

## Urolithiasis in pediatric patients with acute lymphoblastic leukemia

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**We evaluated the incidence, timing, and consequences of urolithiasis in children with acute lymphoblastic leukemia (ALL). A total of 20 patients with urolithiasis were identified from 2095 patients with ALL treated at St Jude Children's Research Hospital on consecutive protocols between 1968 and 1998. For remission induction therapy, all patients received daily prednisone; continuation chemotherapy regimens differed by protocol with some including pulses of prednisone or dexamethasone and others no glucocorticoid. Patients with urolithiasis were older at diagnosis of ALL than those without urolithiasis (median age, 7.5 vs 5.0 years;  $P=0.03$ ) and less likely to be black ( $P=0.03$ ) than white or Hispanic, but sex and treatment era did not differ. Presenting symptoms included abdominal or flank pain, hematuria, and dysuria. All stones analyzed biochemically were calcium stones. The incidence of urolithiasis after completion of therapy was 1.8 per 10000 person-years. Compared to this baseline rate, the relative risk of urolithiasis was 45 ( $P<0.01$ ) during induction therapy, 22 ( $P<0.01$ ) during continuation therapy with glucocorticoids, and 5.1 ( $P>0.05$ ) during continuation therapy without glucocorticoids. Urolithiasis occurred 4.5 times more often during continuation treatment with glucocorticoids than without ( $P<0.05$ ). Seven patients (35%) had recurrent urolithiasis. Patients with ALL are at risk of developing calcium renal stones during chemotherapy, especially when a glucocorticoid is included.**

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### Introduction

Approximately 80% of pediatric patients with acute lymphoblastic leukemia (ALL) are cured with modern chemotherapy regimens.<sup>1–4</sup> Unfortunately, such regimens can cause complications, including bone demineralization, that can persist many years after the completion of therapy.<sup>5,6</sup> The underlying cause of osteopenia is thought to be a combination of direct effects of ALL on bone and demineralization induced by glucocorticoid therapy, an essential component of all treatment regimens for pediatric ALL. Other potential risk factors include ectopic parathyroid hormone production, paracrine lymphokines, reduced physical activity, use of methotrexate, cranial radiation therapy, reduced sunlight exposure, and reduced calcium intake. The standard treatment for osteopenia in pediatric patients is vitamin D and calcium supplementation.<sup>7</sup> However,

in the setting of glucocorticoid therapy, vitamin D and calcium supplementation may cause hypercalcemia<sup>8–10</sup> and increased urinary calcium excretion with consequent risk for urolithiasis.<sup>11–13</sup>

Little is known about the incidence, timing, and causes of urolithiasis in children with ALL and the composition of stones. In this study, we define the incidence, timing, clinical consequences, risk factors, and outcome of urolithiasis, as well as the stone composition in children with ALL. Furthermore, we examined the relation of urolithiasis to the timing and intensity of glucocorticoid administration to determine the safest time during ALL therapy to treat osteopenia, if early treatment is necessary.

### Patients and methods

Patients with urolithiasis were identified by a computer-assisted review of the medical charts of 2289 patients with ALL treated at St Jude Children's Research Hospital on consecutive protocols between August 1968 and August 1998. In all, 194 patients were excluded because they never achieved complete remission. Of the 2095 evaluable patients, the median age at the time of diagnosis was 5.0 years (range, 1 month to 20.0 years); 87% of the patients were white, 11% black and 2% other races. For remission induction therapy, all patients received prednisone at a dose of 40 mg/m<sup>2</sup> per day for four consecutive weeks. For this study of urolithiasis, remission induction was considered to last 6 weeks, to account for any carryover effect of daily corticosteroids on urine calcium excretion. Continuation treatment was defined as any treatment given 6 weeks or more after ALL diagnosis, and included consolidation treatment in some protocols. Continuation treatment regimens differed by protocol: some patients received prednisone, some dexamethasone, and some no glucocorticoid at all. In early protocols (1968–1971), prednisone 40 mg/m<sup>2</sup> per day was given for 14 consecutive days as part of each 12-week cycle of chemotherapy. In recent protocols that included a glucocorticoid, it was given for seven consecutive days every 4 weeks at a dose of 40 mg/m<sup>2</sup> per day (prednisone) or 6 mg/m<sup>2</sup> per day (dexamethasone). All patients were seen at least weekly by their oncologists while receiving chemotherapy, and at least annually after completion of therapy. The median duration of follow-up was 15.9 years (range, 2.3–33.9 years) and data collection was closed as of October 2002. The study was approved by the institutional review board.

