**E-cigarette or vaping product use-associated lung injury (EVALI) epidemy of 2019 and how to prevent it from happening again – a review.**

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**ABSTRACT**

The EVALI (E-cigarette or Vaping product use-Associated Lung Injury) epidemic of 2019 was a major public health challenge, attracting the attention of both the scientific community and the public. In a short period of time, thousands of cases of acute lung injuries and deaths were reported among e-cigarette users, previously unrelated to the risk, shedding new light on the safety of these devices and exposing gaps in the regulations regarding their use.

This paper aims to review the literature on the EVALI epidemic, with particular emphasis on epidemiology, identification of the etiological agent, clinical presentation and treatment. Based on the collected data, the authors also analysed the possibilities of preventing similar events in the future, emphasizing regulations, health education of patients and increasing physicians' awareness of EVALI.

**Material and methods of research**

The review was based on articles obtained from PubMed, Google scholar and Scopus scientific data base in the years 1980-2024 using the following key words: EVALI, E-cigarette or vaping product use-associated lung injury, ENDS/ENNDS, e-cigarette, vitamin E acetate.

**Keywords:** EVALI; E-cigarette or vaping product use-associated lung injury; ENDS/ENNDS; e-cigarette; vitamin E acetate.

**Introduction**

Modern e-cigarettes are a relatively new invention on the market, the first reports of mass production of e-cigarettes come from 2004, as a result of cooperation between Chinese pharmacist Hon Lik and the Golden Dragon Holdings group, which resulted in the release of a product with the commercial name Ruyan, granting them the world's first, market-relevant e-cigarette patent in 2007 [1][2].

In just a few years, the idea of electronic cigarettes spread throughout the world and today it is a dynamically developing industry that constitutes significant competition for manufacturers of classic cigarettes.

According to the WHO, supporters and manufacturers of e-cigarettes have created the image of e-cigarettes as a healthier alternative to classic cigarettes, which is eagerly reached for by both current cigarette smokers and previously nicotine-free individuals [3][4].

The main reasons for reaching for e-cigarettes include: the desire to stop smoking traditional cigarettes (especially based on the belief that they are less harmful than traditional cigarettes or less addictive), use by friends, the possibility of choosing a flavour, and in some cases also their more favourable price compared to traditional cigarettes.

In addition, in recent years, a significant increase in the concentration of nicotine in the cartridges used in e-cigarettes has been demonstrated, which increases the degree of addiction of new users, making it difficult to quit and increasing the population of e-cigarette smokers [5][6][7][8].

Due to the growing number of active e-cigarette smokers, the impact of their use on the user's health has begun to be looked at. And although many years of observation are needed for a full assessment, it has already turned out that the use of e-cigarettes can generate symptoms of acute lung injury, which has been defined as E-cigarette or vaping product use-associated lung injury (EVALI) [9].

This syndrome, and in particular the most up-to-date data on its epidemiology, pathophysiology, clinical picture and treatment methods, will be the subject of this review.

**EPIDEMIOLOGY**

In early 2019, numerous reports of acute lung injury in e-cigarette smokers in the United States caught the attention of the Centers for Disease Control and Prevention. Due to the similar clinical picture and association with e-cigarettes, the disease entity of the epidemic nature was named E-cigarette or vaping product use-associated lung injury (EVALI). Data on patients were collected from all fifty states, the District of Columbia, and two US territories (Puerto Rico and the US Virgin Islands).
According to the CDC, during the year (as of February 18, 2020), the number of confirmed, hospitalized cases in the US was 2,807, of which 68 patients died. The median age of the deceased patients was 49.5 years. The largest age group of those hospitalized was young adults aged 18-24 (37% of all hospitalized patients) (Fig. 1). Of the patients hospitalized or died from EVALI, 66% were men.

Figure 1 Age group distribution among CDC-confirmed EVALI cases

As many as 2,022 of the hospitalized patients informed their physicians about the use of psychoactive substances, of which: (as of January 14, 2020) 82% reported vaping products containing THC, 33% reported only and exclusively vaping products containing THC, 57% reported vaping products containing nicotine, and 14% reported only and exclusively vaping products containing nicotine (Fig. 2) [9].

Figure 2 THC and nicotine products use in e-cigarettes among EVALI hospitalized patients.

**PATHOPHYSIOLOGY**

**Vitamin E acetate toxicity**

Information obtained from patients about using e-cigarettes in a manner inconsistent with their intended use – i.e. to heat products other than dedicated nicotine oils – seemed to be of key importance in explaining the pathophysiology of this syndrome from the very beginning of the EVALI epidemic.

It was established that preparations containing THC obtained on the illegal market and heated in the e-cigarettes of EVALI patients used vitamin E acetate (VEA) as a thickener [10].

The suspicion of VEA as a probable trigger of EVALI was confirmed by performing bronchoalveolar lavage fluid (BALF) tests on patients. VEA was found in 48 of 51 (94%) patients with EVALI, while VEA was not present in healthy control patients [11].

