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Hemolytic-uremic syndrome in Switzerland: a nationwide surveillance 1997–2003

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Abstract Hemolytic-uremic syndrome (HUS) is a leading cause of acute renal failure in childhood. In its typical presentation, it is preceded by an episode of diarrhea mostly due to Shiga-toxin-producing *Escherichia coli*. There is important geographical variation of many aspects of this syndrome. Nationwide data on childhood HUS in Switzerland have not been available so far. In a prospective national study through the Swiss Pediatric Surveillance Unit 114 cases (median age 21 months, 50% boys) were reported between April 1997 and March 2003 by 38 pediatric units (annual incidence 1.42 per 10^5 children ≤16 years). Shiga-toxin-producing *E. coli* were isolated in 32 (60%) of tested stool samples, serotype O157:H7 in eight. Sixteen children presented with only minimal renal involvement, including three with underlying urinary tract infection. Six patients presented with atypical hemolytic-uremic syndrome, and six with HUS due to invasive *Streptococcus pneumoniae* infection. Mortality was 5.3%, including two out of six children with *S. pneumoniae* infection. The severity of thrombocytopenia and the presence of central nervous system involvement significantly correlated with mortality. In conclusion, childhood HUS is not rare in Switzerland. Contrasting other countries, *E. coli* O157:H7 play only a minor role in the etiology. Incomplete manifestation is not uncommon.

Keywords Hemolytic-uremic syndrome · Children · Enterohemorrhagic *E. coli* (EHEC) · Shiga toxin · Renal failure · Clinical spectrum

Abbreviations

HUS	hemolytic-uremic syndrome
D+ HUS	typical HUS (enteropathic or non-enteropathic)
D− HUS	atypical HUS
cHUS	complete HUS
iHUS	incomplete HUS
Stx	Shiga toxin
EHEC	enterohemorrhagic *Escherichia coli*
NENT	Swiss National Centre for Enteropathogenic Bacteria
SPSU	Swiss Pediatric Surveillance Unit
STEC	Shiga-toxin-producing *Escherichia coli*
UTI	urinary tract infection
CI	confidence interval

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Introduction

Childhood hemolytic-uremic syndrome (HUS) is not very frequent but mostly a severe multisystem disorder charac-

terized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal impairment. It is associated with significant morbidity and mortality, including acute and chronic renal failure and long-term multi-organ complications in a substantial number of affected children. In its typical (D+ HUS), mostly enteropathic form, childhood HUS occurs after a prodromal episode of usually bloody diarrhea caused by a Shiga toxin (Stx)-producing pathogen, most commonly enterohemorrhagic *Escherichia coli* (Stx-producing EHEC = STEC), worldwide primarily of serotype O157:H7. However, other serotypes are increasingly reported [15, 25] as well. On average, enteropathic HUS appears six (5–10) days after the onset of gastrointestinal symptoms and affects 3–9% (up to 20% in epidemic forms) of infected children [3, 6]. Risk factors for the development of HUS include young age, bloody diarrhea, fever, elevated leukocyte count, elevated C-reactive protein, as well as treatment with antimotility agents, antibiotics, and non-steroidal anti-inflammatory drugs [1, 4, 8, 17, 36]. Elevated leukocyte count, severe gastrointestinal prodromi, early anuria, and age below 2 years are considered predictors of a severe course [26].

More rarely, STEC cause a typical, but non-enteropathic HUS in the context of an extra-intestinal, mostly urinary tract infection (UTI) [16, 29].

Finally, in some patients, the clinical presentation is not related to diarrhea and/or Stx-producing pathogens; these forms have formerly been referred to as atypical HUS (D− HUS). The etiology of D− HUS is diverse, including other infections, disorders of complement regulation, von Willebrand proteinase deficiency, and more [5, 9, 10, 21]. As infection with *Streptococcus pneumoniae* represents another major infectious cause of non-Stx-associated HUS these cases should be classified separately.