The diagnosis of urolithiasis was confirmed by intravenous pyelography, abdominal computed tomography, renal ultrasonography, passage of the stone, or by a combination of these methods. Demographic information, risk factors for urolithiasis, symptoms, method of diagnosis, prior glucocorticoid therapy, treatment of the stone, and adverse sequelae were recorded for

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patients with urolithiasis. The biochemical composition of the stones was recorded when available.

Fisher's exact test was used to test for demographic differences between patients with and without urolithiasis. The Monte Carlo estimate of the exact *P*-value was used because of the large size of the contingency tables. The relative risk of stone formation during antileukemic therapy (remission induction and continuation treatment with or without glucocorticoids) was compared to the risk after completion of all chemotherapy using the  $\chi^2$  test. The 95% confidence intervals were calculated using the test-based method. All analyses were performed using SAS.<sup>14</sup>

## Results

Urolithiasis was found in 20 (0.9%) of the 2095 patients; two of these were included in a previous report.<sup>11</sup> In all, 13 patients

were male (65%), 18 were white (90%), two were Hispanic (10%), and none were African American (Table 1). The median age at diagnosis of ALL was 7.4 years in patients with urolithiasis compared to 5.0 years in those who did not develop urolithiasis (*P*=0.03). Patients 10 years old or younger and black patients had a lower incidence of urolithiasis, but there were no significant differences in the distribution of sex, treatment era, or leukemia risk category (Table 1). The most common presenting symptoms were abdominal or flank pain (*n*=15), hematuria (*n*=15), visualization of a stone in the urine (*n*=12), and dysuria (*n*=7) (Table 2). A total of 14 patients required hospitalization, and six required cystoscopy (Table 3). Seven of the 20 patients experienced delayed or missed administration of chemotherapy as a result of their stone or its treatment. Azotemia and anuria did not occur, and no patient required lithotomy or lithotripsy for the removal of the initial stone.

**Table 1** Comparison of demographic features of pediatric patients with acute lymphoblastic leukemia with or without urolithiasis

| Clinical feature                    | Urolithiasis (n=20)        | No urolithiasis (n=2075)          | P-value (two-sided) |
|-------------------------------------|----------------------------|-----------------------------------|---------------------|
| Median age at ALL diagnosis (range) | 7.4 years (2.1–17.4 years) | 5.0 years (1 month to 20.0 years) | 0.03                |
| Age category (years)                |                            |                                   | 0.05                |
| 0–10                                | 12                         | 1655                              |                     |
| 11–20                               | 8                          | 420                               |                     |
| Sex                                 |                            |                                   | 0.26                |
| Male                                | 14                         | 1150                              |                     |
| Female                              | 6                          | 925                               |                     |
| Race                                |                            |                                   | 0.03                |
| White                               | 18                         | 1804                              |                     |
| Black                               | 0                          | 232                               |                     |
| Other                               | 2                          | 39                                |                     |
| ALL risk category <sup>a</sup>      |                            |                                   | 0.61                |
| Low                                 | 14                         | 1543                              |                     |
| Standard                            | 6                          | 532                               |                     |
| Treatment era <sup>b</sup>          |                            |                                   | 0.39                |
| 1968–1977                           | 4                          | 699                               |                     |
| 1978–1987                           | 8                          | 772                               |                     |
| 1988–1998                           | 8                          | 604                               |                     |

<sup>a</sup>The definitions of low, standard, and high risk changed during the study period. This table reflects the risk category assigned at the time of diagnosis of each patient.

<sup>b</sup>Based on the year of ALL diagnosis.  
ALL, acute lymphoblastic leukemia.

