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Short Report

Weight gain during treatment course of allogenic hematopoietic stem cell transplantation in patients with hematological malignancies affects treatment outcome

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ABSTRACT

Background aims: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective treatment for patients with hematological malignancies; however, allo-HSCT does not come without the cost of treatment-related morbidity and mortality. Early detection of risk factors could be helpful in identifying patients who could benefit from early interventions. Many patients gain weight during the allo-HSCT treatment, although little is known about the impact of weight gain.
Methods: Weight gain in 146 consecutively enrolled adult patients undergoing allo-HSCT was explored.
Results: In total, 141 patients (97%) gained weight along the course of allo-HSCT. Median weight increase was 4.8 kg (range 0.0–16.1 kg), with median increase in body weight 6.5% (range 0.0%–30.8%). Maximum weight increase was observed at day +7 (range day −8, +44). Weight gain was associated with increased incidence of acute graft-versus-host disease. Patients with weight gain >10% had a significantly greater 5-year mortality compared with those with lower weight gain ($P = 0.031$, rank sum test).
Conclusions: Weight gain is a simple variable with the ability to provide prognostic information for patients undergoing allo-HSCT.

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT), used in the treatment of hematological diseases [1], is associated with a high risk of transplant-related morbidity and mortality. Factors related to the risk of developing complications during the course of allo-HSCT can be divided into patient-related factors, i.e., age and comorbidity, disease factors, i.e., disease stage and disease risk classification, and treatment-related factors, i.e., previous treatment, type of conditioning regimen, immunosuppressive therapy post-transplantation, organ toxicity, and immune-mediated complications [2,3].

Weight changes following a diagnosis of acute leukemia and allo-HSCT treatment have been investigated previously, although most of these studies focused on the association between weight loss and outcome during the allo-HSCT process [4–6]. Among doctors working in the field, the impression is that the majority of patients gain weight during the transplantation course. Weight gain may be influenced by fluid treatment following the conditioning regimen, endothelium damage with fluid leakage, immune reconstitution, and complications such as acute graft-versus-host disease (aGVHD), and veno-occlusive disease (VOD), and infection/sepsis requiring fluid treatment. For pediatric patients who undergo allo-HSCT, significant weight gain has been reported to be associated with complicated transplantation course, including need for treatment in pediatric intensive care units [7–9]. However, the course and potential complications related to weight increase during transplantation for adult patients are poorly studied. We hypothesized that both weight gain in itself and when, during the transplant process, the weight gain reached its maximum could be associated with the outcome of the transplant. The aim of this study was to explore the association of occurrence and timing of weight gain and outcome in an unselected, consecutively enrolled population of patients undergoing allo-HSCT.

Methods

Patients

The study was approved by the local ethics committee (Regional Ethics Committee III, University of Bergen, Norway), and written informed consent for collection of clinical information was obtained

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from all participants. The study included 146 eligible consecutive adult patients with allo-HSCT (90 men, 56 women; median age 51 years, range 15–73 years) transplanted with a family donor at a single institution between 2006 and 2020. The decision to perform an allotransplantation was taken by the Norwegian Advisory Board for Stem Cell Transplantation and based on national guidelines.

The clinical characteristics of the patient are presented in Table 1. The majority of patients had acute myeloid leukemia (n = 75), followed by acute lymphocytic leukemia (n = 25) and myelodysplastic syndrome (n = 20). Most patients received GVHD prophylaxis with cyclosporine A and methotrexate (n = 141) in accordance with standard recommendation [10], two patients received cyclosporine A alone, two patients received cyclosporine A and mycophenolate mofetil and one patient revived cyclosporine A and sirolimus. Patients were transplanted with granulocyte colony-stimulating factor mobilized peripheral blood stem cells derived from HLA-matched family donors. Only patients with aplastic anemia (n = 4) received bone marrow grafts. Weight was measured upon admission and daily during the course of allo-HSCT, and weight and weight increase was registered retrospectively.

