RESEARCH ARTICLE

Risk Factors for the Development of Hospital-Associated Venous Thromboembolism in Adult Patients Admitted to a Children’s Hospital

Stephanie R. Moss, MD,a,b,c,d,e Ashley M. Jenkins, MD,a,b,c Alicia K. Caldwell, MD,a,b,c Brian F. Herbst Jr, MD,a,b,c Matthew E. Kelleher, MD, MEd,a,b,c Benjamin Kinnear, MD, MEd,a,b,c Lilliam Ambroggio, PhD, MPH,a,b,e Lori A. Herbst, MD,a,b,c Ranjit S. Chima, MD,a,b,c Jennifer K. O’Toole, MD, MEd,a,b,c

BACKGROUND AND OBJECTIVES: Hospital-associated venous thromboembolism (HA-VTE) is a leading cause of preventable in-hospital mortality in adults. Our objective was to describe HA-VTE and evaluate risk factors for its development in adults admitted to a children’s hospital, which has not been previously studied. We also evaluated the performance of commonly used risk assessment tools for HA-VTE.

METHODS: A case-control study was performed at a freestanding children’s hospital. Cases of HA-VTE in patients ≥18 years old (2013–2017) and age-matched controls were identified. We extracted patient and HA-VTE characteristics and HA-VTE risk factors on the basis of previous literature. Thrombosis risk assessment was performed retrospectively by using established prospective adult tools (Caprini and Padua scores).

RESULTS: Thirty-nine cases and 78 controls were identified. Upper extremities were the most common site of thrombosis (62%). Comorbid conditions were common (91.5%), and malignancy was more common among case patients than controls (P = .04). The presence of a central venous catheter (P < .01), longer length of stay (P < .01), ICU admission (P = .005), and previous admission within 30 days (P = .01) were more common among case patients when compared with controls. Median Caprini score was higher for case patients (P < .01), whereas median Padua score was similar between groups (P = .08).

CONCLUSIONS: HA-VTE in adults admitted to children’s hospitals is an important consideration in a growing high-risk patient population. HA-VTE characteristics in our study were more similar to published data in pediatrics.

ABSTRACT

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Dr Moss conceptualized and designed the study, performed data collection and interpretation, and drafted the initial manuscript; Drs Jenkins, Caldwell, B. Herbst, Kelleher, and Kinnear contributed to the design of the study, performed data collection and interpretation, and reviewed and revised the manuscript; Dr Ambroggio contributed to the design of the study, performed data analysis and interpretation, and reviewed and revised the manuscript; Dr L. Herbst contributed to the design of the study, performed data interpretation, and reviewed and revised the manuscript, Drs Chima and O’Toole provided content expertise, contributed to the design of the study, performed data interpretation, and reviewed and revised the manuscript, and all authors approved the final manuscript as submitted.
Improved survival rates for chronic conditions originating in childhood have contributed to increasing numbers of adult patients being cared for in children’s hospitals. This population has a high burden of chronic illness, including malignancy, congenital heart disease, cerebral palsy, cystic fibrosis, epilepsy, and sickle cell disease. Their hospitalizations are associated with higher cost, longer length of stay, and increased ICU mortality compared with children. One proposed driver of these differences is the development of acquired conditions. Hospital-associated venous thromboembolism (HA-VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a such condition. HA-VTE is a leading cause of preventable in-hospital mortality in the general adult population, with an estimated 100,000 deaths annually; survivors have increased morbidity and hospitalization cost, with the direct cost per occurrence being estimated at >$25,000.

The Agency for Healthcare Research and Quality and American College of Chest Physicians recommend that all patients admitted to the hospital have a venous thromboembolism (VTE) risk assessment performed, and new guidelines from the American Society of Hematology recommend thromboprophylaxis for all acutely ill medical patients. Multiple VTE risk assessment tools exist and when used are effective at increasing rates of thromboprophylaxis and decreasing rates of HA-VTE in adults. However, most studies used to validate these tools excluded or had low frequency of patients <40 years old. Current pediatric risk assessment tools are based on data that included only a small number of patients ≥18 years old or excluded them entirely. Consequently, there are critical gaps in our understanding of the epidemiology of and risk factors for HA-VTE, and the performance of validated risk assessment tools, in younger adults ages 18 to 40 years. The vast majority (87%) of adults admitted to children’s hospitals also fall within this age range.