Despite these general characteristics, several studies indicate important geographical variation of clinical, epidemiological, and microbiological features of this syndrome. So far, some single center data [18, 20], but no systematic report on the characteristics of childhood HUS have been available for Switzerland. This was the reason to undertake this study between April 1997 and March 2003, using the SPSU, an ongoing national surveillance system.

Methods

The SPSU was established in 1995 to assess epidemiological and clinical features of selected rare childhood diseases leading to hospitalization. It is operated under the auspices of the Swiss Pediatric Society and the Swiss Federal Office of Public Health. The surveillance period for HUS lasted from April 1, 1997, to March 31, 2003. Cases were defined as children ≤16 years of age with: (1) acute hemolytic anemia,

(2) microscopic evidence of red blood cell fragmentation, (3) thrombocytopenia (platelet count $\leq 150 \times 10^9$/L), and (4) acute renal impairment (urinalysis disclosing either (a) red blood cells, cellular casts, and pathological proteinuria or (b) dysmorphic red cells and pathological proteinuria, with or without (c) creatinine levels above the upper limit of normal for age, or an increase in creatinine of ≥50% above baseline). HUS was diagnosed based on the presence of at least three criteria or two criteria plus isolation of a Stx-producing pathogen.

SPSU reply cards have been sent to all Pediatric Units of Swiss Hospitals at monthly intervals. For each reported case, the respective hospital was provided with a detailed standardized questionnaire. Patients who did not meet the case definitions were rejected. A follow-up questionnaire was sent to the treating physician after 1 year.

Cases with preceding diarrhea (enteropathic) and/or evidence of Stx-producing pathogens in cultures of stool, urine, or blood were classified as typical HUS (D+ HUS). Patients with *S. pneumoniae*-associated HUS were classified separately and the remaining non-Stx-associated cases were referred to as atypical (D− HUS). HUS was moreover referred to as complete (cHUS) in children who fulfilled the above-mentioned serum creatinine definition of renal impairment and as incomplete (iHUS) if the renal impairment manifested only with proteinuria and/or hematuria or a mild documented rise in serum creatinine level (<50% over baseline). If available, stool samples of children with enteropathic HUS were processed for STEC in the Swiss National Center for Enteropathogenic Bacteria (NENT) [12].

Significance between groups was determined by Student's *t* test, by one-way analysis of variance (ANOVA) with Bonferroni multiple comparison post test, and corresponding non-parametric tests as appropriate for continuous, and Fisher's exact test for categorical variables. Results are expressed as mean±standard deviation (SD) or as median with range. Qualitative parameters are given as a proportion (percentage). Two-sided tests were used throughout, and *P* values<0.05 were considered statistically significant.

Results

Between April 1997 and March 2003, all SPSU reply cards and HUS questionnaires were returned (100%). A total of 114 HUS patients (median age 21 months; range 20 days to 13 years; 57 girls and boys, each) were identified. One hundred patients (88%) were ≤5 years old. Typical and atypical HUS accounted for 102 (89%) and six (5%) cases, respectively, and in six (5%) patients HUS was due to invasive infection with *S. pneumoniae*. The disease was complete in 98 (86%) and incomplete in 16 (14%) children. The average annual

incidence was 1.42 cases (range, 0.61–1.92) per 100,000 children ≤16 years of age.

Typical versus atypical and pneumococcal HUS

HUS was typical in 102 children, including 99 with enteropathic and 3 with non-enteropathic forms as a consequence of a STEC-associated UTI. In contrast to typical HUS, which predominantly occurred during the warm season with 70/102 cases (69%) diagnosed between May and September, nine of 12 atypical and *S. pneumoniae*-associated cases (75%) occurred between October and April ($P<0.01$).

