Pediatric Nephrology (2020) 35:2205–2210
https://doi.org/10.1007/s00467-020-04713-1

EDITORIAL COMMENTARY

"Disproportionate" hyperuricemia in children with hemolytic uremic syndrome (HUS): should we regard this as a "medical emergency"?

Ron Hogg[1]

Received: 30 June 2020 / Accepted: 8 July 2020 / Published online: 27 July 2020

Introduction—definitions

In the 65 years since Gasser first described a group of children with features of hemolytic uremic syndrome (HUS) [1], there have been many changes in terminology when different aspects of the pathophysiology and treatment options of HUS are described. In this review, I will mainly use the generic term HUS since I will be reviewing reports that were published before and after the distinctions between "typical" and "atypical" or D+/D−, for example, and before the role of Shiga toxin was described. However, it is reasonable to conclude that most of the patients to be reviewed in this commentary had typical D+ HUS associated with Shiga toxin–producing *Escherichia coli* (STEC).

It will also be relevant to comment on the different levels of serum uric acid (SUA) that have been used to define the presence of hyperuricemia (HU) in children based on age and sex. In some studies, age- and sex-appropriate upper levels have been used as the basis of HU, whereas others use arbitrary levels such as 7 or 8 mg/dL (41.7 or 47.6 μmol/L). It will also be appropriate to discuss what level of SUA should be regarded as "nephrotoxic" in infants and young children.

The primary purpose of this commentary is to discuss the findings in the article by Cho et al. that appear in this issue of Pediatric Nephrology [2] and consider how the results may lead to possible changes in the management of children with typical HUS.

✉ Ron Hogg
ronjhogg@gmail.com

[1] Kailua Kona, HI, USA

Historical perspective of the prevalence of HU in children with HUS

Although it is well accepted that in all forms of acute kidney injury (AKI) serum levels of uric acid will increase when glomerular filtration rates (GFR) fall, there are some children with HUS who appear to have a level of HU that is "disproportionate to the degree of renal failure." This term was first used by Alan Gruskin and colleagues to describe a scenario that they encountered in 1969 when they were performing studies of the transperitoneal movement of solutes (including uric acid) in two infants with HUS [3]. These authors subsequently monitored the SUA levels in a series of 26 children and reported their findings in 1984 [4], as shown in Table 1, in which findings in children with HU and HUS published over the past 50 years are provided.

The first report of a series of children with severe HU associated with HUS was published by Kaplan and Thomson in 1976 [5] (Table1). These authors found elevated SUA levels, ranging from 10 to 29 mg/dL, in 18 children with HUS. Nine of the children had SUA concentrations over 20 mg/dL, and in one child, it was reported that 5.5 g of uric acid was removed in PD fluid over 53 h. Five years later, in 1981, two reports of severe HU in children with HUS were reported [6, 11]. Goldberg et al. referred to the level of HU in their patients as being "extreme" [11]. Brasher and Siegler reported that the SUA was greater than 20 mg/dL in 10 of the 23 patients in whom SUA levels were obtained [6].

In 1984, Gruskin and colleagues described details of the studies they performed in 1969 and provided data on the 26 patients they monitored from 1968 to 1983 [4]. The initial SUA levels in their patients ranged from 3.6 to 30 mg/dL with the mean value being 12.9 ± 4.7 mg/dL. In 22 of the 26 children, the SUA was above 8 mg/dL, and all but one of the children had HU based on their age- and sex-related