Furthermore, only 1 published study, limited to an oncology population with patients up to 24 years old, has specifically evaluated adults admitted to children’s hospitals. Our primary objective was to describe HA-VTE and associated risk factors in adult patients admitted to a quaternary-care, freestanding children’s hospital. We hypothesized that HA-VTE would be associated with ICU admission, surgery, comorbid conditions, and the presence of a central venous catheter (CVC). Our secondary objective was to evaluate the performance of 2 commonly used risk assessment tools for HA-VTE in adults in this population.

METHODS

Case Definition

Case patients were defined as patients ≥18 years old with a diagnosis of HA-VTE. We defined HA-VTE as radiologic evidence of DVT or PE identified ≥48 hours after admission or within 30 days of hospital discharge, consistent with national safety work for HA-VTE. Cases were identified from monthly review of radiology reports and discharge diagnosis codes as a part of ongoing patient safety work through the Solutions for Patient Safety VTE initiative. When a case patient had >1 episode of HA-VTE during the study period, only the first episode was included to avoid counting patients more than once.

Control Definition

Controls were matched by age and date of admission or within 30 days of hospital admission. Surgery was defined as patients requiring at least a 48-hour admission for HA-VTE diagnosis, controls with a length of stay <72 hours were excluded. Controls were matched to cases in a ratio of 2:1 without replacement. When >2 potential controls were identified, patients whose birth dates and admission dates were closest to those of matched case patients were chosen.

Risk Factors

Multiple risk factors were documented and evaluated for association with HA-VTE. BMI was calculated by using the first height and weight recorded for the admission. If no admission height was recorded, the most recent height documented was used. Comorbid conditions were defined as any chronic medical problem listed in a patient’s past medical history at the time of admission. Length of stay was measured in days from the date of admission to the date of discharge. ICU use was defined as admission or transfer to an ICU during the index admission. The presence or placement of a CVC (including implantable venous access devices [ports], peripherally inserted central catheters, and tunneled or nontunneled CVC) was documented. Previous admission was defined as at least 1 overnight stay in the hospital in the 30 days before the index (associated with HA-VTE diagnosis) admission. Surgery was defined as a procedure requiring incisions excluding cardiac catheterization and endoscopies.

Thrombosis Risk Assessment Tools

Midway through the study period, a VTE risk assessment algorithm for adolescents was developed at our institution but was only in use for certain surgical populations. There was no standard VTE risk assessment for adult patients. We calculated Caprini and Padua scores for all patients at the time of admission. These scores were chosen because they are 2 of the most commonly used prospective quantitative risk assessment tools in the adult population; both assign additive points to known risk factors for HA-VTE. Owing to the design of our study, we applied these scores retrospectively to our patient population. The Caprini score (31 elements, each 1–5 points) categorizes risk as follows: 0 points is minimal risk, 1 to 2 points is low risk, 3 to 4 points is moderate risk, and ≥5 points is high risk. The Padua score (11 elements, each 1–3 points) considers risk as follows: <4 points is low risk, and ≥4 points is high risk.
Both scores assess for the presence of comorbid medical conditions, recent history of surgery and trauma, reduced mobility, and history of thrombosis or known coagulopathy. The Caprini score has more elements because it counts individual comorbid conditions, whereas the Padua score combines them into broader categories. In addition, the Caprini score assesses for the presence of a CVC.