STEC were isolated in 32/53 stool samples (60%) examined by the NENT. In three children with UTI-associated HUS, STEC were isolated from the urine and also from a blood culture in one. Eighteen different serotypes were identified, including O157:H7 in eight, O145:H25 in five, O26:H11 in four, and O55:H7 in three samples; the remaining 14 serotypes were identified only once or twice, each. Although serotype O157:H7 was the most frequently isolated serotype, it only accounted for eight of 35 (23%) classified pathogens. In 11 additional children with typical, enteropathic HUS STEC were identified by private laboratories but not further differentiated.

There was no association between isolation of *E. coli* O157:H7 and presentation or clinical course of the disease. Bloody diarrhea was present in 75% of those with and 46% of those without O157:H7 isolation, respectively. Dialysis became necessary in 13% and 39% of these groups, respectively. There was no fatality among children with O157:H7 isolation. O157:H7 was even found in one patient with incomplete HUS, however, complicated by severe intussusception in this case.

Shiga toxin production was documented in 37 of 102 patients with D+ HUS. Unfortunately, the number of samples being tested for Stx is not known. Stx1 was found in seven, Stx2 in 23, and both in seven patients. There was no association of either type with complete or incomplete forms of the disease.

In six children the disease was the consequence of an infection with *S. pneumoniae*. In one previously reported patient the disease complicated an acute infectious mononucleosis [28], while in two patients atypical HUS occurred as a consequence of cobalamin C disease and factor H deficiency, respectively. Classification was not possible in the remaining three patients.

Complete versus incomplete HUS

Hemolytic-uremic syndrome was incomplete in 16/114 (14%) patients. They presented with acute hemolytic anemia, evidence of red blood cell fragmentation, and altered urinalysis. Thrombocytopenia was present in 12 children. However, these children did not fulfill the case definition with regard to their serum creatinine levels. Hemolytic-uremic syndrome was typical in 14 patients with iHUS, including 11 with enteropathic forms (bloody diarrhea in five) and three with UTI. Duration of prodromal diarrhea was longer in iHUS compared to cHUS (10 days versus 5 days, $P<0.01$). STEC were isolated in five of seven examined fecal specimens (serotype O157:H7 in one case), both not significantly different from cHUS. Private laboratories disclosed Shiga-toxin-producing *E. coli* in two further children. No stool sample was available in two cases with an incomplete form of enteropathic HUS. Additionally, in children with iHUS anemia and thrombocytopenia were significantly ($P<0.01$) less pronounced than in children with cHUS (Table 1). Accordingly, blood transfusions were significantly less often needed ($P<0.01$) in patients with iHUS as compared to those with cHUS. Finally (Table 1), in iHUS the duration of hospital stay was significantly shorter compared to survivors with cHUS (9 versus 16 days, $P<0.01$) and neurological involvement was less frequent ($P<0.05$). One girl with O157:H7-associated iHUS developed intussusception requiring surgical intervention.

HUS associated with urinary tract infection

The causative infection was localized in the urinary tract in three children with iHUS. All presented with an acute febrile UTI without any evidence of an intestinal infection. These patients presented with microangiopathic hemolytic anemia and thrombocytopenia; two of them additionally with arterial hypertension. An underlying malformation of the urinary tract was found in one patient.

Mortality

Six patients died (Table 2), corresponding to an overall mortality of 5.3%. All had suffered from cHUS. None of the patient with atypical HUS (D−) died. A causative infectious agent was identified in three children (*S. pneumoniae* in two, STEC in one). The highest mortality (2/6=33%) was observed for HUS associated with invasive *S. pneumoniae* infection ($P<0.05$). Five of the six patients with a fatal outcome (83%) had suffered from severe neurological symptoms, as compared to 18% of survivors with cHUS. Thus, in the presence of severe neurological symptoms, the relative risk of fatal outcome was 17.3 (95% CI, 2.1–140.3, $P<0.01$). In contrast to the survivors with cHUS (platelet count, $46\pm45\times10E^9$/l), patients who died presented with more severe thrombocytopenia (platelet count, $12\pm10\times10E^9$/l; $P<0.01$). Using arbitrary cut-offs in these patients, thrombocytopenia below $20\times10E^9$/l and below $12\times10E9$/l were associated with a relative risk for fatal outcome of 10.5 (95% CI, 1.3–86.0, $P<0.05$) and 14.0 (95% CI, 2.9–68.4, $P<0.01$), respectively.

