysenteriae* type 1.<sup>6</sup> This outbreak has been associated with a

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concurrent increased frequency of HUS. In order to describe this new clinical experience in Zimbabwe, we undertook a retrospective study to document clinical and laboratory features, treatment and outcome of children presenting with dysentery related HUS.

**MATERIALS AND METHODS**

The study was conducted at the two referral hospitals in Harare during the period January 1993 to June 1994. The study group consisted of children aged up to 12 years who developed HUS following dysentery. The diagnosis of HUS was based on the presence of microangiopathic anaemia (HB < 10g/dl with evidence of fragmented red blood cells) and uraemia (urea > 8 mmol/L). Since thrombocytopenia is not always present in HUS, cases with a normal platelet count (i.e.  $\geq 150\ 000 \times 10^9/L$ ) were also included in the study.<sup>7</sup> Anuria was defined as failure to pass urine for 24 hours or more and oliguria as a daily urine volume less than 15ml per kilogram weight in 24 hours.<sup>8</sup>

**Data collection:** The following information was retrieved from case files: socio demographic features, initial treatment of dysentery, clinical and laboratory features, clinical course and management of HUS and the immediate outcome.

**Laboratory methods:** The standard biochemical and haematological tests were done on admission and over the course of the illness as required. Blood culture samples were taken in children in whom sepsis was suspected on admission or during the course of the illness. Appropriate standard procedures were used for the identification of organisms from both blood and stool samples at the referral hospitals.<sup>9</sup>

**Statistical analysis:** Data was analysed by computer software using EPI Info v5. Categorical data was evaluated by Yates corrected chi-square and Fisher's exact test when the expected frequencies were less than five.

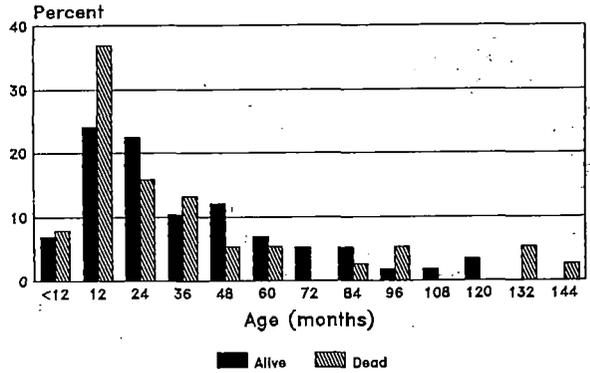
Continuous data were analysed by the Student's t test. A p value of less than 5 pc was considered statistically significant.

**RESULTS**

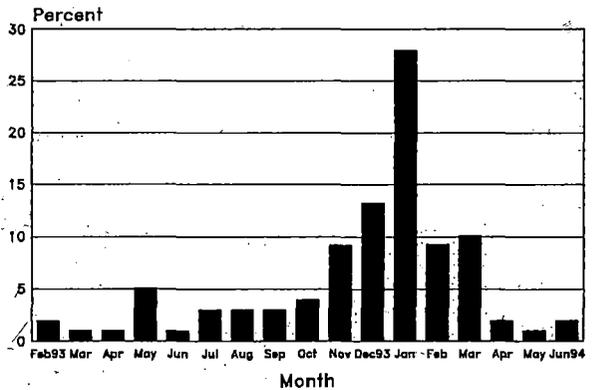
**Socio Demographic Features.**

Ninety six children were seen during the period of 18 months. There were 62 males and 34 females. The age ranged from seven months to 12 years and the peak age group was 12 to 23 months. (Figure I). There was a

*Figure I: Age distribution and outcome of 96 children with HUS.*



*Figure II: HUS distribution by month.*



seasonal trend as noted by the increased frequency of cases during the hot and rainy season (October to March) as shown in Figure II.

Thirty six children resided in urban and peri-urban areas of Harare City. The rest lived in various parts of the surrounding provinces. In 84 cases details regarding the water supply were available. Seventy two had access to tapwater, 10 borehole water, one river and one well water. Twenty eight patients gave a history of recent travel and inadequate information was available about the water supply in the area visited. In 32 cases a definite history of contact with dysentery mostly with close relatives was noted and five of these contacts had died prior to the patient's admission to the referral hospitals.

