

## REVIEW ARTICLE

## Toxicology

# E-cigarette or vaping product use-associated lung injury (EVALI) features and recognition in the emergency department

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**Abstract**

Since August 2019, the pulmonary disease termed e-cigarette or vaping product-use associated lung injury (EVALI), has resulted in 2758 hospitalizations and 64 deaths in the United States. EVALI is considered in patients who have vaped or dabbled within 90 days of symptom onset, and have abnormal lung imaging in the absence of any pulmonary infection. The majority of EVALI patients are otherwise healthy adolescents and young adults. The leading etiology of EVALI is contamination of delta-9-tetrahydrocannabinoid (THC) e-liquids with vitamin E acetate. Although the exact pathophysiology of vitamin E acetate-induced lung injury is unknown, vitamin E acetate may lead to pulmonary lipid accumulation and/or interfere with surfactant functioning. EVALI symptoms are vague but consist of a constellation of constitutional, pulmonary, and gastrointestinal symptoms. Patients often present multiple times to healthcare facilities as their clinical condition worsens with a considerable mortality risk. The diagnosis of EVALI hinges on obtaining history leading to the recognition of vaping/dabbing. Physicians need to be persistent, but nonjudgmental, in obtaining vaping histories, especially in THC-prohibited states. Radiographical findings of non-specific bilateral ground-glass infiltrates are best detected on computed tomography. Management for EVALI requires a multidisciplinary approach focused on supportive respiratory care and ruling-out infectious causes. Corticosteroids may be of benefit. Most patients who are hypoxic, have comorbidities, or lack appropriate follow-up within 24–48 hours should be admitted for monitoring. Patients may benefit from substance abuse counseling and should be instructed to avoid vaping. As the outbreak continues, cases should be reported to local health departments and poison control centers.

**KEYWORDS**

e-cigarette, EVALI, lung injury, nicotine, pulmonary, THC vaping

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## 1 | INTRODUCTION

Vaping devices include e-cigarettes, vape pens, dab pens, and personal vaporizers, or so-called “mods” based on the ability to alter specifications and modify the smoking experience. All devices share a similar mechanism: a battery-powered heated coil vaporizes a liquid contained in a cartridge producing an aerosol, which is then inhaled through a mouthpiece. In contrast, dabbing aerosolizes a wax concentrate of cannabis by dabbing it onto a modified device consisting of a heated nail with an overlying dome attached to a water pipe that the user inhales through.<sup>1</sup> Although these methods are vastly different, adolescents may describe dabbing as the act of vaping delta-9-tetrahydrocannabinoid (THC) through a traditional vaping device.

E-cigarette liquids, or e-liquids, within the cartridge may contain a myriad of substances besides the active components nicotine, THC oil, and cannabidiol (CBD) oil. These substances include solvents (humectants), diluents (cutting agents), or flavoring agents. Harmful exposures related to vaping may occur from the high temperature-induced degradation or reactions among the chemical constituents,<sup>2</sup> metals released from the coil or e-liquid itself (such as arsenic, cadmium, and nickel),<sup>3</sup> and/or fungal and bacterial contaminants on the coil or in the e-liquid.<sup>4</sup>

E-cigarette devices have grown in popularity over the last decade. Common reasons for adolescents to start e-cigarette use include experimentation, attraction to flavorings, and the low risk perception of e-cigarettes.<sup>5,6</sup> E-cigarette users can use either premade cartridges or fill their devices with an “e-juice,” both of which can contain a combination of nicotine, THC oil, CBD oil, flavorings, and/or other substances. With the legalization of medical and recreational cannabis in a growing number of states across the United States, THC cartridges have pervaded the mainstream market and are obtainable in brick-and-mortar shops as well as online.<sup>7</sup> Although e-liquid manufacturers are required to disclose ingredients by the Food and Drug Administration (FDA),<sup>8</sup> studies have shown vast discrepancies in nicotine content alone.<sup>9</sup> Lacking accountability and enforcement of e-liquid components has led to potential health risks secondary to constituents without long-term human inhalational safety data.