**Table 2** Characteristics of urinary tract stones and presenting signs and symptoms in pediatric patients with acute lymphoblastic leukemia

| Clinical feature                      | Yes (%) <sup>a</sup> | No | Unknown |
|---------------------------------------|----------------------|----|---------|
| Hematuria (gross or microscopic)      | 15 (88)              | 2  | 3       |
| Gross                                 | 8                    | —  | —       |
| Microscopic only                      | 7                    | —  | —       |
| Abdominal or flank pain               | 15 (94)              | 1  | 4       |
| Perineal or scrotal pain              | 1 (7.7)              | 12 | 7       |
| Dysuria                               | 7 (47)               | 8  | 5       |
| Urinary frequency                     | 2 (15)               | 11 | 7       |
| Urinary tract infection               | 1 (6.6)              | 14 | 5       |
| Fever                                 | 5 (36)               | 9  | 6       |
| Emesis                                | 8 (50)               | 8  | 4       |
| Hypertension                          | 2 (15)               | 11 | 7       |
| Stone seen in urine                   | 12 (63)              | 7  | 1       |
| Stone type                            |                      |    |         |
| Calcium oxalate                       | 8                    |    |         |
| Calcium phosphate                     | 2                    |    |         |
| Calcium oxalate and calcium phosphate | 1                    |    |         |
| Unknown                               | 9                    |    |         |

<sup>a</sup>Percentage of patients for whom data were available who had a positive finding.

Of these, 16 patients (80%) had at least one identifiable risk factor for urolithiasis, and nine (45%) had two or more risk factors. Within the 90 days before urolithiasis was diagnosed, 14 patients (70%) had received glucocorticoids and seven (35%) had been immobilized (defined as bed rest for 7 days or more). Seven patients (35%) had a family history of urolithiasis in a first-degree relative (Table 4). All stones analyzed biochemically were calcium stones (calcium oxalate in patients 4, 5, 6, 8, 9, 17, 19, and 20; calcium phosphate in patients 2 and 10; and calcium oxalate and phosphate in patient 7), and none were uric acid stones, consistent with the probable mechanism of steroid-induced hypercalciuria.

At the time urolithiasis was diagnosed, two patients were receiving induction chemotherapy, nine were receiving continuation chemotherapy that contained a glucocorticoid, two were receiving continuation therapy without a glucocorticoid, three had completed therapy, two were receiving induction chemotherapy after relapse, one was receiving continuation chemotherapy after relapse, and one (patient 20) was receiving

palliative care for secondary acute myeloid leukemia that recurred after allogeneic bone marrow transplantation (Tables 4 and 5). Three patients have died: patient 12 of toxicity, patient 8 of hematologic relapse of ALL, and patient 20 of progressive leukemia. Patient 20 developed secondary acute myeloid leukemia 14 years after ALL was diagnosed and underwent allogeneic bone marrow transplantation. Relapse of acute myeloid leukemia occurred after transplantation and urolithiasis developed while he was hospitalized with active leukemia. Two patients relapsed but achieved a second remission, such that 17 patients are alive 3.9 to 31.8 (mean 16.7) years from the time of initial ALL diagnosis.

In children receiving glucocorticoids, the incidence of urolithiasis per 10 000 person-years was 83 during induction therapy with daily prednisone and 41 during continuation therapy with pulses of glucocorticoid (Table 5). In contrast, the incidence per 10 000 person-years was only 9.3 during continuation therapy without glucocorticoids and 1.8 after the completion of all chemotherapy. The relative risk of urolithiasis

**Table 3** Morbidity associated with urolithiasis in pediatric patients with acute lymphoblastic leukemia

| Morbidity or procedure   | Yes (%) <sup>a</sup> | No | Unknown |
|--|----------------------|----|---------|
| Creatinine increase of more than 0.5 mg/dl above baseline levels | 0                    | 14 | 6       |
| Anuria   | 0                    | 20 | 0       |
| Delay in cancer therapy  | 7 (35)               | 13 | 0       |
| Hospitalization  | 14 (70)              | 6  | 0       |
| Cystoscopy   | 6 (30)               | 14 | 0       |
| Lithotomy or lithotripsy   | 0                    | 20 | 0       |
| Recurrent urolithiasis   | 7 (35)               | 13 | 0       |

<sup>a</sup>Percentage of patients with a positive finding among those for whom data were available.