Thirty nine cases (41 pc) were referred by the two infectious diseases hospitals in Harare and 31 (32 pc)

came from the hospitals in surrounding provinces. Twenty three cases (24 pc) were referred from the local clinics and three were self referral.

There were seven children below the age of 15 months and all were being breast fed except for one infant who had been breast fed for 10 months only.

In 90 patients weights were available. Fifty three patients (60 pc) were of normal nutrition (weight for age) > 80 pc, and 25 (27 pc) were underweight (< 80 pc weight for age). Severe malnutrition was present in 12 children: six had marasmus, six had kwashiorkor and two had marasmic kwashiorkor (Wellcome classification).<sup>10</sup>

Prior antibiotics had been prescribed for dysentery in 70 patients. Ten different drugs were used: a single drug in 23 (33 pc) two in 24 (34 pc) children and three or more in 18 (26 pc) children. Cotrimoxazole was the most frequently used drug for dysentery. Other commonly used drugs included chloramphenicol, cephalosporin and metronidazole. Nalidixic acid was used in seven patients only.

#### Presenting Features and Clinical Course.

The duration of bloody diarrhoea ranged from two to 28 days (median eight days) prior to admission. The time of onset of HUS following dysentery ranged from four to 30 days (median 11 days).

Pallor was present in approximately 80 pc of the children on admission (see Table I). In more than half there were changes in sensorium which included drowsiness, lethargy and coma. Fourteen had a history of seizures on arrival. Severe neurological manifestation as defined by seizures, coma and hemiplegia developed

Table I: Presenting features in 96 patients with haemolytic uraemic syndrome (HUS).

Features	Number of patients	pc
Pallor	76	79
Altered consciousness	50	52
Dehydration	44	46
Vomiting	38	40
Anuria	27	28
Fever	20	21
Abdominal distention	15	16
Seizures	14	15
Jaundice	4	4
Generalised lymphadenopathy	4	4

Table II: Laboratory features in children with HUS.

	Initial	During the course of the illness
	Median (min-max)	Median (min-max)
Haemoglobin g/dl	6,1 (3-10,0)	4,5 (2,4 - 8,5) lowest level
platelet 10 <sup>9</sup> x L	88 (7 - 372)	32 (6 - 239) lowest level
leucocyte 10 <sup>9</sup> x L	48 (5,6 - 140)	58 (9 - 192) peak level
Sodium mmol/L	118 (101 - 140)	115 (100 - 140) lowest level
Potassium mmol/L	4,8 (2,3 - 8)	5,7 (3,1 - 8,8) peak level
Urea mmol/L	23,5 (8,3 - 114,0)	33,8 (13,4 - 83,0) peak level
Creatinine μmol/L	300 (69 - 967)	405 (99 - 998) peak level

in 29 (30 pc) children, during the course of the illness. Ten were severely dehydrated and 34 had some dehydration on arrival at the hospital.

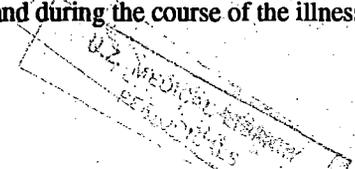
Anuria was present in 27 children and 10 more children became anuric during the course of the illness. The duration of anuria ranged from one to 36 days with a median of three days. Oliguria was recorded in six children.

Forty six (48 pc) children continued to pass bloody diarrhoea in the hospital for periods ranging from two to 18 days. Nineteen children developed a tender distended abdomen. Toxic megacolon, ileus and intestinal perforation were suspected in these cases. Rectal prolapse was present in six children.

In 56 children blood pressure was measured on admission and in all cases it was found to be normal for age. Thirteen children developed spontaneous bleeding from the mucous membranes mainly from the mouth and nose and in four petechiae and purpura were also present. Four bled from the upper gastro-intestinal tract. Concurrent pneumonia was present in five children and in two pleural effusion was diagnosed.

#### Laboratory Findings.

Table II summarises the laboratory findings at presentation and during the course of the illness.