Table 1 Historical review of publications describing HU in patients with HUS

Year (ref)	Author(s) country	Patients	SUA (mg/dL)
1976 [5]	Kaplan and Thomas, South Africa	18 children with HUS	Mean SUA 16.6 mg/dL (> 20 mg/dL in 9/18 pts.)
1981 [6]	Brasher and Siegler, USA	23/60 children with HUS seen 1970–1978	Mean SUA > 20 mg/dL in 10 (43%) of 23 patients
1984 [4]	Gruskin et al., USA	26 children with HUS seen 1968–1983	SUA > 8 mg/dL in 22 of 26 children tested
1988 [7]	O'Regan and Rousseau, Canada	9 of 14 children with HUS	SUA ranged from 10.2 to 18.7 mg/dL
2012 [8]	Balestracci et al., Argentina	19 of 29 children with HUS seen 2005–2012	SUA ranged from 10.5 to 28 mg/dL
2016 [9]	Ardissino et al., Italy	a) 38 children with HUS in 2012–2014 compared with b) 38 children in 2006–2009	SUA median a) 8.7 mg/dL (IQR 6.7–11.1 mg/dL) vs b) 8.6 (6.7–9.8 mg/dL)
2020 [10]	Balestracci et al., Argentina	9 children with HUS seen 2016–2018	SUA range: 8.3 to 19.2 mg/dL (median 11.4 mg/dL)
2020 (personal communication)	Balestracci, Argentina	SUA was measured in 103 of 105 children with HUS seen from 2007 to 2020	SUA was > 10 mg/dL in 60 (58%) of 103 patients; > 8 mg/dL in 67 (65%)
2020 [2]	Cho et al., Korea	42 children with HUS seen 2005–2017	Median SUA 12.5 mg/dL (IQR 10.2–14.5 mg/dL)

upper limit of SUA. In 1988, O'Regan and Rousseau described HU in 9 of 14 children with HUS aged 11 months to 4 years; these children had SUA levels ranging from 10.2 to 18.8 mg/dL [7].

More than 20 years elapsed before the next report of HU in children with HUS was published by Balestracci et al. [8]. In 2012, these authors reported SUA levels in 29 Argentinian children admitted to their hospital with D+ HUS over a period of 5 years. Overall, 22 of the patients (median age 1.9 years) had SUA levels > 8 mg/dL. SUA levels were higher at baseline in 19 of the 29 children (65%) who required dialysis (median 14 mg/dL; range 10.5–28.0 mg/dL) than in 10 who did not need dialysis (SUA 5.4 mg/dL; 4.1–18.7 mg/dL, $p = 0.003$) [8]. In 2016, Ardissino et al. described 38 Italian children with HUS who presented between 2012 and 2014 (SUA median level of 8.6 (IQR 6.3–9.8 mg/dL)). The findings were comparable to those found in another 38 children they treated from 2006 to 2009 (SUA 8.7 (6.7–11.1 mg/d)) [9].

In a publication that appeared earlier this year in Pediatric Nephrology, Balestracci et al. described 9 additional patients with HU and HUS [10]. Their baseline SUA levels ranged from 8.3 to 19.2 mg/dL, median 11.4 mg/dL. Dr. Balestracci has kindly provided an update on the prevalence of HU in children with HUS referred to Hospital General de Niños Pedro de Elizalde, Buenos Aires, from 2007 to 2020 (personal communication). During that time, 58% of 103 patients had SUA levels > 10 mg/dL on admission to their hospital (details in Table 1). It is apparent from this historical review that since its first recognition 50 years ago, severe HU in children with HUS has been described intermittently in major pediatric nephrology centers around the world.

Review of the study by Cho et al.

Study population

Cho et al. conducted a retrospective analysis using the medical records of children with typical HUS who were admitted to their hospital in Seoul, Korea, from 2005 to 2017. From 2013 to 2017, 16 patients with SUA levels > 7 mg/dL (41.7 μmol/L) were given a single dose of rasburicase (treatment group). They compared the hospital courses and 1-year outcomes of these patients with those of 40 children with HU and HUS treated from 2005 to 2012 (control group). The control group did not receive rasburicase, but Cho et al. reported that the rest of their management was comparable to that used in the treatment group. After 2017, rasburicase was not available in their country for off-label use in children with HUS. The levels of SUA (median SUA 12.5 mg/dL (IQR 10.2–14.5 mg/dL)) in the patients treated by Cho et al. are certainly consistent with the previous reports described above.