Diagnosis of aGVHD, VOD, and reconstitution

To summarize, the diagnosis of aGVHD was based on careful clinical evaluation and additional skin biopsies harvested from patients with skin involvement alone. The diagnosis of aGVHD for patients with liver and/or gastrointestinal involvement was also based on careful clinical evaluation and additional biopsies, except for one patient with liver involvement for whom aGVHD was a clinical diagnosis. Patients with only suspected skin involvement grade I without biopic confirmation were not graded as having aGVHD, given the uncertainty of the diagnosis. aGVHD was diagnosed in 35 of 131 patients available for aGVHD assessments, whereas VOD was diagnosed in only two patients.

Weight gain and time of maximal weight gain

Weight was measured upon admission and daily during the course of allo-HSCT, and absolute weight and weight increase was registered retrospectively. For further analysis, we wanted to examine whether (i) weight gain and (ii) the time point of maximum weight increase during the course of allo-HSCT were associated with the outcome of the transplantation. The patient population was

Table 1
Demographic data of patients included in the study.

	All patients	Weight increases <10%	Weight increase ≥10%	*P* value	WI^{early}	WI^{late}	*P* value
	N = 146	n = 109	n = 37		n = 69	n = 72	
Demographic data							
Age, y, median (range)	51 (15–73)	50 (15–73)	55 (19–67)	n.s.	52 (17–73)	51 (15–67)	n.s.
Sex, female/male	56/90	38/71	18/19	n.s.	20/49	35/37	0.0244
Weight, kg, median (range)	73.0 (41.5–133)	75.0 (41.5–133)	65.3 (46.5–117)	0.0005	75 (41.5–108)	69 (50–133)	n.s.
Height, cm median (range)	174 (149–197)	176 (149–197)	171 (1.58–1.97)	n.s.	178 (149–197)	172 (152–197)	n.s.
BMI, kg/m^2, median (range)	23.7 (16.6–39.7)	24.8 (16.6–39.7)	22.3 (17.9–35.3)	0.0006	24.4 (16.6–32.7)	23.2 (16.9–39.7)	n.s.
Diagnosis		n = 109	n = 37		n = 69	n = 72	
AML	75	44	31	n.s.	34	41	n.s.
ALL	25	16	9	n.s.	10	15	n.s.
MDS	20	11	9	n.s.	8	10	n.s.
MF	8	7	1	n.s.	4	2	n.s.
AA	5	2	3	n.s.	4	0	n.s.
CML	3	1	2	n.s.	2	1	n.s.
CMML	3	1	2	n.s.	1	2	n.s.
MPN	3	2	1	n.s.	2	1	n.s.
CLL	2	2	0	n.s.	2	0	n.s.
HL	1	1	0	n.s.	1	0	n.s.
PLL	1	1	0	n.s.	1	0	n.s.
Conditioning		n = 109	n = 37		n = 69	n = 72	n.s.
BuCy	79	42	37	n.s.	39	40	n.s.
FluBu	28	18	10	n.s.	11	14	n.s.
FluTre	18	13	5	n.s.	8	10	n.s.
FluBu-ATG	5	5	0	n.s.	3	1	n.s.
Cy-ATG	5	2	3	n.s.	3	1	n.s.
Cy-TBI	3	2	1	n.s.	0	3	n.s.
FluCy	2	2	0	n.s.	2	0	n.s.
Eto-TBI	2	1	1	n.s.	0	2	n.s.
BEAM	1	1	0	n.s.	0	1	n.s.
CloBu	1	0	1	n.s.	1	0	n.s.
FluCy-TBI	1	1	0	n.s.	1	0	n.s.
FluBuThi	1	1	0	n.s.	1	0	n.s.
Weight increase		n = 109	n = 37		n = 69	n = 72	
Weight increase, kg, median (range)	4.75 (0–16.1)	3.8 (0.0–8.0)	6.9 (5.9–16.1)	<0.0001	4.0 (0.3–14.2)	6.0 (0.3–16.1)	0.008
Weight increase, percent, median (range)	6.6 (0–30.8)	5.1 (0–9.9)	12.8 (10.1–30.8)	<0.0001	5.5 (0.5–17.7)	8.4 (0.4–30.8)	0.004
Day of maximal weight median increase (range)	6 (−8 to 44)	2 (−8 to 44)	11 (-2-24)	0.0002	−2 (−8 to 6)	12 (7–44)	<0.0001
Acute GVHD (n = 131)		n = 102	n = 29		n = 63	n = 63	
Yes/no, (%)	35/131 (27%)	22/80 (22%)	13/16 (45%)	0.018	18/45 (29%)	17/46 (27%)	n.s.