Data Extraction
We developed a standardized tool to extract data from the electronic medical record (Epic, Verona, WI). Data included patient demographics, any comorbidities, Caprini and Padua scores, thromboprophylaxis use (mechanical and/or pharmacologic), the discharge date, the number of readmissions in the following 12 months, and the date of death when applicable. Additionally, thrombosis location, presenting symptoms, time to thrombosis (measured in days from the admission date to the date of confirmatory imaging study), and diagnostic method were abstracted for cases. Construct validity evidence for the abstraction tool was gained from multiple sources according to Messick's validity framework.24 First, we gained content and response process evidence through blueprinting and an iterative process involving pilot chart review and group discussion to adjudicate disagreement. Next, we gained internal structure evidence (reliability) by having 6 authors (S.R.M., A.K.C., B.F.H., A.M.J., M.E.K., and B.K.) independently perform a preliminary chart review. Data were recorded by using a secure Research Electronic Data Capture database.25 All 6 reviewers independently abstracted data from 30 patient charts. A Fleiss $\kappa$ coefficient was estimated to determine the reliability between reviewers on 5 measures (ICU use, previous admission within 30 days, presence of a CVC, and Caprini and Padua scores).26 Strength of agreement was categorized as poor ($\kappa = 0–0.2$), fair (0.2–0.4), moderate (0.4–0.6), good (0.6–0.8), and excellent (0.8–1.0).26 After determining interrater reliability, the remaining charts were each reviewed by 2 of the 6 reviewers. Disagreement was adjudicated by a third reviewer.

Statistical Analysis
Because of nonnormal distribution of continuous variables, the Wilcoxon rank test was used to compare case patients and controls. Categorical variables were compared with $\chi^2$ or Fisher exact tests as appropriate. $P < .05$ was considered statistically significant. All associations were evaluated by bivariate analysis because of the limited number of events. Conditional logistic regression was done to estimate the association of risk assessment scores with the development of HA-VTE. All analyses were conducted by using SAS version 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS
During the study period from January 2013 to December 2017, there were 7539 admissions of 4470 unique patients 18 years old, with the most common comorbidities being malignancy, cerebral palsy, congenital heart disease, and cystic fibrosis. Forty-five episodes of HA-VTE in 41 unique patients ages 18 to 37 years were identified; 2 of these 41 patients were excluded because they were systemically anticoagulated on extracorporeal membrane oxygenation and were felt to have a more severe pathology than other case patients. Thus, there were 39 case patients matched to 78 controls.

Interrater Reliability
ICU use ($\kappa = 1.0$), previous admission within 30 days ($\kappa = 0.80$), and presence of a CVC ($\kappa = 1.0$) had excellent agreement. Caprini ($\kappa = 0.60$) and Padua ($\kappa = 0.52$) scores had moderate agreement.

Patient Characteristics
The case patients and controls were well matched with a median age of 21.8 years for case patients and 21.6 years for controls ($P = .81$; Table 1). Of patients, 51.3% were male. Consistent with existing literature of adults admitted to children’s hospitals,1 comorbid medical conditions were common; 97% of case patients and 89% of controls had at least 1 comorbidity documented. The presence of malignancy or bone marrow transplant was statistically higher in case patients than in controls (33% vs 17%; $P = .04$; Table 1), whereas all other comorbidities assessed were similar between groups (Supplemental Table 4). Thirty-three percent of case patients and 31% of controls received any thromboprophylaxis ($P = .78$).

VTE Characteristics
Upper-extremity DVT was most common, accounting for 62% of thromboses. Lower-extremity DVT accounted for 18%. PE was present in 15% of cases. There was 1 case of simultaneous DVT in both upper- and lower-extremity veins and 1 case of thrombosis in a conduit circuit. The median time to thrombosis development was 13 days from admission (interquartile range [IQR]: 6–25).

Risk Factors for HA-VTE
The prevalence of a CVC was higher (77% vs 35%; $P < .01$) for case patients, and 87% (26 of 30) of case patients with a CVC had line-associated HA-VTE. Two patients had a CVC placed after HA-VTE diagnosis, and 2 patients with a CVC at the time of diagnosis had a thrombus at a different location. In total, 26 of 39 (67%) cases of HA-VTE were line associated. Case patients also had a longer median length of stay (28 [IQR 5–54] vs 6 [IQR 4–9] days; $P < .01$; Table 2). Case patients were more likely than controls to have a previous admission within 30 days (51% vs 26%; $P = .01$). ICU use was more common among case patients (56% vs 30%; $P = .005$); 86% of case-patient ICU stays occurred before the diagnosis of HA-VTE, and 14% occurred after the thrombosis was identified. Although surgery during the index admission or in the 30 days before was not statistically different between case patients and controls (46% vs 35%; $P = .23$), more case patients underwent a port placement or removal than did controls (13% vs 1%; $P = .02$; Supplemental Table 5).