Protocol details and short-term impact of treatment given by Cho et al.

Cho et al. administered a single dose of rasburicase (median dose 0.10 (IQR 0.09–0.13) mg/kg body weight) to their patients at a median 17 (IQR 8–25) hours after hospital admission and 7 (− 2 to 20) hours before starting dialysis, which was instituted in 6 (46.2%) of the treatment group versus 19 (65.5%) of the control group ($p = 0.24$). HU persisted for a total of only 36

(19–58) hours in the treatment group versus 120 (87–153) hours in the control group ($p < 0.001$). The period of hospital stay was also less in the treatment group (median 9 days versus 12 days, $p = 0.003$). Specific details regarding how low the SUA levels fell in the patients were not provided.

Comparison of the rasburicase protocol used by Cho et al. with previous reports

It is appropriate to compare the protocol used by Cho et al. with that described in other children with HUS and HU, but also with the protocols reported in children with tumor lysis syndrome (TLS) where the wealth of data is more extensive.

The first report of rasburicase use in a child with HUS involved a 9-month-old Caucasian male infant in 2012 [12]. The patient was in kidney failure with serum creatinine (SCr) 2.73 mg/dL on admission and no urine output for 12 h. He was given a single 1.5-mg dose of rasburicase (0.18 mg/kg) after his SUA was found to be 12.3 mg/dL. The patient had a dramatic response with the SUA falling by 97% to 0.3 mg/dL in less than 12 h. The patient was also given IV furosemide and generous fluid resuscitation, which may also have contributed to the fall in SUA. His kidney function improved over the next few days, but he continued to have evidence of hemolysis necessitating a blood transfusion on hospital day 5, at which time his serum creatinine was 1.61 mg/dL and his Hb was 5.9 g/dL. He was discharged after 7 days (SCr 0.69 mg/dL and SUA 3.9 mg/dL).

The second report of rasburicase use in children with HUS was published earlier this year by Balestracci et al. [10]. They treated 9 children (median age 2 years) with STEC-HUS and SUA levels > 8 mg/dL with a single dose of rasburicase 0.2 mg/kg. The laboratory studies' performed pre-treatment included SUA: median 11.4 mg/dL, range 8.3 to 19.2 mg/dL and SCr median 3.35 mg/dL, range 1.5–9.1 mg/dL. Repeat studies obtained within 24 h of rasburicase infusion showed a fall of SUA by 83% to 1.8 mg/dL (0.3–5.0 mg/dL, $p = 0.009$). However, the urine output continued to fall and the SCr rose to 3.4 mg/dL (2.3–9.1 mg/dL), so dialysis was started in all 9 patients. The patients were discharged from hospital after 16 (6–28) days with much improved SUA levels ranging from 3.2 to 5.8 mg/dL.

Response to rasburicase in children with tumor lysis syndrome

The introduction of recombinant uric oxidase (rasburicase) over 20 years ago signaled a dramatic improvement in the management of HU and a marked reduction in the incidence of TLS and AKI requiring dialysis in children with hematologic malignancies. Two of the pivotal studies that documented both the speed and magnitude of the fall in SUA levels, exceeding 80% within 4 h of a single dose of 0.2 mg/kg, are shown in Table 2 [13, 14]. It is noteworthy that these findings led to the FDA approving rasburicase in these children many years before the same was true in adults.

One of the main deterrents to the use of rasburicase is its high cost. This has led to some studies exploring the use of lower doses to treat TLS than that recommended by the manufacturer, i.e., 0.2 mg/kg daily for up to 5 days. The results of 2 such studies by Jayabose et al. [16] and Gopakumar et al. [17], which Cho et al. referenced in their decision to use a median dose of only 0.1 mg/kg, show inferior responses to those obtained with the recommended dose. A recent review and meta-analysis by Yu et al. concluded that doses of 0.15 or 0.20 mg/kg are needed to produce excellent responses in young children with HU [18], confirming the findings reported by Pui et al. [14].