Unless otherwise stated, values are given as median (variation range). For statistical analysis, the Mann–Whitney *U* test was used to compare continuous variables and the Fisher exact test for categorical variables. Height and weight were registered at the start of conditioning therapy.
AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; ATG, anti-thymoglobulin; BMI, body mass index; Bu, busulphan; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CMML, chronic myelomonocytic leukemia; Cy, cyclophosphamide; ETO, etoposide; Flu, fludarabine; GVHD, graft-versus-host disease; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; MF, myelofibrosis; MPN, myeloproliferative neoplasm; n.s. not significant; PLL, prolymphocytic leukemia; TBI, total body irradiation; Thi, thiotepa; Tre, treosulfan; WI^{early}, maximal weight increase >day 7; WI^{late}, maximal weight increase <day 7.

divided into two different cohorts for each of the following parameters. We divided the patient cohort in two main groups; patients who gained <10% increase in body weight (WI^{low}), and a second group that gained ≥10% (WI^{high}). The choice of a cutoff of weight gain ≥10% was based on sensitivity analysis for treatment outcome in addition to previous studies of pediatric hematopoietic stem cell transplant recipients. In these studies, weight gain from 7% to 10% was observed as critical for outcome [7–9]. Furthermore, for time point of maximal weight gain, patients with maximal weight increase before 7 days were classified as early weight increase (WI^{early}), and patients with maximal weight increase on day 7 or later were classified as late weight increase (WI^{late}). The cut-off was wet to the median day of maximal weight increase.

Statistical analyses and graphical presentation

Descriptive statistics were used to describe the basic features of the data, performed by calculation of median and range. Comparison of continuous variable was done by Mann–Whitney *U*test, and the Fisher exact test was used to compare dichotomous variables. Kaplan–Meier plots were used to visualize the relationship between weight gain and survival, and rank sum test and Cox proportional hazard method was used to assess the significance of associations. Statistical analyses and graphical presentation were made using R, version 4.2.0 (The R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org) and GraphPad Prism Version 9.0 (Chicago, IL, USA).

RESULTS

Weigh increase is common among allo-grafted patients during the course of allo-HSCT

We reported weight increase as percent increase of body weight during the course of allo-HSCT. Of the 146 patients included in the study, 141 patients (97%) gained body weight during the course of allo-HSCT. The median weight increase was 4.8 kg (range 0.0–16.1 kg), and the median percentage increase in body weight was 6.6% (range 0.0–30.8%) (Table 1). The weight gain in women (median 4.9 kg) was not statistically different from that in men (4.7 kg, $P = 0.6$). We analyzed weight gain in different age cohorts, young (<40 years, n = 40), mature (40–60 years, n = 67), and aged (>60 years, n = 39). The median weight increases in the groups were 4.75 kg, 5.3 kg, and 3.6.kg, there the >60 years group had significant lower weight increase compared to two first ($P = 0.0197$ and $P = 0.0217$, respectively, Mann–Whitney *U*test). Statistical analysis revealed no significant associations between weight gain and sex, diagnosis or conditioning regimen in our analysis (Table 1). The distribution curve of maximum weight increase during the course of allo-HSCT demonstrated one early peak compatible with conditioning and pre-engraftment and one late peak compatible with engraftment.

Weight gain during the course of allo-HSCT for the 141 of 146 patients consecutively enrolled in the study was explored. The median day of maximum weight increase was observed at day +7 (range day −8 to + 44) (Table 1, Figure 1). As presented in Figure 1, the distribution curve of maximum weight gain demonstrated two peaks. The population of patients was thus divided into two main categories; the first group demonstrated weight gain early during the transplantation course, i.e., during conditioning and pre-engraftment, with a peak at day −2 (Figure 1). The second group gained weight late during the transplantation process, i.e., with a peak around the time of engraftment, with at peak at day 10/12 post-transplantation (Figure 1).