In August 2019, the first clusters of previously healthy patients with severe lung injury and a common association with e-cigarette use were recognized by clinicians in Wisconsin and Illinois.<sup>10</sup> As of February 4, 2020, the pulmonary disease, now termed e-cigarette or vaping product-use associated lung injury (EVALI), has hospitalized 2758 patients in all 50 states and 2 US territories according to the Centers for Disease Control and Prevention (CDC). This epidemic has resulted in 64 deaths across 28 states and the District of Columbia.<sup>11</sup>

EVALI patients often present multiple times to healthcare facilities as their clinical condition worsens<sup>10</sup> and this portends a considerable morbidity and mortality risk, as highlighted by 13.5% of EVALI deaths occurring within a median of 3 days following discharge.<sup>12</sup> Most patients present with respiratory, gastrointestinal, and constitutional symptoms, such as fever.<sup>10</sup> Because the symptoms of EVALI

**TABLE 1** CDC case definition: probable versus confirmed EVALI

<b>Confirmed case</b>	Vaping or dabbing history within 90 days before symptom onset + Pulmonary infiltrate or ground-glass opacities on chest x-ray OR chest CT + Negative for pulmonary infection on initial workup after studies including a minimum of negative respiratory viral panel and influenza PCR; other studies if suspected include urine antigen testing for <i>Streptococcus pneumoniae</i> and <i>Legionella</i> , sputum culture if productive cough is reported, bronchoalveolar lavage culture if performed, and HIV-related opportunistic respiratory infection testing <sup>a</sup> + No evidence of alternative diagnoses, such as autoimmune disease or malignant process
<b>Probable case</b>	Vaping or dabbing history within 90 days before symptom onset + Pulmonary infiltrate or ground-glass opacities on chest x-ray OR chest CT + Positive for pulmonary infection on initial workup, but the primary clinical team believes that the infection is not the single cause of the underlying pulmonary disease OR the minimum infectious testing was not performed + No evidence of alternative diagnoses, such as autoimmune disease or malignant process

<sup>a</sup>Minimum criteria include negative respiratory viral panel, influenza polymerase chain reaction or rapid test if local epidemiology supports testing. All other clinically indicated respiratory infectious disease testing must be negative (such as blood culture, urine antigen for *Streptococcus pneumoniae* and *Legionella*, sputum culture if productive cough is present, bronchoalveolar lavage culture if performed, and human immunodeficiency virus-related opportunistic respiratory infections are of concern).

are easily misinterpreted for other pulmonary or gastrointestinal disease processes such as pneumonitis, gastroenteritis, or even appendicitis, assessment of vaping history, recognition of EVALI symptoms, and exclusion of infectious/noninfectious etiologies are essential for all emergency physicians. Identifying possible EVALI cases early can decrease unnecessary ancillary testing and invasive procedures and allow for prompt reporting to national health agencies. This article aims to describe the EVALI presentation, diagnosis, management, and disposition in the emergency department (ED).

## 2 | EVALI

The CDC has implemented a case definition to help with their epidemiologic evaluation (Table 1). Per these criteria, EVALI is suspected in patients with the presence of a pulmonary illness and abnormal lung imaging, in those who have a history of vaping or dabbing within

90 days of symptom onset and in the absence of known or suspected infectious etiology. Although 90 days was chosen for inclusion, patients in a recent case series reported vaping between 3 and 9 days prior to presentation.<sup>13</sup>

### 3 | ETIOLOGY INVESTIGATION

The CDC and FDA, in coordination with state/local health departments and other professional societies, have performed a multi-angle investigation of possible EVALI causes. No single brand and/or site of purchase have been linked throughout the investigation. Although both nicotine and THC vaping were initially linked to EVALI, >85% of patients with EVALI reported recent THC vaping.<sup>14</sup> THC use may still be under-reported due to the stigma and fear of ramifications of illicit drug use.<sup>15</sup>

Testing remnants from liquid cartridges has linked one component in particular, vitamin E acetate.<sup>16,17</sup> Interestingly, most THC cartridges (52%) seized and analyzed during the EVALI outbreak in 2019 contained vitamin E acetate, whereas THC cartridges seized by law enforcement in 2018 did not contain any vitamin E acetate.<sup>16</sup> Further linking vitamin E acetate to EVALI, a recent study found vitamin E acetate in 48 of 51 (94%) bronchoalveolar lavage fluid samples from 16 different states, whereas vitamin E acetate was not found in bronchoalveolar lavage samples from e-cigarette users with no lung injury.<sup>18</sup> The exact pathophysiologic mechanism linking vitamin E acetate to lung injury may stem from its inability to be absorbed by the pulmonary tissue leading to accumulation and interference with surfactant.<sup>18</sup> Although vitamin E acetate in THC containing cartridges is the prime suspected etiology for EVALI, 13% of EVALI patients endorsed exclusive vaping of nicotine-containing cartridges or e-liquids.<sup>15</sup> At this point, the possibility of an alternative etiology or multiple implicating agents cannot be excluded.