Duration of HU in HUS patients given rasburicase: is this important?

The duration of HU in the patients given rasburicase by Cho et al. was significantly reduced but was still potentially a long time (median 36h, IQR 19-58h) when compared with the 4-h duration shown in the studies listed in Table 2 when doses of 0.15–0.20 were used. After many years of controversy, recent studies have demonstrated clearly that HU increases the risk of AKI by both crystal-dependent and crystal-independent mechanisms in adults [19–21], children [15, 22], and experimental animals [23]. The subject is more complex, and less easy to evaluate, in a situation where there is a co-existing primary glomerular disorder, as in the case of a child with HUS. However, it seems reasonable to speculate, but harder to prove, that if significant nephrotoxicity occurs consistently with a certain level of HU in patients without a glomerular disease, the same level of HU might be expected to induce similar, or even worse, additive damage to kidneys with a glomerular disease. A review of the data supporting the role of HU in causing or potentiating AKI is beyond the scope of this commentary but has been covered extensively in the references given above.

Follow-up and outcome of children with HUS

The study by Cho et al. differed from previous reports describing the response of patients with HU and HUS to rasburicase by providing "relatively" long-term follow-up information. The authors were able to obtain complete 1-year follow-up data in 82% (13/16) of the patients treated with rasburicase and 73% (29/40) of the control group. They restricted their analyses to patients in whom the 1-year follow-up evaluation

Table 2 Response to rasburicase in children with acute hyperuricemic conditions

Year (ref)	Author and country	Patients	Initial dose of rasburicase	Response after 1 dose (time measured)
2001 [13]	Goldman et al. USA	27 children with leukemia or lymphoma. 10 of 27 had HU, i.e., SUA 11.7 ± 2.5 mg/dL	0.20 mg/kg	After 4 h, the SUA fell by 86% overall, and to < 4 mg/dL in all 10 with HU
2001 [14]	Pui et al. USA	65 children, adolescents, and young adults with HU and leukemia or lymphoma	0.15 or 0.2 mg/dL	After 4 h, the median SUA fell with both doses from 9.7 to 1 mg/dL
2010 [15]	Hobbs et al. USA	7 infants with SUA > 8 mg/dL associated with AKI from various causes	0.17+/− 0.04 mg/kg	"Within 24 h," SUA fell 93%, from 13.6 ± 4.5 to 0.9 ± 0.6 mg/dL
2015 [16]	Jayabose et al. India	41 children with hematologic malignancies and SUA levels ranging from 4.3 to 45.5 mg/dL (median 8.5 mg/dL)	Median dose 0.12 mg/kg; range 0.08 to 0.24 mg/kg	After 6 h, SUA fell 80%, range 40% to 98%. Single dose was not enough in 12 children
2017 [17]	Gopakumar et al. India	18 children with leukemia or lymphoma associated with HU	Mean dose 0.085 mg/kg	After 4 h, the mean SUA level fell by 64.8%. After 24 h, SUA fell by 74.5%

included measurement of blood pressure, proteinuria, and estimated GFR. The 3 patients who received rasburicase but were not included in the analysis showed no renal sequelae post-discharge but did not have a complete 12 months of follow-up evaluation.

The estimated GFR (eGFR) at the 1-year follow-up visit was significantly lower in the control group compared with that in the treatment group (92.1 versus 111 ml/min/1.73m^2, $p = 0.009$). Differences in the frequency of hypertension and proteinuria, albeit low grade, were also suggestive, but not statistically significantly more frequent, in the control group. When the three indicators of progressive risk were combined, the renal sequelae were seen significantly more often in the control group (62.1% versus 7.7%, $p = 0.001$).