Patients with maximal weight increase before 7 days were classified as WI^{early}, and patients with maximal weight increase on day 7 or later were classified as WI^{late}. The clinical and demographical data for the two groups are demonstrated in Table 1. Statistical analysis revealed no significant associations between time of maximal weight gain and age, diagnosis, or conditioning regimen (Table 1).

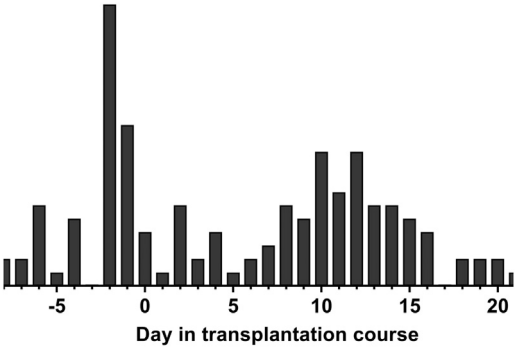

Figure 1. Weight increase during the course of transplantation. In total, 141 out of 146 patients gained weight during the course of allo-HSCT. The figure represents number of patients with maximum weigh increase on the given day during the transplantation course. Day 0 is the day of transplantation. The median day of maximum weight increase was observed at day +7 (range from −8 to + 44).

High weight increase is associated with aGVHD

Of the 146 patients included in the study, 131 were available for aGVHD evaluation. In total, 15 patients were excluded from evaluation due to premature death or lack of engraftment. Therefore, 36 of 131 patients (27%) developed signs of aGVHD, defined as grade II or greater, which required systemic immunosuppressive treatment. In total, 22% of the patients in the WI^{low} group developed aGVHD. In contrast, 45% of the patents in the WI^{high} group developed aGVHD ($P = 0.018$) (Table 1, Figure 2). In contrast, whether weight gain occurred early (WI^{early}) or late (WI^{late}) was not associated with development of aGVHD.

Amount of weight increase is associated with increased risk of mortality

We used Kaplan–Meier plots, rank sum test and Cox proportional hazard method to assess the association between maximal weight gain and the survival of the patient. The median weight gain for the patients was 6.5%, interquartile range (IQR) 3.8%–10.1%. The median weight-gain of those who died (7.2%, IQR 4.1%–11.3%) was not significantly greater than for those who survived (6.1%, IQR 3.3%–9.5%, $P = 0.3$ by Mann–Whitney *U* test). Sensitivity analysis employing different thresholds for high weight gain from 5% to 16% showed a consistent trend with lower survival in the group with the greatest weight gain (Figure 2). The difference was increasingly significant for greater thresholds. By Cox proportional hazard analysis, the difference was significant for threshold value 10% ($P = 0.031$), but not the other threshold values (≥5% $P = 0.63$, ≥6% $P = 0.60$, ≥8% $P = 0.088$) (Figure 2). In contrast, no significant difference in survival rates were found comparing patients in the WI^{early} and WI^{late} group (data not shown).

Discussion

To conclude, this retrospective analysis showed that weight gain is a simple variable with the ability to provide prognostic information for adult patients undergoing allo-HSCT. Fluid administration is essential in patients undergoing allo-HSCT, and changes in body weight during the course of allo-HSCT has been an important clinical parameter to monitor. In clinical practice, both daily fluid balance and body weight are used to guide fluid therapy and are part of daily routines at most transplantation centers [11]. For pediatric patients, the awareness of weight increase in the allo-HSCT setting has been