Table 1 Clinical and laboratory data during the acute phase in 114 patients with hemolytic-uremic syndrome

		Typical D+ HUS	S. pneumoniae HUS	Atypical D− HUS	cHUS	iHUS
Number of children	N (% of total)	102 (89)	6 (5)	6 (5)	98 (86)	16 (14)
Presentation	Complete (cHUS)	N (% of total)	88 (77)	6 (100)	4 (66)		
	Incomplete (iHUS)	N (% of total)	14 (12)		2		
Age (months)	Median (range)	21 (0–161)	29 (19–56)	14 (6–105)	23 (3–161)	19 (0–99)
Sex, male	N (%)	52 (51)	2	3	48 (49)	9 (56)
Pathogen	STEC[a], O157:H7	N	8			7	1
	STEC[a], other strain	N	35			28	7
	S. pneumoniae	N		6		6	0
	Epstein Barr Virus	N			1	1	0
Prodromi	Diarrhea	N (%)	94 (92)	1		83 (85)	11 (69)
	Bloody diarrhea	N (%)	49 (48)			44 (45)	5 (31)
	Urinary tract infection	N (%)	3 (3)			0 (0)	3 (19)
	Respiratory tract infection	N (%)	11 (11)	6	4	19 (19)	2 (13)
	Fever	N (%)	46 (45)	5	1	47 (48)	5 (31)
Symptoms/laboratory tests	Hemoglobin (g/l)	Mean±SD	60±18	49±18	72±22	58±18	74±15***
	Thrombocytopenia	N (%)	95 (93)	6	5	94 (96)	12 (75)
	Platelets (x10E9/l)	Mean±SD	59±77	16±17****	70±69	44±44	138±143***
	Plasma creatinine peak (umol/l)	Mean±SD	304±237	312±182	128±95	335±226	52±15
	Oliguria	N (%)	36 (35)	5	4	45 (46)	0 (0)
	Anuria	N (%)	48 (47)	4	0	52 (53)	0 (0)
	Anuria duration, days	Median (range)	8 (1–31)	6 (1–10)		8 (1–31)	0 (0)
	Arterial hypertension	N (%)	41 (40)	3	3	43 (44)	4 (25)
	Neurological, total	N (%)	21 (21)	1	0	22 (22)	0 (0) **
Treatment	Packed red cells transfusion	N (%)	71 (70)	6	2	73 (74)	6 (38)***
	Dialysis	N (%)	49 (48)	4	1	54 (55)	0 (0)
	Dialysis duration, days	Median (range)	12 (2–120)	12 (1–20)	14	12 (1–120)	0 (0)
Hospital stay	Duration, days	Median (range)	15 (1–100)	12 (1–57)	16 (1–60)	16 (1–100)	9 (1–52)***
Death		N (%)	4 (4)	2	0	6 (6)	0 (0)

D+ HUS diarrhea or STEC-associated hemolytic uremic syndrome, *D− HUS* not diarrhea or STEC-associated hemolytic uremic syndrome, *S. pneumoniae HUS Streptococcus pneumoniae*-associated hemolytic uremic syndrome, *cHUS* complete hemolytic uremic syndrome, *iHUS* incomplete hemolytic uremic syndrome, *STEC* Shiga-toxin-producing *Escherichia coli*, *SD* standard deviation

**P<0.05 compared with cHUS; ***P<0.01 compared with cHUS; ****P<0.05 compared with D+ and D− HUS (ANOVA)

[a] Stool specimen were not tested in all patients with D+ HUS (see "Results")