Performance of Risk Assessment Tools
Caprini and Padua scores were calculated retrospectively for all patients at the time of admission. Median Caprini score was ≥5
both case patients and controls (OR 7.69; 95% CI: 2.13–25.00) for developing HA-VTE progressively increased (Table 3). Patients at high risk for HA-VTE by Caprini score had 11.14 times greater odds of developing HA-VTE than patients at minimal risk (95% confidence interval [CI]: 1.26–98.22). Patients at high risk by Caprini score also had greater odds of developing HA-VTE than patients at moderate (OR 2.56; 95% CI: 1.01–6.25) or low (OR 7.42; 95% CI: 2.13–25.00) risk. Patients at higher risk for HA-VTE by Padua score did not develop HA-VTE more often compared with lower-risk patients (OR 2.03; 95% CI: 0.92–4.52).

**Patient Outcomes**

Mortality during the index admission was higher in case patients than in controls (10% vs 1%; P = 0.04; Table 1). However, neither subsequent mortality during the study period (3% vs 10%; P = .27) nor overall all-cause mortality (13% vs 12%; P = .99) were statistically different. The number of readmissions in the 12 months after the index admission was similar between case patients and controls.

**TABLE 1** Case-Control Demographics and Comorbidities of Adult Patients Admitted to a Children’s Hospital (n = 117)

<table>
<thead>
<tr>
<th></th>
<th>Case (n = 39)</th>
<th>Control (n = 78)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (IQR)</td>
<td>21.8 (19.6–25.1)</td>
<td>21.6 (19.7–25.0)</td>
<td>.81</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td>.43</td>
</tr>
<tr>
<td>Male</td>
<td>22 (56.4)</td>
<td>38 (48.7)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17 (43.6)</td>
<td>40 (51.3)</td>
<td></td>
</tr>
<tr>
<td>BMI (IQR)</td>
<td>24.4 (21.4–26.7)</td>
<td>23.6 (20.6–25.8)</td>
<td>.06</td>
</tr>
<tr>
<td>Admission Caprini score, median (IQR)</td>
<td>5–3 (3–4 to 5+)</td>
<td>3–4 (1–2 to 3–4)</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td>Admission Padua score, median (IQR)</td>
<td>&lt;4 (&lt;4–4+)</td>
<td>&lt;4 (&lt;4–4+)</td>
<td>.08</td>
</tr>
<tr>
<td>Oral contraceptive use, n (%)</td>
<td>4 (10.3)</td>
<td>5 (5.1)</td>
<td>.44</td>
</tr>
<tr>
<td>Presence of any comorbidity, n (%)</td>
<td>38 (97.4)</td>
<td>69 (88.5)</td>
<td>.16</td>
</tr>
<tr>
<td>Malignancy or BMT, n (%)</td>
<td>13 (33.3)</td>
<td>13 (16.7)</td>
<td>.04*</td>
</tr>
<tr>
<td>Previous venous thromboembolism, n (%)</td>
<td>7 (17.9)</td>
<td>7 (9.0)</td>
<td>.23</td>
</tr>
<tr>
<td>Mortality during admission, n (%)</td>
<td>4 (10.3)</td>
<td>1 (1.3)</td>
<td>.04*</td>
</tr>
<tr>
<td>Overall all-cause mortality, n (%)</td>
<td>5 (12.8)</td>
<td>9 (11.5)</td>
<td>.99</td>
</tr>
</tbody>
</table>

Continuous variables were analyzed by using Wilcoxon rank tests, and categorical variables were analyzed by using χ² tests; when counts were <5, Fisher exact tests were performed.