### 4 | EVALI PATIENT DEMOGRAPHICS

As of January 2020, 76% of patients were <35 years old and 15% were <18 years old.<sup>11</sup> Males comprised 66% of hospitalized EVALI patients.<sup>11</sup> Young adults and adolescents are disproportionately affected by EVALI, which is likely a reflection of the age group that dominates e-cigarette use.<sup>19</sup> A majority of patients were white (73%), whereas 15% were Hispanic.<sup>20</sup> THC product use was reported by 82% of EVALI patients and nicotine product use by 57%, with both being used in 41% and exclusive THC use in 33%.<sup>20</sup> At least 1 chronic condition, such as asthma, chronic obstructive pulmonary disease, or cardiac disease, was recorded in 70.6% of patients that were re-hospitalized for EVALI, and 83.3% of those that died.<sup>12</sup> At our institution, adolescents (n = 13) who were hospitalized for EVALI were mostly females (54%), were predominantly Hispanic (46%), vaped THC (92%), and had few co-morbid conditions (asthma only in 15%).

**TABLE 2** Relevant assessment questions for patients with suspected EVALI

Vaping history components for suspected EVALI	
<i>Substance vaped</i>	THC, nicotine, and/or other
The following should be asked of each substance vaped:	
<i>Substance origin</i>	Illicit or legitimate means
<i>Diluents</i>	Cutting oils
<i>Flavoring</i>	Flavored or unflavored
<i>Cartridge cleanliness</i>	Disposable or refilled
<i>Vaping onset</i>	Recent or long-term
<i>Last vaping use</i>	≤90 days (included in case definition)
<i>Frequency</i>	Daily, weekly, or monthly (multiple times daily poses risk)
<i>Additional social history</i>	Other substance use

### 5 | PATIENT HISTORY

The CDC has published guidelines for establishing probable or confirmed cases of EVALI. The first and most important criterion is the use of a vaping device within 90 days of symptom onset. Due to stigma or fear of legal ramifications regarding illicit substance use (such as THC), patients may be reluctant to discuss this history. In adolescents or the seriously ill, gathering a collateral history from family or friends may reveal a history of use. Similarly, history should be obtained from the patient privately to address reluctance of discussing illicit use in front of family and friends. Like other sensitive history gathered in the ED, confidentiality and nonjudgmental questioning should be employed. In addition, repeat questioning may help as the patient-physician relationship is being established.<sup>21</sup>

Similar to eliciting medication history where over-the-counter medications are sometimes overlooked, clinicians should recognize that patients will not willingly volunteer e-cigarette use even if asked about smoking habits. When gathering a history of e-cigarette use, eliciting specifics may inform the plan of care: how often does the patient vape, when was the patient's last use, what type of oil was used (nicotine, THC, etc), where did the patient get the oil (illicit or legitimate means), is the patient refilling the cartridge, and is the patient mixing his/her own e-liquid<sup>21</sup> (Table 2). At this time, the amount of exposure required to cause EVALI is unclear. Proposed factors that help pinpoint the patients who are at most risk for EVALI include (i) using THC containing products, (ii) using >5 times per day, and (iii) acquiring products from informal sources (eg, dealer or friend).<sup>14</sup>

### 6 | CLINICAL PRESENTATION OF EVALI

EVALI encompasses a syndrome of respiratory, gastrointestinal, and constitutional symptoms. Symptoms of EVALI include nausea, vomiting, diarrhea, abdominal pain, chest pain, cough, and shortness of breath. Constitutional symptoms of fever, chills, fatigue, and recent weight loss are also frequently encountered. In a composite of

3 published EVALI case series,<sup>10,22,23</sup> dyspnea (86%), cough (80%), and chest pain (49%) were the most commonly reported respiratory symptoms at presentation. In addition, subjective fever (79%), nausea (71%), and vomiting (70%) were the most commonly reported constitutional and gastrointestinal symptoms, respectively.