**Vitamin E** is a group of fat-soluble compounds with antioxidant properties. Vitamin E occurs in two main forms: tocopherol and tocotrienol, each of which can occur in one of four forms: alpha- (α-), beta (β-), gamma (γ-) and delta (δ-) [12].

Only alpha-tocopherol (Fig. 3) of all forms is selectively used in the human body, due to the presence of alpha-tocopherol transfer protein (alpha-TTP), and the remaining forms of vitamin E are removed from the circulation [13].

Vitamin E is commonly found in the diet, with its natural source being vegetable oils, and its deficiencies are rare [14].

A synthetic form of vitamin E, often used on an industrial scale in dermatological products or dietary supplements, is a combination of alpha-tocopherol with an acetate ester – vitamin E acetate (VEA) [15] (Fig. 4).



Figure 3 Alpha-tocopherol – the form of vitamin E with the greatest biological utility



Figure 4 Vitamin E acetate (VEA) – used as a diluent in THC preparations

As mentioned, VEA was also used as a diluent in illegal preparations containing THC. Heating these preparations in e-cigarettes led to the appearance of VEA in the gas mixture inhaled during vaping.

VEA, as a strongly lipophilic substance, can interact with phospholipid bilayers, including the surfactant lining the epithelium of the lung alveoli, leading to its destabilization [16][17]. In addition, macrophages accumulate in the lung alveoli, which are unable to metabolize the absorbed VEA, and thus the lung alveoli are not properly cleared. This situation leads to dysfunction in the lung alveoli, causing inflammation in the lungs referred to as *lipoid pneumonia* [18].

Initially, this mechanism was indicated as the main basis of EVALI, confirmed by the presence of both lipid-loaded macrophages and VEA in the BALF of sick patients.

It should be mentioned, however, that despite the strong correlation, there is a lack of sufficient studies clearly indicating *lipoid pneumonia* as the basis of EVALI. Butt et al (2019) in their letter indicate that the occurrence of *lipoid pneumonia* features such as lipid-laden macrophages may be a marker of exposure to products heated in e-cigarettes rather than a marker of toxicity, especially since the radiological image of the lungs of patients with EVALI does not always show typical features of *lipoid pneumonia*. It is currently known that EVALI can occur in many forms of lung damage, among which, in addition to *lipoid pneumonia*, *acute eosinophilic pneumonia* and *respiratory-bronchiolitis interstitial lung disease* are mentioned [19][20].

Several other possible mechanisms of EVALI have been postulated:

**Direct toxic effects of ketones**

It has been shown that the conditions in e-cigarettes during VEA heating can initiate the reaction of ketone formation, which has toxic properties and leads to direct irritation of the user's lungs [21].

**Impaired immune response**

As shown by the epidemiological data presented in this paper, some patients (14%) reported vaping only nicotine-containing products (Fig. 2), in which the use of VEA as a solvent is much less common than in products containing THC.

Nicotine in these products is usually diluted in **propylene glycol** **(PG)** or **vegetable glycerol (VG)**. It has been shown that prolonged inhalation of PG or VG vapours by mice leads to an impairment of their immune response in the lungs, by the mechanism of stimulating necrosis and weakening the antimicrobial activity of both alveolar macrophages and neutrophiles. In addition, mice exposed to PG or VG vapours have been shown to increase the virulence of *Staphyloccus aureus* in the lungs [22]. In a mouse model, inhalation of PG or VG has also been shown to lead to a delayed response to influenza A virus infection [23]. Therefore, e-cigarette users who develop lower respiratory tract infections may experience significant lung damage through increased tissue damage due to a delayed or attenuated immune response, but studies in a human model are required.

**CLINICAL PRESENTATION AND DIAGNOSTICS**

**Symptoms**

Patients present with many nonspecific flu-like symptoms, which makes EVALI diagnosis exceptionally difficult. Based on the interview of 339 EVALI patients, the following symptoms were demonstrated:

* Respiratory symptoms (cough, chest pain, shortness of breath) – frequency of occurrence 95%
* Gastrointestinal symptoms (abdominal pain, nausea and vomiting, diarrhea) – frequency of occurrence 77%
* General symptoms (fever, weight loss, chills) – frequency of occurrence 85%

According to the CDC, it is impossible to distinguish EVALI from influenza using only basic evaluation methods (signs and symptoms) [9][24].

**Signs**

Common findings in EVALI patients include tachycardia – 55% of cases, tachypnea – 45% of cases, saturation below 95% (without oxygen support, at rest) – 57% of cases. Auscultation of the patient, even in severe EVALI, does not indicate any characteristic changes.

Laboratory test results also remain ambiguous. The following are observed: increased WBC, increased inflammatory markers (CRP, procalcitonin, erythrocyte sedimentation rate), increased liver transaminases, mild hyponatremia and hypokalemia [25][9]. As advised by the CDC, in each suspected EVALI, in addition to a thorough interview, a urine THC test should be performed, due to the probable etiology presented earlier [9].