**Table 4** Clinical features of pediatric patients with acute lymphoblastic leukemia and urolithiasis

| Patient number | Age <sup>a</sup> (years) | Sex | Race | Phase of therapy         | Glucocorticoid <sup>b</sup> | Months <sup>c</sup> | Predisposing conditions <sup>d</sup> |
|----------------|--------------------------|-----|------|--------------------------|-----------------------------|---------------------|--------------------------------------|
| 1              | 11.9                     | M   | W    | Induction                | Prednisone                  | 1                   | None                                 |
| 2              | 13.0                     | M   | W    | Induction                | Prednisone                  | 1                   | Immobilization                       |
| 3              | 3.5                      | F   | W    | Continuation             | Prednisone                  | 32                  | None                                 |
| 4              | 4.6                      | F   | W    | Continuation             | Prednisone                  | 19                  | None                                 |
| 5              | 5.3                      | F   | W    | Continuation             | None                        | 4                   | None                                 |
| 6              | 5.6                      | M   | W    | Continuation             | Prednisone                  | 19                  | Family history                       |
| 7              | 7.4                      | M   | W    | Continuation             | None                        | 30                  | Family history                       |
| 8              | 8.7                      | F   | W    | Continuation             | Dexamethasone               | 16                  | Immobilization                       |
| 9              | 12.3                     | M   | W    | Continuation             | Dexamethasone               | 12                  | Immobilization                       |
| 10             | 14.6                     | F   | W    | Continuation             | Dexamethasone               | 27                  | None                                 |
| 11             | 16.5                     | M   | W    | Continuation             | Prednisone                  | 24                  | None                                 |
| 12             | 17.2                     | M   | H    | Continuation             | Prednisone                  | 5                   | Immobilization                       |
| 13             | 17.4                     | M   | W    | Continuation             | Prednisone                  | 10                  | Family history                       |
| 14             | 2.4                      | F   | W    | Therapy completed        | None                        | 206                 | None                                 |
| 15             | 5.8                      | M   | W    | Therapy completed        | None                        | 137                 | None                                 |
| 16             | 13.5                     | M   | W    | Therapy completed        | None                        | 103                 | None                                 |
| 17             | 6.2                      | M   | H    | Induction for relapse    | Dexamethasone               | 65                  | Family history, Immobilization       |
| 18             | 7.5                      | M   | W    | Induction for relapse    | Prednisone                  | 33                  | Immobilization, Family history       |
| 19             | 2.1                      | M   | W    | Relapse continuation     | Dexamethasone               | 101                 | Family history                       |
| 20             | 3.5                      | M   | W    | Secondary AML, after BMT | None                        | 177                 | Immobilization, Family history       |

F, female; M, male; W, white; H, hispanic; AML, acute myeloid leukemia; BMT, bone marrow transplantation.

<sup>a</sup>Age at the time of diagnosis of acute lymphoblastic leukemia.

<sup>b</sup>The glucocorticoids listed are those used during the 90 days preceding urolithiasis diagnosis. All patients received prednisone daily during induction therapy. Continuation therapy differed by protocol, and included 7-day pulses of prednisone or dexamethasone, or no glucocorticoid.

<sup>c</sup>Months between the diagnosis of acute lymphoblastic leukemia and diagnosis of urolithiasis.

<sup>d</sup>Predisposing conditions evaluated were immobilization (bed rest for 7 days or more in the 3 months before stone formation), hypercalcemia, diuretic use during the 3 months before stone formation, and a history of urolithiasis in a first-degree relative.

**Table 5** Timing of urolithiasis and incidence in pediatric patients with acute lymphoblastic leukemia

| Phase of therapy                     | Number of patients with urolithiasis <sup>a</sup> | Person-years of follow-up during this phase of therapy | Incidence of urolithiasis (per 10 000 person-years) | Relative risk of urolithiasis (95% confidence interval) | p-value |
|--------------------------------------|---|--|---|---|---------|
| Induction                            | 2   | 241  | 83  | 45 (5.4, 303)   | <0.01   |
| Continuation with glucocorticoids    | 9   | 2173   | 41  | 22 (6.4, 103) <sup>b</sup>                              | <0.01   |
| Continuation without glucocorticoids | 2   | 2153   | 9.3   | 5.1 (0.6, 34) <sup>b</sup>                              | 0.11    |
| Therapy completed                    | 3   | 16297  | 1.8   | 1.0   |         |
| Total                                | 16 <sup>a</sup>                                   | 20864  | 7.7   | —   |         |

<sup>a</sup>Three patients with relapsed acute lymphoblastic leukemia and one with secondary acute myeloid leukemia were excluded from this analysis.