Table 2 Clinical and laboratory data in six patients with fatal outcome from hemolytic-uremic syndrome

			Total	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Presentation				D+	D+	D+	*S. pneumoniae*	*S. pneumoniae*	D+
Age (months)		Median	21	3	11	15	26	56	58
Sex				Male	Female	Female	Female	Female	Female
Pathogen	STEC	N	1		O145:H25		Yes	Yes	
	S. pneumoniae	N	2						
Prodromi	Diarrhea	N	5	Yes	Yes	Yes	No	Yes	Yes
	Bloody diarrhea	N	2	No	Yes	No	No	No	Yes
	Respiratory tract infection	N	4	No	No	Yes	Yes	Yes	Yes
	Fever	N	3	No	No	Yes	Yes	Yes	No
Symptoms/laboratory tests	Hemoglobin (g/l)	Median	61	40	117	12	40	81	111
	Platelets (x10E9/l)	Median	9	4	31	8	6	10	14
	Plasma creatinine (μmol/l)	Median	291	437	295	252	199	237	270
	Oliguria	N	6	Yes	Yes	Yes	Yes	Yes	Yes
	Anuria	N	5	Yes	Yes	Yes	No	Yes	Yes
	Arterial hypertension	N	3	Yes	No	Yes	No	Yes	No
	Neurological symptoms	N	5	Seizure	Comma	Seizure	–	Disoriented	Seizure
	Cerebral CT imaging			Ischemic encephalopathy	Cortical necrosis	Edema, bleeding		Edema, meningitis	Infarction
Treatment	Packed red cells transfusion	N	5	Yes	Yes	Yes	Yes	Yes	No
	Dialysis	N	5	PD	PD	PD/HD	No	No	PD

PD peritoneal dialysis, *HD* hemodialysis; for abbreviations of D+ HUS, D− HUS, and *S. pneumoniae*, please see footnote Table 1

One-year follow-up

Of a total of 108 survivors, 80 (74%) had a reported 1-year follow-up examination, including 74/98 (76%) of the D+ HUS, four of six (67%) of the D− HUS, and two of four (50%) of the *S. pneumoniae* groups, respectively.

Among the children with D+ HUS persistent renal impairment was reported for 13 (18%) and end-stage renal failure requiring dialysis for four (5%) children. Twelve patients (16%), including five with normal renal function, suffered from persistent arterial hypertension. One patient had persistent hematuria. Other complications were recurrent bloody diarrhea in four (5%) and seizures in three patients (4%; all with renal impairment). Rare complications such as endocrine and exocrine pancreatic insufficiency with insulin-dependent diabetes, reactive arthritis after an *E. coli 0157:H7* infection and cardiomyopathy (with end-stage renal failure) were noted in one patient, each. One patient presented with residual hemiplegia in consequence of carotid artery thrombosis during the acute phase. Another patient was subject to laser therapy because of retinal bleeding.

In the subgroup of D− HUS two patients (50%) were in end-stage renal failure (*P*<0.05, compared to D+ HUS), one suffered from HUS relapses. Two children (50%) were treated for isolated arterial hypertension. No other rare complications were reported. No sequelae were reported by the two patients with *S. pneumoniae*-associated HUS.

Ten questionnaires were received from patients who initially suffered from iHUS (*n*=16). The only long-term consequence reported by these patients was recurrence of bloody diarrhea in one case.

Clinical and laboratory presentation during the acute phase was similar in children with normal renal function at follow-up, compared to those with chronic kidney disease and reduced glomerular filtration after 1 year.

Only the need for transfusion was significantly associated with reduced renal function at 1 year (*P*<0.05); for the duration of dialysis (39±38 versus 10±4 days) and the incidence of seizures (31% versus 10%) during the acute phase, the respective figures remained just below statistical significance (*P*=0.06 for both).