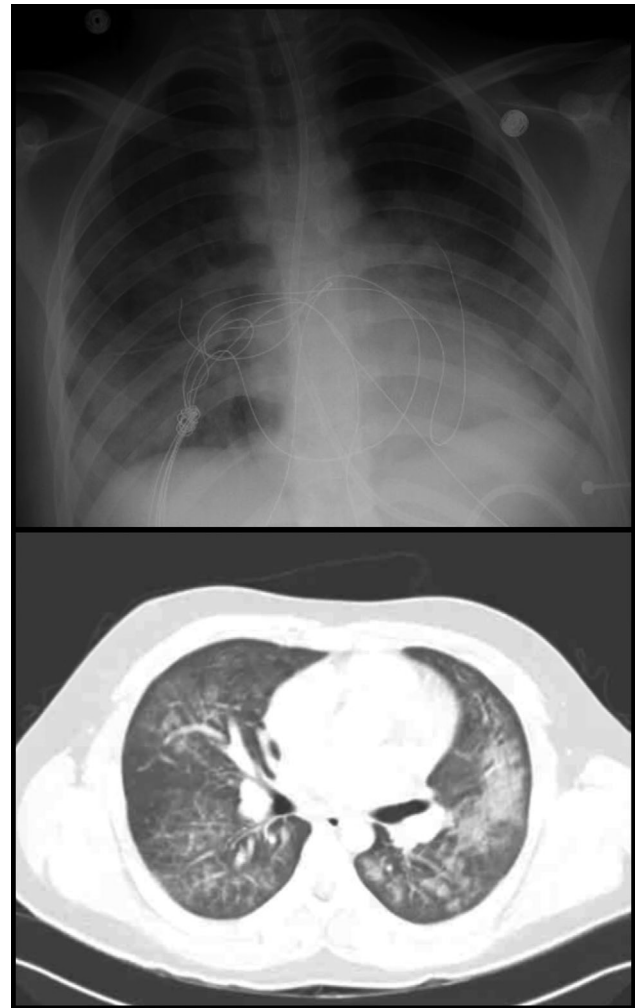
Some patients with EVALI may appear ill and present with symptoms that closely mimic pneumonia with severe sepsis. Common presenting signs in the composite of the EVALI patients in the 3 studies are fever (79%), tachycardia (74%), tachypnea (55%), and/or hypoxia (42%).<sup>10,22,23</sup> Patients may be dehydrated from severe gastrointestinal fluid losses and insensible losses due to fever. Others may present with predominant gastrointestinal distress and little, if any, respiratory complaints.

On initial laboratory evaluation, patients with EVALI may have an elevated white blood cell count, mildly elevated liver transaminases (typically aspartate transaminase and alanine transaminase are <100 U/L), and an elevated erythrocyte sedimentation rate. Electrolyte derangement may also be present due to gastrointestinal losses.<sup>10</sup> Creatinine elevation is infrequently seen but may occur due to prerenal causes, such as hypovolemia with dehydration.

By the CDC inclusion criteria for EVALI, all patients have abnormal radiographs; either chest x-ray or computed tomography (CT). Initial chest x-ray was abnormal and 94% of patients in 3 case series, with findings including nonspecific bilateral opacities or infiltrates.<sup>10,22,23</sup> The 6% with negative chest x-rays have positive findings on chest CTs. The most frequent CT finding is bilateral diffuse and basilar ground glass opacities with subpleural sparing<sup>24</sup> (Figure 1). This nonspecific pattern is also suggestive of atypical pneumonia or diffuse alveolar hemorrhage. Patients presenting with predominant gastrointestinal symptoms may have incidental pulmonary findings on CT of abdomen/pelvis, especially because pulmonary findings are typically seen in the lower dependent lung fields.<sup>25</sup> In addition, CT is more sensitive for pneumothorax and/or pneumomediastinum, both of which have been reported in EVALI as illustrated by 2 recent case series where these were noted on CT in 18% and 10% of patients, respectively.<sup>10,22</sup>