<sup>b</sup>The relative risk of urolithiasis during continuation with glucocorticoids vs continuation without glucocorticoids was 4.5 (95% confidence interval, 1.1–30), a risk that was significantly different ( $p=0.03$ ).

was 45 (95% confidence interval, 5.4–303) during induction, 22 (6.4–103) during continuation therapy, and 5.1 (0.6–34) during continuation therapy without glucocorticoids, when compared to the risk after completion of therapy. The relative risk during continuation therapy with glucocorticoids compared to the risk during continuation therapy without glucocorticoids was 4.5 (1.1–30). Four patients (patients 17, 18, 19, and 20 in Table 4) developed urolithiasis while receiving salvage therapy after relapse and are not included in Table 5.

Seven patients (2, 3, 4, 6, 11, 15, and 16 in Table 4) developed nine episodes of recurrent urolithiasis 1 month to 26 years after the initial event. Of the seven patients with recurrence, two had no risk factors for urolithiasis, three had one risk factor, and two had two risk factors, a distribution similar to that of patients who did not have recurrence. There were also no significant differences in age, sex, race, predisposing conditions, or duration of follow-up between patients who developed recurrent urolithiasis and those who did not.

## Discussion

### Risk factors and timing of urolithiasis

In this single-institution study spanning 30 years and including over 20 000 person-years of follow-up, urolithiasis occurred in 0.9% of pediatric patients treated for ALL, an incidence much higher than that estimated for otherwise healthy children and adolescents. Risk factors for urolithiasis in the general pediatric population include white race,<sup>15,16</sup> male sex,<sup>17,18</sup> a family history of urolithiasis,<sup>19–21</sup> hypercalciuria,<sup>20,21</sup> immobilization,<sup>16,19</sup> urinary tract infection,<sup>22</sup> and glucocorticoid therapy.<sup>11</sup> In our patients, a family history of urolithiasis, immobilization, and glucocorticoid therapy were important risk factors. The role of glucocorticoids is particularly striking, and the rate of urolithiasis was 45 times higher in patients during induction therapy and 22 times higher in patients during continuation therapy with pulses of glucocorticoids than in patients who had completed therapy. No population-based incidence rates for pediatric urolithiasis have been reported, but for adults the rate is 7–21 per 10 000 person-years.<sup>23</sup> Our rate of 1.8 per 10 000 person-years for children who had completed therapy and 9.3 per 10 000 person-years for those receiving continuation chemotherapy without glucocorticoids represent rates close to those for the general adult population. These rates probably overestimate the rate for healthy children because of ascertain-

ment bias. Patients in our study had regular office visits with their oncologists so there were more opportunities to diagnose urolithiasis. Furthermore, after diagnosis of leukemia, patients and parents may be more attentive to new symptoms, such as flank pain or hematuria, and so urolithiasis that caused minor symptoms may have been more likely to come to medical attention. Since all of our patients had the same schedule of follow-up, regardless of the chemotherapy regimen used, our finding of increased urolithiasis during continuation therapy in patients treated with glucocorticoids should not be affected by ascertainment bias.

### Presenting symptoms and morbidity of urolithiasis

The most common symptoms of urolithiasis in pediatric patients are hematuria; pain in the abdomen, flank, or pelvis; and urinary tract infection.<sup>15,16,20,21</sup> Hematuria occurred in 88% of our patients and abdominal or flank pain in 94%; both findings are common presenting symptoms of urolithiasis in the general pediatric population. Urinary tract infection was documented in only one patient, but five had fever at diagnosis of urolithiasis. Urolithiasis imposes significant morbidity. Most patients suffer moderate to severe pain, and many require hospitalization. Surgical intervention for stone removal is necessary in 59–79% of the cases.<sup>16,21,24</sup> In our patients, 94% had pain, 70% required hospitalization, and 30% required cystoscopy. In addition to the expected morbidity, pediatric patients with ALL and urolithiasis may also experience delays in chemotherapy because of hospitalization and the need for invasive procedures. Seven of 20 patients (35%) experienced delayed administration or missed doses of chemotherapy as a result of their stone or its treatment. However, delays usually lasted a week or less, and all seven of these patients remain alive, six in continuous complete remission and one in second remission after a testicular relapse. Neither acute renal failure nor long-term renal dysfunction was observed in any patient, and none required lithotomy or lithotripsy for stone removal.