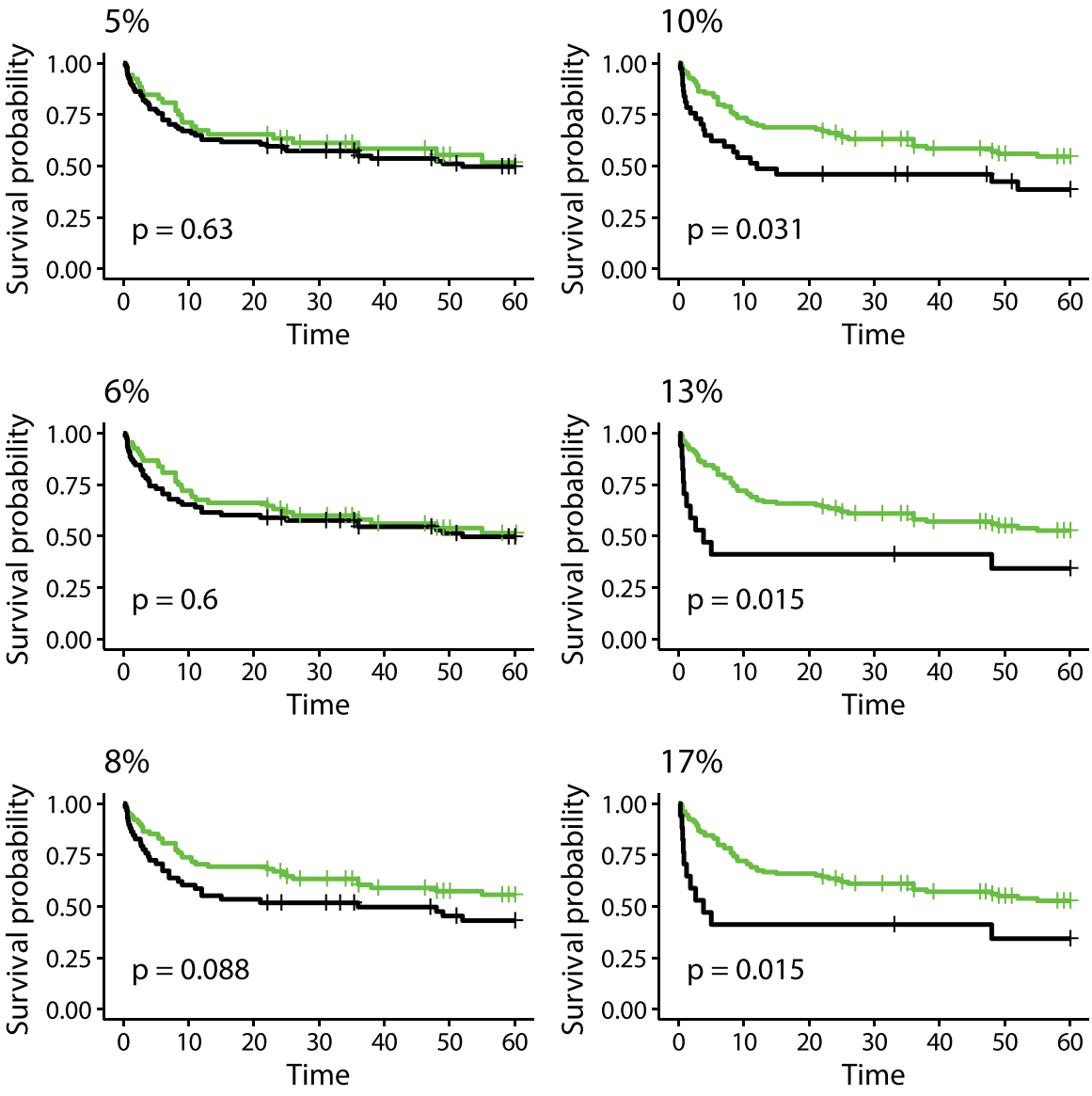

Figure 2. Weight increase during the course of transplantation is associated with increased mortality

We used Kaplan–Meier plots, rank sum test and Cox proportional hazard method to assess the association between maximal weight gain and the survival of the patient. The median weight gain per person was 6.5%, IQR 3.8%–10.1%. The median weight gain of those who died (7.0%, IQR 4.2%–11.3%) was not significantly greater than for those who survived (6.1%, IQR 3.2%–9.5%, $P = 0.3$ by Mann–Whitney *U*test). By sensitivity analysis, employing different thresholds for high weight gain from 5% to 16%, we demonstrated a consistent trend with lower survival in the group with the greatest weight-gain (black line) compared with those with lower weight gain (green line). The difference was increasingly significant for greater thresholds. (Color version of figure is available online).