Comparison of the 1-year follow-up data with previous reports

One of the most compelling aspects of the paper by Cho et al. is the low percentage of patients in the rasburicase group who showed any renal sequelae after 1 year of follow-up, especially the eGFR. This compared favorably not only with the patients in their control group but also with previous 1-year follow-up findings in the literature [24–29]. This optimistic finding must, however, be viewed with caution since multiple reports have now documented that patients may develop significant abnormalities in blood pressure, proteinuria, and/or reduced eGFR after 5 or 10 years that were not evident at the 1-year follow-up [24–29].

Why do some children with HUS develop "disproportionate" HU?

The events responsible for the development of severe HU in some patients with HUS have not been clearly delineated, but there are some attractive candidates. These may involve increased release or production in addition to decreased excretion by the kidneys and gastro-intestinal tract. One mechanism might be an increase in release of uric acid from red and white blood cells. This possibility was explored by Gruskin et al. following their pivotal observations in two infants with HUS in 1969 [3, 4]. They measured uric acid release before and after freeze lysis of centrifugally separated red cells, white cells, and platelets that were suspended in a uric acid–free salt solution. They reported that "significant quantities" of uric acid were released from red and white cells but not from platelets. Their findings may be pertinent to the consistent finding that leukocytosis, along with hemoconcentration and duration of oligo-anuria, is among the most often quoted determinants of a guarded prognosis in children with typical HUS.

Looking to the future

The results obtained by Cho et al. suggest that children with HUS and marked HU may derive short-term and (at least relatively) long-term benefits from rasburicase, but at this time, the most pressing need will be to determine the prevalence of HU in this patient population. This can be achieved by including measurement of SUA levels as soon as a diagnosis of HUS is reached (or perhaps even in patients with

persistent bloody diarrhea). It is apparent from the foregoing that "disproportionate" HU may be a significant feature in at least some children with HUS.

One thing that is not clear, at least to me, is why there were no reports of HU in children with HUS for 22 years (to the best of my knowledge) after the impressive findings published between 1976 and 1990. There may be many factors that contribute to this situation. I believe one reason is that SUA levels are not measured routinely in many children with AKI, including those with HUS. Serum UA levels are not included in some of the commonly used "test bundles," such as the comprehensive metabolic profile (CMP-14). Although this test contains most of the analytes of interest in a child with AKI, the absence of serum uric acid is most pertinent to the current topic. I have been assured that cost is not a deterrent, since the addition of SUA to the other analytes would be very small. The same concern is not present when a SMAC 20 is chosen, since this includes SUA levels.

A second possibility is that uric acid has traditionally been considered a consequence of AKI rather than a contributing cause. A third possible reason in the past for not requesting SUA levels in patients with HUS is the absence of a medication that produces a rapid reduction in SUA levels. This problem now has a potential solution in the form of rasburicase, the recombinant form of urate oxidase used by Cho et al. Last, but not the least, there are no prospective controlled trials that show safety and efficacy data associated with the use of rasburicase to reduce HU in patients with HUS.

Whether children with HUS and markedly elevated SUA levels should be treated with off-label rasburicase in the absence of an FDA indication for its use at the present time is at the discretion of individual pediatric nephrologists and the parents of affected children. In the absence of controlled studies, a single dose of rasburicase might be an appropriate option to consider (and discuss) if a child with HUS is found to have a SUA > 10 mg/dL. However, the optimal way to test whether rasburicase is indicated in children with HUS and HU would be a double-blind placebo-controlled clinical trial. In the meantime, the optimal management of children with typical HUS will continue to include aggressive and early volume repletion, or perhaps expansion [9], and prompt dialysis when indicated. In addition, we eagerly await the results of multicenter trials evaluating the role of eculizumab in children with typical HUS [30].

Concluding remarks: opinion section

Based on the foregoing review, I believe that it may now be appropriate for pediatric nephrologists to regard severe HU in children with HUS in much the same way as our pediatric oncology colleagues approach children with hematologic malignancies. By instituting early and aggressive use of rasburicase, they have almost eradicated TLS in their patients. Although it is doubtful that such a dramatic response would be seen in children with HUS, immediate administration of rasburicase to the children who are found to have high levels of uric acid, especially those with levels above 10 mg/dL, might provide a significant benefit to the patients without having a negative impact on the benefits that have been well documented with the various supportive measures described above or the improvement in neurological, and perhaps renal, outcomes that may be disclosed by the current trials of eculizumab. Of course, the potential benefit of treating severe HU would first require that SUA levels be measured in these patients.