### Composition of stones

The stones of 11 patients in our series were analyzed biochemically, and all were calcium stones. Although patients with ALL frequently present with elevated uric acid and may experience tumor lysis syndrome with additional production of uric acid, no urate stones were seen in this large series of

patients. This may be because of the routine use of allopurinol and in recent years urate oxidase<sup>25</sup> to reduce uric acid levels. The finding of calcium stones and the increased risk of urolithiasis in patients treated with glucocorticoids suggest that the mechanism of stone formation is steroid-induced bone demineralization followed by hypercalciuria.<sup>8–13</sup>

### Risk factors for recurrence

Nine episodes of recurrent urolithiasis developed in seven of the 20 patients (35%), a finding consistent with the rates of recurrence reported in the literature (6.5–44%).<sup>15,16,18,21,24</sup> In adults, the recurrence rate is 60% within 10 years of the first episode of urolithiasis.<sup>26</sup> Recurrence as late as 13 years after the initial episode in children has been reported,<sup>18</sup> and in patient 3 the second bout of urolithiasis occurred 26 years after the first. Methods to prevent recurrent calcium stones include hyperhydration, thiazide diuretics, and potassium citrate,<sup>27,28</sup> but randomized trials documenting safety and efficacy in pediatric patients have not been reported. To our knowledge, none of these methods has been used in the setting of pediatric ALL and its treatment. Our current practice to prevent recurrence includes adequate hydration and avoidance of supplemental calcium or vitamin D during phases of therapy that include glucocorticoids, but no specific pharmacologic intervention. A recent clinical trial in adults with calcium oxalate stones showed that a diet containing a normal amount of calcium, but reduced amounts of animal protein (52 g per day) and salt (50 mmol of sodium chloride per day) reduced both urinary calcium and oxalate excretion and recurrent stone formation.<sup>29</sup>

### Implications for calcium supplementation in pediatric patients with ALL and osteopenia

In the absence of calcium supplementation, the relative risk of urolithiasis is much greater during induction therapy than of other times, and significantly higher during continuation therapy with glucocorticoids than without. Since most modern ALL treatment protocols include pulses of glucocorticoids during continuation therapy, does this mean that calcium supplementation always poses unacceptable risk? Among our patients who were receiving continuation therapy with glucocorticoids but no calcium supplements, the relative risk for urolithiasis was 22 compared to patients who had completed therapy; however, the absolute risk of urolithiasis was quite low: only 41 cases per 10 000 person-years (Table 5). Therefore, only 1% of patients treated with continuation therapy that includes pulses of glucocorticoids for 2.5 years would be expected to develop urolithiasis. If calcium supplementation is added, the risk of urolithiasis in these patients is not known. However, severe osteopenia in pediatric patients with ALL can be associated with significant morbidity, including vertebral compression fractures.<sup>30,31</sup> Strauss *et al*<sup>32</sup> recently reported a 28% 5-year cumulative incidence of fractures in pediatric patients with ALL treated on two consecutive Dana Farber Cancer Institute/Consortium protocols (DFCI 87-01 and 91-01), but the contribution of osteopenia to this high fracture rate is unknown. A diet with normal amounts of calcium but low amounts of protein and sodium led to reduction in urinary calcium and oxalate excretion in adults with calcium oxalate stones,<sup>27</sup> so if supplemental calcium is used, clinicians should also consider reducing dietary protein and sodium. Whether the benefits of calcium supplementation during continuation treatment would

outweigh the risks of urolithiasis must be determined by clinical trials. Such trials must include careful monitoring for morbidity caused both by fractures and by urolithiasis. Patients with a history of urolithiasis should be excluded from such trials, since the risk of recurrence is 35% even in the absence of calcium supplements.

### Conclusions

Pediatric patients with ALL are at risk of developing calcium renal stones during chemotherapy, especially when a glucocorticoid is included. After an initial episode of urolithiasis, the risk of recurrent stones is 35%.

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