taken more into account when assessing this patient group [7–9]. However, the association between weight gain and outcome in adult patients with leukemia undergoing allo-HSCT has been poorly studied. In this retrospective study, 97% of the patients experienced weight gain at some point during the course of transplantation, and data demonstrated large differences within the patient cohort. The median increase in weight among allo-HSCT recipients was 4.7 kg, corresponding to a median increase in body weight of 6.5%. The time of maximum weight increase shows a bimodal distribution (Figure 1). The first patient population had signs of weight gain early during the transplantation course, i.e., during conditioning, with a peak at day −2. In contrast, the second patient population had signs of weight gain late in the transplantation process, i.e., during time of engraftment with a peak at day +12.

Weight gain during the course of allo-HSCT is complex and often multifactorial. These include intravenous fluid treatment in conjunction with the conditioning regimen, endothelial damage from both conditioning and possible infectious complications, reduced nutritional status including low albumin, as well as the risk of fluid retention in severe multiorgan disease [11–13]. It seems reasonable to assume that early weight gain with a peak at day −2 pre-transplantation (Figure 1) is associated with fluid administration in conjunction with conditioning regimens to avoid known complications such as tumor lysis syndrome, hemorrhagic cystitis and nephrotoxic effects [14]. The second peak, observed at day 10–12 post-transplantation (Figure 1), is probably multifactorial. This includes damages of endothelial and other barriers related to cytotoxic condition regimen, edema and fluid retention related to decrease in serum albumin and reduced in nutrition status as well as general fluid retention related to inflammatory processes caused by infectious complications, reconstitution syndrome or aGVHD or a combination of all these [14–17].

Furthermore, an association between maximal weight gain and aGVHD and between weight gain and bone marrow reconstitution was observed. Clinical studies have suggested that endothelial dysfunction and damage are involved in the development and severity of aGVHD [18]. Since aGVHD is an inflammatory process, it is likely that both endothelial cells and capillary leakage are important in the pathogenesis [13,18], and hence that weight gain is associated with the development of aGVHD. Finally, we found a significant correlation between weight increase and mortality risk among allo-HSCT recipients. This is also coincident with a report from Kerbauy *et al.* [19], in which they describe an association between weight gain in the first 10 days after HSCT and increased risk for early mortality.

Our study has some limitations. Being a retrospective study, our study cannot conclude on whether there is a causal relationship between weight increase and complications and risk of mortality, or a spurious associations caused by other confounding factors. As aGVHD usually occurs later than day +25, it is reasonable to conclude that weight gain occurs before the development of aGVHD. Although the true causes of the complications and mortality probably are multifactorial, weight gain is still a useful parameter in the clinical follow-up of these patients.

Because weight measurement is an easy-to-use, low-resource, and non-invasive procedure, it could be well suited as a predictive measure. We hence conclude that weight gain during the course of allo-HSCT is an important parameter and should be closely monitored in the course of transplantation. We have shown that weight gain seems to be associated with the development of serious complications, such as aGVHD and mortality. Larger and prospective studies are important to possibly confirm the observation, and assess whether weight gain should be given extra attention by the attending physician and form the basis of early interventions. We conclude that weight gain is a simple variable that can be easily used to inform clinicians on the prognosis of patients post-allo-HSCT, and further studies are needed to determine its etiology.

Declaration of Competing Interest

The authors have no commercial, proprietary or financial interest in the products or companies described in this article.

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Author Contributions

Conception and design of the study: S.J and H.R. Acquisition of data: S.J, B.B and H.R. Analysis and interpretation of data: S.J, B.B, A.K.V, Ø.W and H.R. Drafting or revising the manuscript: S.J, B.B, A.K.V, Ø.W and H.R. All authors have approved the final article.

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