**TABLE 2** Case-Control Bivariate Analysis Comparing HA-VTE Risk Factors Among Adult Patients Admitted to a Children’s Hospital (n = 117)

<table>
<thead>
<tr>
<th></th>
<th>Case (n = 39)</th>
<th>Control (n = 78)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of a CVC, n (%)</td>
<td>30 (76.9)</td>
<td>27 (34.6)</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td>Length of stay, d, n (IQR)</td>
<td>28 (5–54)</td>
<td>6 (4–9)</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td>Previous admission within 30 d, n (%)</td>
<td>20 (51.3)</td>
<td>20 (25.6)</td>
<td>.01*</td>
</tr>
<tr>
<td>Surgery, n (%)</td>
<td>18 (46.2)</td>
<td>27 (34.6)</td>
<td>.23</td>
</tr>
<tr>
<td>ICU use, n (%)</td>
<td>22 (56.4)</td>
<td>23 (29.5)</td>
<td>.005*</td>
</tr>
</tbody>
</table>

Continuous variables were analyzed by using Wilcoxon rank tests, and categorical variables were analyzed by using χ² tests; when counts were <5, Fisher exact tests were performed.

**DISCUSSION**

This single-center case-control study highlights similarities and differences in incidence, characteristics, and risk factors associated with HA-VTE in adult patients (18–57 years old in our sample) admitted to a freestanding children’s hospital compared with pediatric and adult-aged populations. The incidence of HA-VTE in our study population was 5.2 per 1000 admissions over the 5-year study period. This is compared with 9 to 10 per 1000 admissions in adults21,22 and 3 to 5 per 1000 admissions in pediatrics26,29 although the incidence is higher (7.4 per 1000) in the pediatric ICU setting.30 PE occurred in 15.4% of cases, a lower frequency than has been reported in adults (32%–56%)21,31,32 but consistent with previous pediatric literature (11%–15%).29,33 Overall mortality during the study period was 12%, demonstrating that this population overall is at high risk for adverse events. HA-VTE was associated with higher in-hospital mortality, which may indicate that HA-VTE itself increases risk of death or may reflect higher illness severity.

The majority of thromboses occurred in the upper extremities and at a higher percentage than what is documented in either the adult or pediatric literature.28,34,35 We attribute this to the high prevalence of CVCs in our population. Similarly, CVC-associated thrombosis risk may explain why more case patients than controls underwent port placement or removal as opposed to the surgery itself. Association between CVCs and thrombosis has been well documented in both adult and pediatric literature.28,37 The presence of a CVC is the strongest risk factor for thrombosis in the pediatric population.29,38,39 In our sample, 67% of thromboses were CVC associated, and only 2 patients with a CVC at the time of HA-VTE diagnosis had thrombus at a different body site. Therefore, younger adults admitted to children’s hospitals may be more similar to pediatric patients than to older adult patients in this respect, with CVCs conferring greater risk of thrombosis than other comorbidities. The Caprini score assessed HA-VTE risk reasonably well in our study population because case patients had statistically
higher scores than controls. Furthermore, patients at high risk by Caprini had significantly higher odds of developing HA-VTE than patients at minimal risk. By contrast, case patients and controls had similar Padua scores, and a higher Padua score was not associated with higher odds of developing HA-VTE. The Caprini score includes points for the presence of a CVC, whereas Padua does not. Our population’s high prevalence of CVCs may have driven better performance of the Caprini score. Ultimately, although the Caprini score performed better in our population, our small sample size does not allow for validation of either risk assessment tool for adults admitted to children’s hospitals more broadly.

Patients who developed HA-VTE had significantly longer lengths of stay than controls. Although this may reflect treatment of the thrombosis itself, the median time to thrombosis was more than double the median length of stay for controls. The longer length of stay may indicate illness severity. ICU use (another marker of illness severity) was also more frequent in case patients and more often occurred before HA-VTE diagnosis. Previous admission within the last 30 days was also associated with HA-VTE, likely reflecting underlying illness severity and that more hospitalization days, even if not contiguous, increase the risk for HA-VTE. We therefore hypothesize that longer length of stay for adults in pediatric hospitals is a risk factor for developing HA-VTE.