Acknowledgments Dr. Hogg wishes to acknowledge the assistance from Drs Alejandro Balestracci, Bernard Kaplan, Joseph Laycock, and Elisabeth Rousseau in the preparation of this manuscript.

Compliance with ethical standards

Conflict of interest The author declares no conflict of interest.

References

1. Gasser C, Gautier E, Steck A, Siebenmann RE, Oechslin R (1955) Hemolytic uremic syndrome: bilateral necrosis of the renal cortex in acute acquired hemolytic anemia. Schweiz Med Wochenschr (Article in German) 85:905–909
2. Cho MH, Ahn YH, Lim SH, Kim JH, Ha I-S, Cheong HI, Kang HG (2020) Rasburicase improves the outcome of acute kidney injury from typical hemolytic uremic syndrome. Pediatr Nephrol. https://doi.org/10.1007/s00467-020-04644-x
3. Naiman JL, Mellon M, Gruskin AB (1970) Disproportionate hyperuricemia in hemolysis associated with renal failure. Abstr Soc Pediatr Res
4. Gruskin AB, Naiman JL, Polinsky MS, Baluarte HJ, Kaiser BA, Perlnan SA, Morgenstern BZ (1984) Uric acid perturbations in the hemolytic uremic syndrome. In: Strauss J (ed) Acute renal disorders and renal emergencies, Developments in nephrology, vol 7. Springer, Boston, pp 33–42
5. Kaplan BS, Thomson PD (1976) Hyperuricemia in the hemolytic-uremic syndrome. Am J Dis Child 130:854–856
6. Brasher C, Siegler RL (1981) The hemolytic-uremic syndrome. West J Med 134:193–197
7. O'Regan S, Rousseau E (1988) Hemolytic uremic syndrome: urate nephropathy superimposed on an acute glomerulopathy? An hypothesis. Clin Nephrol 30:207–210
8. Balestracci A, Martin SM, Toledo I (2012) Hyperuricemia in children with post-diarrheal hemolytic uremic syndrome. Pediatr Nephrol 27:1421–1422
9. Ardissino G, Tel F, Possenti M, Testa S, Consonni D, Paglialonga F, Salardi S, Borsa-Ghiringhelli N, Salice P, Tedeschi S, Castorina P, Colombo RM, Arghittu M, Daprai L, Monzani A, Tozzoli R, Brigotti M, Torresani E (2016) Early volume expansion and outcomes of hemolytic uremic syndrome. Pediatrics 137:e20152153
10. Balestracci A, Meni Battaglia L, Martin SM, Toledo I (2020) Rasburicase in hemolytic uremic syndrome related to Shiga toxin-producing Escherichia coli: a report of nine cases. Pediatr Nephrol 35:1133–1137