The median level of haemoglobin fell from 6,1 g/dl on admission to a level of 4,5 g/dl during the hospital stay. Seventy one (74 pc) children had a platelet level of  $(150 \times 10^9/L)$  on presentation and of these 26 (27 pc) had platelet levels below  $50 \times 10^9/L$ . Children with bleeding into the mucous membranes or skin had platelet counts which ranged from seven to  $81 \times 10^9/L$  and the median was  $18 \times 10^9/L$ . Prothrombin time was done in seven, in four activated partial thromboplastin time and in two fibrinogen degradation products were looked for. The results were normal except in one child where both prothrombin time and activated partial thromboplastin time were prolonged but the levels of fibrinogen degradation products were not available.

Leucocytosis (white blood cell count  $> 20 \times 10^9/L$ ) was recorded in 82 (85 pc) at presentation and in 47 (49 pc) the levels were greater than  $50 \times 10^9/L$ . The median level for the peak leucocytosis was  $58 \times 10^9/L$ . No significant association was found between the initial leucocyte count and anuria ( $X^2 = 1,26$ ;  $df = 2$ ;  $p = 0,531$ ).

Initial sodium levels were available in 89 children, 49 (55 pc) were hyponatraemic with plasma sodium concentration  $< 120$  mmol/L with 16 being below 110 mmol/L. During the course of the illness, a further 19 children became hyponatraemic. There was no significant difference in the degree of hyponatraemia in children with seizures and in those without seizures ( $t = 0,40$ ;  $df = 94$ ;  $p > 0,05$ ). Hyperkalemia (potassium level  $> 5,5$  mmol/L) was recorded in 54 (56 pc) children.

Stool samples were cultured in 37 (39 pc) children before, at referring hospitals or on admission. In three *Shigella dysenteriae* type 1 were isolated, and in one each *S. Flexneri* and *Salmonella* group B.

Blood cultures were performed in 34 children suspected of sepsis and bacteremia was present in 11

children. The following organisms were isolated. *Staphylococcus aureus* in four, group D *Streptococcus* in two, and one each of Haemolytic *Streptococcus*, *Klebsiella sp*, *Strep.pneumoniae* and *Shigella dysenteriae*.

Twenty four children were tested for the presence of Human Immunodeficiency Virus (HIV) antibodies on the basis of severity of illness. Only four were positive for antibodies. These four children also had clinical features suggestive of HIV infection consisting of generalised lymphadenopathy, oral thrush and pneumonia. The constellation of such features were absent in the rest of the children.<sup>11</sup>

#### Management.

Blood transfusions were given in 78 (81 pc) children and 70 pc received two or more transfusions. Sixteen cases were given single or multiple platelet transfusion. Fresh frozen plasma was given to three children. Peritoneal dialysis was performed in 26 (27 pc) of the children and of these 22 (60 pc) were anuric. Four children without anuria were dialysed on the basis of rapidly rising creatinine levels. In 13 the dialysis was done within 48 hours of developing anuria whilst in

Table III: Clinical and laboratory features present at the time of death in 38 children.

	Number	pc
Anaemia (Hb $< 6$ g/dl)	19	50
Anuria	16	42
Hyperkalemia ( $K^+ > 6$ mmol/L)	15	39
Hyponatremia ( $Na < 120$ mmol/L)	13	34
Intestinal obstruction/perforation	6	16
Seizures	6	16
Coma	6	16
Bleeding from mucous membranes	5	13
Pneumonia	4	11

Table IV: Outcome in 37 anuric patients.

	Alive	Dead	Total	CFR	p-value
Dialysed	10	12	22	55 pc	
Not dialysed	2	13	15	86 pc	0,043
Dialysis within 48 hours of developing anuria	7	7	14	50 pc	
Dialysis after 2 days of anuria	3	5	8	63 pc	0,454

CFR: Case fatality rate.

nine, dialysis was performed later than 48 hours. Dialysis was stopped in one child after two days because of signs of intestinal perforation and also in a further two children who had remained anuric for 18 and 38 days respectively.