Discussion

Hemolytic-uremic syndrome was first described by Gasser and coworkers in 1955 in Switzerland [14]. However, except some single center studies [18, 20], nationwide data on childhood HUS in Switzerland have not been available so far. This report summarizes the results of the first

nationwide prospective cross-sectional study performed between April 1997 and March 2003 using the SPSU network. In addition to the widely established features [25], this study reveals some particular aspects of childhood HUS: enterohemorrhagic *E. coli* of serotype O157:H7 only play a minor role in etiology of HUS in Switzerland, and infection with this strain is not associated with the most severe courses of the disease. Fourteen percent of the patients presented with only minor renal involvement, including three patients in whom HUS was caused by a STEC-associated UTI. Finally, the degree of thrombocytopenia and severe neurological symptoms were significantly associated with the risk of fatal outcome, whereas young age was not associated with the severity of the disease.

HUS is associated with significant morbidity and mortality during the acute phase. It is a leading cause of acute renal failure and results in long-term renal and extra-renal complications in a substantial number of affected children. It consists of a heterogeneous group of hemolytic disorders and new insights into pathophysiology have demonstrated, that HUS represents one clinical manifestation of a broader spectrum referred to as thrombotic microangiopathy [31], characterized by injury to the vascular endothelium which can be triggered by a number of different etiologies. Our survey primarily focused on the description of epidemiological and clinical aspects of HUS in Switzerland, whereas rare etiologies of the disease in D− HUS were not systematically tracked. Furthermore, we chose the traditional classification into D+ and D− forms of the disease for the presentation of our data in order to allow comparison with data from other countries. Patients with *S. pneumoniae*-associated HUS were classified separately as a third group.

In accordance with most published reports [2, 15, 26], the presentation of HUS in this study was typical (D+ HUS) in the majority of the patients (89%); these cases occurred significantly more often during summertime. Nevertheless, EHEC were successfully isolated and characterized in only 60% of tested stool samples, an observation that has previously been reported. In addition to technical difficulties to identify EHEC serotypes [7], it is assumed that at clinical onset of HUS, the causative agent has started to disappear from the intestine resulting in negative stool samples in many patients [30]. In North America and worldwide O157:H7 is the predominant serotype of EHEC causing HUS [2]. However, in Australia [11], Germany, and Austria [15] non-0157 STEC strains were more common. In our study, we found similar results with O157:H7 accounting for only eight (25%) of 32 positively tested stool samples and eight of 53 (15%) of all tested specimens respectively [19], underlining the increasingly acknowledged burden of disease associated with non-O157 STEC. Additionally, it is evermore recognized that illness due to non-O157 STEC may be equivalent in severity to illness induced by *E. coli* O157:H7. Accordingly, in the present study we found no association between isolation of *E. coli* O157:H7 and presentation or clinical course of the disease.

In our database, 86% of the patients had major renal involvement (cHUS), 47% required dialysis, and 65% received packed red cell transfusion, data similar to previous reports [2, 15, 26]. It has been described that some patients develop hemolytic anemia and thrombocytopenia with little evidence of renal disease, whereas other children present with important renal disease comparatively associated with few hematological abnormalities [32]. The present study clearly reveals a distinct subgroup of patients with only minor renal involvement. These 14% of patients, referred to as suffering from iHUS (Table 1), also presented with significantly less pronounced hematological abnormalities and therefore less need for transfusion, less neurological involvement, and shorter duration of hospitalization. In contrast, prodromal diarrhea lasted significantly longer compared to patients with cHUS, presumably reflecting a less severe multisystem involvement. Otherwise there were no differences in frequency of bloody diarrhea or causative serotypes of *E. coli* between the two groups. The observed proportion of iHUS is likely to represent an underestimate since many such patients, especially in case of even milder forms are unlikely to reach the hospital, or even to be diagnosed. Of note, in a prospective study in Argentina the incidence of iHUS complicating bloody diarrhea was twice that of cHUS [22]. This is of particular importance because long-term follow-up examinations will be missed in unrecognized cases. There are only few reports describing the various features of iHUS, even in large surveys of cHUS; additionally the case definitions were not universally the same [22, 23, 33]. In rare cases, HUS can originate from UTI [16,29]; in three patients of this series, iHUS was consequence of a STEC-associated UTI. Some authors have suggested that antibiotics may aggravate enteropathic HUS [36]. In contrast, prompt initiation of antibiotic treatment is certainly crucial for a favorable outcome in STEC-associated UTI with consecutive HUS.