Prevention of HA-VTE relies on appropriate risk stratification to mitigate modifiable risk factors and initiate thromboprophylaxis. Thromboprophylaxis has been shown to decrease mortality in adult surgical and intensive care populations. Yet, in our study, there were similar rates of thromboprophylaxis in case patients and controls, suggesting prophylaxis was not as effective in decreasing thrombosis in our population. One potential reason could be that the majority of our cases were CVC-associated, and previous literature suggests that prevention of CVC-associated HA-VTE is difficult even with prophylaxis. Thromboprophylaxis rates were also low, with only 32% of patients receiving any form of prophylaxis and only 39% of patients being at moderate or high risk by Caprini score. A potential confounder may be misclassification of lack of thromboprophylaxis due to our inability to ascertain whether ordered sequential compression devices were used. Additionally, mechanical prophylaxis may have been ineffective in our high proportion of upper-extremity thromboses. Further investigation is needed regarding optimal prevention strategies for HA-VTE in this population.

There were several limitations to our study. It was a single-center study, which may limit generalizability to other settings. We also had a relatively small sample size due to the rarity of events in our institution. Risk factors such as specific comorbid conditions or undergoing surgery were not associated with statistically higher rates of HA-VTE, as might be expected and could prove significant with a larger sample size. The retrospective study design that was reliant on chart review of medical records limited data extraction. We note that our interrater reliability for the risk assessment scores was only moderate. This is consistent with previous work showing only fair to moderate interrater reliability for risk stratification. Because both Caprini and Padua scores are intended to be applied prospectively at the time of admission, there is inherent difficulty in applying them retrospectively, and our moderate interrater reliability likely reflects that. Higher severity of illness may be a confounder for several risk factors for HA-VTE; however, there does not currently exist a validated framework for characterizing comorbidity severity in young adults in the way the complex chronic condition classification does for children.

**CONCLUSIONS**

HA-VTE in adult patients admitted to children’s hospitals is an important consideration in a growing high-risk patient population. This study builds on emerging evidence that adults with chronic conditions originating in childhood may have different characteristics than other pediatric or adult cohorts, especially regarding HA-VTE. Although adult-aged, HA-VTE characteristics in our population were more similar to reported data for HA-VTE in pediatrics. On the basis of the high prevalence of CVC-associated thromboses in the upper extremities in our population, the choice of an HA-VTE risk assessment tool (or the development of such a tool) for adults admitted to pediatric hospitals should include this element. As children’s hospitals continue to care for adults with chronic conditions originating in childhood, improvement in HA-VTE risk identification and stratification will be essential. Further prospective study will be needed to better describe this population and assess strategies for HA-VTE risk stratification and prevention.

**REFERENCES**


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**TABLE 3** Conditional Logistic Regression of Caprini and Padua Scores Among Adult Patients Admitted to a Children’s Hospital (n = 117)

<table>
<thead>
<tr>
<th>Score</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caprini&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>1–2 vs 0</td>
<td>1.49 (0.16–14.25)</td>
</tr>
<tr>
<td>3–4 vs 0</td>
<td>4.37 (0.48–40.16)</td>
</tr>
<tr>
<td>≥5 vs 0</td>
<td>11.14 (1.26–98.22)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3–4 vs 1–2</td>
<td>2.94 (0.79–11.11)</td>
</tr>
<tr>
<td>≥5 vs 1–2</td>
<td>7.69 (2.13–25.00)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>≥5 vs 3–4</td>
<td>2.56 (1.01–6.25)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Padua&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>≥4 vs &lt;4</td>
<td>2.03 (0.92–4.52)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Padua scores were categorized as follows: <4, low risk; ≥4, high risk.
<sup>b</sup> OR refers to the odds of development of HA-VTE based on risk assessment score.
<sup>c</sup> Statistical significance.


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