Children with signs of intestinal obstruction were managed conservatively without surgical intervention. All children were given multiple antibiotics during the hospital course. The two most frequently used agents were cephalosporins (37 pc) and chloramphenicol (36 pc). Nalidixic acid was used in 27 (28 pc) children who presented during the period January 1994 to June 1994. Metronidazole was prescribed in 16 children and in 11 children ampicillin was used.

#### Outcome.

Thirty eight children died giving a case fatality rate of 40 pc. There was no relationship between age and mortality ( $X^2 = 1,98$ ;  $df = 2$ ;  $p = 0,377$ ). Eight died within 48 hours of transfer to the referral hospital whilst the rest were hospitalized for a median of 15 days (range = three to 45 days). Table III lists the important clinical and laboratory abnormalities present at the time of death. Severe anaemia ( $Hb < 6$  g/dl) was recorded in 19 (50 pc) children before death. Fifty four (93 pc) of the live children were transfused whilst only 24 (63 pc) who died were given a blood transfusion ( $X^2 = 11,6$ ;  $df = 1$ ;  $p < 0,001$ ). Almost 40 pc of the children also had severe electrolyte derangements before death.

Twenty five (68 pc) of 37 children with anuria died (Table IV). Twenty two anuric patients were dialysed

of whom 12 (55 pc) died and 13 (86 pc) of the 15 anuric children who were not dialysed died. Of the 12 anuric patients who survived, 10 were dialysed whilst two patients with anuria (lasting one and three days respectively) with normal potassium levels improved on diuretic therapy alone. The case fatality rate in the non anuric patients was 22 pc (Table V). Case fatality rate in anuric patients whether dialysed or not was significantly higher than the non anuric patients ( $X^2 = 17,9$ ;  $df = 1$ ;  $p < 0,001$ ).

Fifty eight children were discharged after a hospital stay ranging from one week to 30 days (median 15 days). Seventeen (29 pc) children had creatinine levels greater than 100  $\mu\text{mol/L}$  at discharge (11 of whom had been dialysed). One child had sustained brain damage and another had to be maintained on anti-convulsant therapy.

## DISCUSSION

Over the last 10 years epidemics due to SD1 related dysentery have been recorded in East and Central Africa<sup>12,13</sup> and in late 1992 a similar outbreak of SD1 related dysentery occurred in Zimbabwe.<sup>6</sup> This outbreak was followed by an increased number of cases of HUS which was previously an uncommon condition among children in Zimbabwe.<sup>5</sup> Similarly large increases in the number of cases of HUS followed epidemics of dysentery due to SD1 in the Indian subcontinent.<sup>14</sup> *Shigella dysenteriae* type 1 or enterohaemorrhagic *E. coli* are associated with the production of

Table V: Comparison of complications in dead and live patients with HUS.

	Alive	Dead	Total	CFR	p-value
Anuria	12	25	37	68 pc	
No anuria	46	13	59	22 pc	< 0,001
Seizures	12	6	18	33 pc	
No seizures	46	32	78	41 pc	0,738
Coma	7	6	13	46 pc	
No coma	51	32	83	39 pc	0,829
Tender distended abdomen	13	6	19	32 pc	
Normal abdomen	45	32	77	42 pc	0,523
Pneumonia	1	4	5	80 pc	
No pneumonia	57	34	91	37 pc	0,078
Bleeding from mucous membrane	8	5	13	38 pc	
No bleeding	50	33	83	39 pc	0,829

CFR: Case fatality rate.

Shiga toxins (verotoxins) which are involved in the pathogenesis of HUS.<sup>15</sup> The relative severity of HUS appears to be directly related to the quantity of Shiga toxin produced by these pathogens.<sup>16</sup>

A recent study has confirmed that SD1 isolates in Zimbabwe are resistant to cotrimoxazole and ampicillin, (the two normally recommended drugs) but sensitive to nalidixic acid.<sup>6</sup> Nalidixic acid became widely available only during the early part of 1994 which explains the wide usage of cotrimoxazole for dysentery in our patients. In Bangladesh an increased risk of developing HUS has been associated with the use of inappropriate antibiotics and delay in treatment of shigellosis.<sup>17</sup>