11. Goldberg A, Mundel G, Tieder M (1981) Hemolytic uremic syndrome with extreme hyperuricemia. Harefuah (Article in Hebrew) 101:307–309
12. Acosta AA, Hogg RJ (2012) Rasburicase for hyperuricemia in hemolytic uremic syndrome. Pediatr Nephrol 27:325–329
13. Goldman SC, Holcenberg JS, Finklestein JZ, Hutchinson R, Kreissman S, Johnson FL, Tou C, Harvey E, Morris E, Cairo MS (2001) A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood 97:2998–3003
14. Pui CH, Mahmoud HH, Wiley JM, Woods GM, Leverger G, Camitta B, Hastings C, Blaney SM, Relling MV, Reaman GH (2001) Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukemia or lymphoma. J Clin Oncol 19:697–704
15. Hobbs DJ, Steinke JM, Chung JY, Barletta GM, Bunchman TE (2010) Rasburicase improves hyperuricemia in infants with acute kidney injury. Pediatr Nephrol 25:305–309
16. Jayabose S, Kumar V, Dhanabalan R, Rajan P, Rathnam K, Viswanathan TK (2015) Low-dose rasburicase in hematologic malignancies. Indian J Pediatr 82:458–461
17. Gopakumar KG, Thankamony P, Seetharam S, Kusumakumary P (2017) Treatment of tumor lysis syndrome in children with leukemia/lymphoma in resource-limited settings-efficacy of a fixed low-dose rasburicase. Pediatr Hematol Oncol 34:206–211
18. Yu X, Liu L, Nie X, Li J, Zhang J, Zhao L, Wang X (2017) The optimal single-dose regimen of rasburicase for management of tumour lysis syndrome in children and adults: a systematic review and meta-analysis. J Clin Pharm Ther 42:18–26
19. Cheungpasitporn W, Thongprayon C, Harrison AM, Erickson SB (2016) Admission hyperuricemia increases the risk of acute kidney injury in hospitalized patients. Clin Kidney J 9:51–56
20. Xu X, Hu J, Song N, Chen R, Zhang T, Ding X (2017) Hyperuricemia increases the risk of acute kidney injury: a systematic review and meta-analysis. BMC Nephrol 18:27
21. Ejaz AA, Johnson RJ, Shimada M, Mohandas R, Alquadan KF, Beaver TM, Lapsia V, Dass B (2019) The role of uric acid in acute kidney injury. Nephron 42:275–283
22. Fathallah-Shaykh SA, Cramer MT (2014) Uric acid and the kidney. Pediatr Nephrol 29:999–1008
23. Haryono A, Nugrahaningsih DAA, Sari DCR, Romi MM, Arfian N (2018) Reduction of serum uric acid associated with attenuation of renal injury, inflammation and macrophages M/M2 ratio in hyperuricemic mouse model. Kobe J Med Sci 64:E107–E114
24. Rosales A, Hofer J, Zimmerhackl LB, Jungraithmayr TC, Riedl M, Giner T, Strasak A, Orth-Holler D, Wurzner R, Karch H (2012) Need for long-term follow-up in enterohemorrhagic Escherichia coli associated hemolytic uremic syndrome due to late-emerging sequelae. Clin Infect Dis 54:1413–1421
25. Spinale A, Ruebner RL, Copelovitch L, Kaplan BS (2013) Long-term outcomes of Shiga toxin hemolytic uremic syndrome. Pediatr Nephrol 28:2097–2105
26. Vaterodt L, Holle J, Huseman D, Muller D, Thumfart J (2018) Short- and long-term renal outcome of hemolytic–uremic syndrome in childhood. Front Pediatr 6:220
27. Pundziene B, Dobiliene D, Cerkauskiene R, Mitkiene R, Medzeviciene A, Darksuviene E, Jankauskiene A (2015) Long-term follow-up of children with typical hemolytic uremic syndrome. Medicina 51:146–151
28. Monet-Didailler C, Godron-Dubrasquet A, Madden I, Delmas Y, Llanas B, Harambat J (2019) Long-term outcome of diarrhea-associated hemolytic uremic syndrome is poorly related to markers of kidney injury at 1-year follow-up in a population-based cohort. Pediatr Nephrol 34:657–662
29. Harkins VJ, McAllister DA, Reynolds BC (2020) Shiga-toxin E.coli hemolytic uremic syndrome: review of management and long-term outcome. Curr Pediatr Rep 8:16–25
30. Lapeyraque A-L, Malina M, Fremeaux-Bacchi V, Boppel T, Kirschfink M, Oualha M, Proulx F, Clermont M-J, Le Deist F, Niaudet P, Schaefer F (2011) Complement blockade in severe Shiga-toxin-associated HUS. N Engl J Med 364:2561–2563