In a minority of patients, the clinical presentation of HUS is atypical (D− HUS), i.e. not related to enterocolitis and/or STEC-infection. The etiology of D− HUS is diverse, including infectious causes such as HIV and more rarely other viral agents, genetic abnormalities of complement regulatory proteins (complement factor H, I, B, or MCP), and von Willebrand proteinase deficiency [5, 9, 10, 21, 24, 35]. In this survey, six patients (5%) presented with D− HUS, and six patients had HUS due to *S. pneumoniae* infection. This figure is slightly higher than in other studies, which reported this association for 38–43% of non-STEC HUS [10]; this might support the impression of an increasing incidence of *S. pneumoniae*-associated HUS [34]. Other identified causes of D− HUS in this series were

cobalamin C disease, factor H deficiency, and infectious mononucleosis in one patient each; for the remaining patients, the origin remained unexplained.

Many studies addressed the short- and long-term course and outcome of HUS. In summary, it is assumed that death or end-stage renal disease occurs in about 12% of D+ HUS and 25% of survivors demonstrate long-term renal sequelae [13], whereas prognosis in non-Stx-associated HUS seems to be even worse. Given the important methodological differences between studies, comparison proves difficult and the subject still remains controversial [13]. Age under 2 years [8], HUS due to *E. coli* O157:H7 [15], high leukocyte count [15, 17], D− and pneumococcal HUS [9, 25], central nervous symptoms [13, 27], and the need of dialysis during the acute phase [13] have all been associated with a severe course and a worse long-term prognosis, respectively. We report on a highly significant association between both, severe thrombocytopenia and central nervous manifestations, with risk of death during the acute phase and a significant association between both, the need for transfusion and the long-term prognosis (renal function). Additionally, we observed a tendency towards worse outcome with signs of chronic kidney disease or even end-stage renal disease in children with longer duration of dialysis and in those with seizures. The small number of patients certainly prohibits firm interpretation of these observations and, therefore, further studies are mandatory. The overall mortality in this series was 5.3%, similar to 3–5% reported in the literature [15, 25, 26]. Compared to D+ HUS (4%), children with pneumococcal HUS (33%) had a significantly higher mortality ($P<0.05$), supporting the results of other studies that suggest a more severe acute course of HUS due to *S. pneumoniae* [10, 34]. Children with iHUS showed no renal sequelae at 1 year after the acute disease. Whether this holds true for the long-term prognosis remains to be studied. In their review, Garg et al. [13] found an association between the severity of the acute illness and an adverse long-term outcome in children with D+ HUS. However, these authors found also several studies suggesting that patients with less severe forms of HUS may still demonstrate renal sequelae at follow-up, in several even after apparent complete recovery from acute HUS. These observations emphasize the necessity of long-term follow-up after HUS, even in case of mild acute disease or initial apparent complete recovery. Therefore, unless other data become available, we suggest, that children with iHUS also deserve careful long-term follow-up. In order to recruit these children for appropriate care, the awareness of these mild forms of HUS needs to be increased.

Taking the limitations of the cross-sectional design of this study, i.e. the limited number of patients and the short follow-up period, into account, we conclude that this first, prospective, national study on childhood HUS in Switzerland establishes robust clinical, epidemiological, and bacteriological data, emphasizing the need for further long-term studies, especially to identify children at risk for long-term sequelae after minor renal involvement or initial apparent complete recovery of acute disease.

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