The very low yield of SD1 from stool culture samples on presentation with HUS may be explained by the fact that the rate of excretion of organisms in the stool usually diminishes six or more days after the onset of dysentery, and possibly by the use of inappropriate microbiological techniques at various health centres.<sup>18,19</sup>

A history of contact with relatives with dysentery in more than a third of the children with HUS emphasises the importance of person to person transmission of *Shigella* infection. A recent study of HUS related to *E. coli* 0157:H7 gastro-enteritis found that contact with individuals suffering from diarrhoea was a more important risk factor for childhood HUS than direct exposure to under cooked meat.<sup>20</sup>

The time interval of up to two weeks between the onset of dysentery and the common presenting features of HUS (pallor, altered conscious level, with or without reduction of urine output) was consistent with the findings reported from the other parts of the world.<sup>21,22,23</sup>

It is important to note that half of our patients were severely anaemic before death and that they had received significantly less frequent blood transfusions compared to patients who survived. The rapid onset of anaemia, with prolonged and severe haemolysis should be recognised and emphasis placed on the need for early and multiple transfusions.<sup>22</sup>

In a high proportion of the children, severe hyponatremia, hyperkalemia and markedly raised creatinine levels were recorded. The presence of anuria was associated with a high mortality in these children. The value of peritoneal dialysis in the treatment of acute renal failure in HUS has been well established. Early and aggressive dialysis therapy has been shown to improve the immediate prognosis for survival.<sup>24</sup> Late

referral, delay in starting dialysis in children with oligoanuria and severe hyponatremia or hyperkalemia contributed to significant mortality in our children. A study from India reported that severe renal injury is often present in children with post dysenteric HUS and the mortality was higher in those with prolonged anuria and total cortical necrosis.<sup>25</sup> A proportion of our patients had evidence of renal impairment at the time of discharge from the hospital indicating the possibility of some renal damage.

Severe neurological involvement such as seizures, coma, and hemiplegia recorded in 30 pc of our children concur with reported rates of 20 to 34 pc in other studies.<sup>26,27</sup> Although some authors have reported strong association between severe neurological findings with death, such association was not found in our study population.<sup>26,28</sup> In contrast to previous findings *E. coli* 0157:H7 related HUS no significant difference in the degree of hyponatremia in children with and without seizures was found in our children.<sup>28</sup>

The majority of the children had significant leucocytosis on admission. This is consistent with granulocyte leukemoid reactions which normally occur during the second week of illness in children with dysentery due to SD1.<sup>22</sup> Butler *et al* found higher peripheral leucocyte counts in children with HUS following SD1 infection than in those who did not develop HUS.<sup>17</sup> In *E. coli* 0157:H7 related HUS the initial peripheral leukocytosis is associated with a poor prognosis.<sup>29</sup> However, in a recent study from India, where SD1 related HUS is frequent, no such correlation was found.<sup>25</sup> There was no association between the level of leucocytosis and anuria in the present study. Further studies are needed to assess the predictive role of leucocytosis in SD1 related HUS.

Bacteremia due to *Shigella* and other bacteria has been found to be more prevalent in infants, malnourished and severely ill patients with shigellosis in Bangladesh.<sup>30</sup> Similar findings in this study underscore the importance of management of presumptive sepsis appropriately.

A significant number of children were underweight or severely malnourished on admission. Shigellosis is known to aggravate pre-existing malnutrition or provoke malnutrition in previously well nourished children.<sup>31,32</sup> Persistent bloody diarrhoea and other severe gastro-intestinal involvement may have further comprised nutrition in a proportion of the children with

HUS. In most patients with shigellosis, caloric requirements exceed basal requirements and therefore appropriate nutritional support (and parenteral nutrition if necessary) should be provided.<sup>33</sup>

In developed countries there has been a dramatic decline in the mortality from *E. coli* O157:H7 related HUS during the acute illness from 30 to 40 pc in the 1960s to as low as 4 pc three decades later.<sup>34,35</sup> The high mortality rate of 40 pc in our children may be partly attributable to lack of previous clinical experience and awareness regarding SD1 related HUS. Earlier recognition, prompt and comprehensive supportive therapy including early dialysis may improve the immediate survival in children with HUS.

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