## 7 | GUIDANCE FOR INITIAL WORKUP FOR EVALI

Because EVALI is a diagnosis of exclusion, empiric infectious treatment and workup should begin immediately. The CDC has recommended minimum testing to include complete blood count, comprehensive metabolic panel, respiratory infectious panel (including influenza), urine legionella if indicated by history, urinalysis, blood cultures, and chest x-ray (Table 1). Testing considerations should also include other infectious etiologies with similar clinical and radiological features, such as coronavirus disease 2019 (COVID-19). Chest CT with or without contrast is also highly recommended if patients exhibit significant respiratory complaints and have risk factors for EVALI even if initial chest x-ray is normal.<sup>21,26-28</sup> Chest CT with intravenous contrast may also be helpful in ruling out other causes of hypoxia, such as pulmonary embolism.

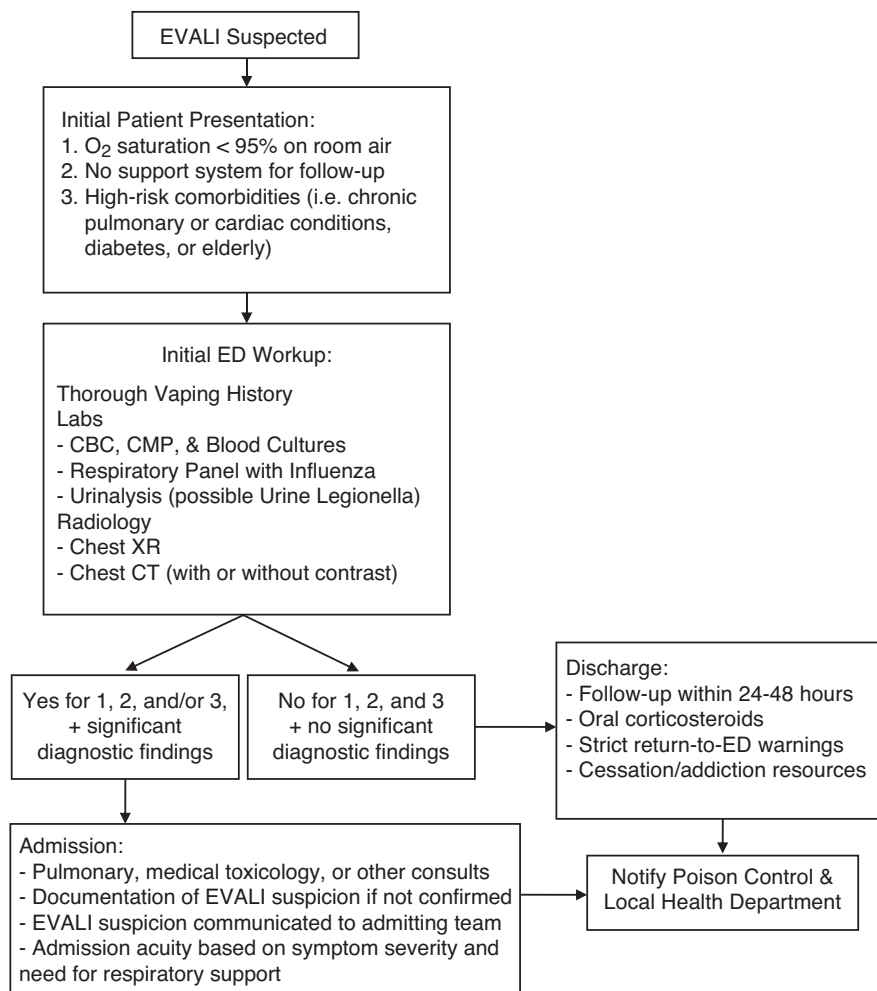


**FIGURE 1** EVALI chest x-ray and chest CT imaging in an otherwise healthy adolescent

## 8 | GUIDANCE FOR MANAGEMENT OF EVALI IN THE ED

Determining need for hospital admission versus discharge requires careful clinical consideration by emergency physicians due to the high risk of rehospitalization and mortality among EVALI patients (Figure 2). One out of every 7 EVALI deaths occurred in a median of 3 days after hospital discharge.<sup>12</sup>

Patients potentially appropriate for outpatient management have normal oxygen saturations  $\geq 95\%$  with no respiratory distress on room air, lack high-risk comorbidities such as chronic obstructive pulmonary disease or congestive heart failure, and have a support system for outpatient follow-up.<sup>28</sup> Due to the considerable degree of rehospitalization and death, ensuring follow-up within 24–48 hours post-discharge is imperative. Briefly discussing with the primary care provider can help ensure close follow up. If a patient lacks adequate outpatient support systems for follow-up, the patient warrants admission due to the potential for rapid illness progression.<sup>28</sup>



**FIGURE 2** EVALI disposition guidance

As expected, a higher incidence of chronic conditions (pulmonary, cardiac, advanced age, and diabetes) was present among patients who died post-discharge.<sup>12</sup> Discharge prescriptions may include a short course of oral corticosteroids with education on pharmacological tapering and antibiotic/antiviral prescriptions if warranted.<sup>28</sup> The dosage and course may vary depending on clinical severity, and the decision may be in conjunction with pulmonary specialists. Glucocorticoids recommended by other institutions<sup>10,22,23</sup> have been shown to improve disease severity and are a treatment modality consistent with standard management of steroid-responsive pulmonary disease practiced by lung specialists. Education on strict return-to-ED warnings, annual influenza vaccination, and access to outpatient cessation and addiction resources should also be provided.<sup>21,28</sup> If the patient intends to continue vaping, the patient should be instructed to avoid THC, illicit substances, and mixing or cutting substances.<sup>21</sup> Patients who smoke nicotine e-cigarettes should not switch to smoking traditional combustible cigarettes. In patients under 18 years of age, the CDC recommends that patients discontinue vaping altogether.

For EVALI patients presenting with abnormal vital signs that require admission, emergency physicians serve as the first line for gathering an adequate vaping history and should present this new differential diag-

nosis for consideration to the admitting team. EVALI patients benefit from consultation with pulmonology, medical toxicology (or local poison center), and/or psychiatry who may recommend further specific testing and evaluation once the patient is admitted.<sup>22</sup> Intravenous or oral steroids are anecdotally beneficial in hospitalized EVALI patients. Recommended doses for admitted patients ranges from methylprednisone 120–500 mg daily<sup>29</sup> or 1 mg/kg for 1–2 days with a transition to oral prednisone.<sup>22</sup>

Admission to the medical floor versus critical care area should be determined by the severity of presenting symptoms and need for non-invasive or invasive respiratory support. Pneumothorax and/or pneumomediastinum are reported in EVALI<sup>10,22</sup> and may worsen with escalation of positive pressure ventilation. Extracorporeal membrane oxygenation has been successful in EVALI and is recommended for patients that are continually hypoxic after standard ventilation management.

## 9 | GUIDANCE FOR REPORTING

Probable or confirmed EVALI cases are reportable to both poison control and the local health department. Because EVALI is a diagnosis of



exclusion, reporting may not be feasible at the time of the patient's initial presentation to the ED. Therefore, in a patient with concern for EVALI, the emergency physician should report the occurrence to the poison control center to initiate longitudinal follow-up and aid in monitoring by the local health department.

## 10 | BEST PRACTICES FOR EMERGENCY MEDICINE IN EVALI

Assessment of e-cigarette use during a social history evaluation for any patients presenting with a constellation of respiratory, gastrointestinal, and/or constitutional symptoms is paramount. Triage screening by non-physician staff may capture use. If the technology allows, consider integration of e-cigarette/vaping history into the electronic medical record system.

## 11 | CONCLUSIONS FOR EMERGENCY MEDICAL CARE OF THE SUSPECTED EVALI PATIENT

Emergency physicians should promptly recognize the risk factors and presentation patterns in EVALI patients. Imaging findings of EVALI may be overlooked due to unfamiliarity of this diagnosis by radiologists. In addition, a thorough vaping history may be difficult to elicit and may require numerous attempts, especially when patients exhibit more severe symptoms. With rapid recognition and diagnosis of EVALI by the multi-disciplinary team, the morbidity and mortality of EVALI can hopefully be mitigated. Further investigation of this phenomenon continues to be warranted.

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KA takes responsibility of the paper as a whole.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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