Since EVALI should be treated as a diagnosis of exclusion, it may be valuable – especially due to the significant similarity of the course to infectious diseases – to perform virological and bacteriological panels for microorganisms that may cause pneumonia [24]. Complete exclusion of other disease processes may require the use of invasive techniques – BALF examination and examination of a sample taken during lung biopsy [20].

**Imaging**

It is recommended to perform a chest X-ray in all patients with a history of e-cigarette use who report respiratory or gastrointestinal symptoms, especially when dyspnea, chest pain or decreased saturation are present [9].

Chest X-rays were performed in 184 EVALI patients, which showed changes on chest X-ray in 155 of them (84%), as well as changes on CT scan in 168 of them (91%). Radiological findings were mostly nonspecific and included bilateral infiltrates, bilateral ground glass opacities, subpleural sparing, pleural effusions and centrilobular nodularity.

However, in 45 of 184 (24%) radiologically examined patients, the lesions were characterized by a specific disease pattern - organizing pneumonia (5.2%), diffuse alveolar damage (3.0%), giant cell interstitial pneumonia (2.2%), hypersensitivity pneumonitis (2.2%) and organizing acute lung injury (2.2%). Pneumothorax was reported in eight (5.9%) patients and pneumomediastinum in four (3.0%) patients [26].

**Treatment**

Depending on the severity of EVALI, different procedures are recommended.

Patients with a typical history, i.e.: respiratory, gastrointestinal and general symptoms, as well as a history of recent e-cigarette use, may be treated on an outpatient basis, under several conditions:

* Normal saturation (≥95% without oxygen support, at rest)
* No respiratory failure or diseases predisposing to it
* Easy access to health care and social support
* Possibility of reporting for a check-up within 24-48 hours of the first visit

All other patients, especially those with concomitant influenza, should be considered as candidates for hospitalization [9].

All patients should always be encouraged to immediately stop using e-cigarettes [24].

Despite the lack of official procedures, the most promising results are obtained with high doses of systemic **glucocorticosteroids**. A case series of 5 EVALI patients showed improvement in all of them after the use of methylprednisone in doses of 120-500 mg intravenously, which was then continued with oral form of the drug [27].
Another study of 60 patients with EVALI showed improvement in 48 of 57 (84%) patients who were given steroids in doses of 120-240 mg daily for 1-4 days and then switched to oral prednisone in doses of 40-60 mg [28].

Despite good response to corticosteroids, they should be used with caution in the case of concomitant respiratory infections. There are studies indicating the risk of increased mortality in patients treated with high doses of corticosteroids and concomitant infections, including COVID-19 [29], influenza [30] and in some fungal lung infections [31].

In addition to suppressing the inflammatory response with glucocorticosteroids, it is also important to implement **antimicrobial therapy**, because, as mentioned earlier, EVALI may be associated with impaired response to infections. Most patients during the EVALI epidemic received ceftriaxone in combination with azithromycin, although this is not always the case, and antibiotic therapy in patients with EVALI should be in accordance with local antimicrobial treatment guidelines [32].

The CDC also recommends **oxygen therapy** for all EVALI patients with oxygen saturation <95% at rest [9].

The first follow-up visit of patients should occur within 24-48 hours of diagnosis (in the case of outpatients) or discharge from the hospital (inpatients) and include an assessment of general condition, oxygen saturation, and a discussion with the patient about the risks associated with continued e-cigarette use.

The second follow-up visit should take place within 1-2 weeks and include an assessment of oxygen saturation and, if necessary, a chest radiograph.

The last follow-up visit should take place within 1–2 months and include assessment of lung function (DLCO test) and repeat chest X-ray or CT scan if indicated [9].

**Prognosis**

Although the course of EVALI may vary greatly across the patient population, the overall prognosis is good. It is important to remember that there is a possibility of a severe course of EVALI complicated by acute respiratory failure and death, even in young and disease-free individuals.
The latest statistics published by the CDC report 68 deaths out of 2,807 confirmed EVALI cases, which gives a mortality rate of approximately 2.42% [9].

The average hospitalization time for EVALI patients is 6.7 days, and in the age group over 50 years of age it increases to over two weeks (14.8 days) [24].

EVALI relapses are common – within 14 days of discharge from the hospital, the readmission rate reaches 50% in the case of continued use of e-cigarettes, which is why patient education is important. Cases of EVALI relapse have also been observed after glucocorticosteroid treatment during the tapering period [32].

There are still no studies describing the long-term effects of EVALI, therefore it is important to monitor these patients after treatment.

**Prevention**

The goals indicated as important in terms of preventing the occurrence of a new EVALI epidemic or similar epidemiological incidents and limiting their potential effects include:

* the need to increase EVALI awareness among doctors [32],
* asking patients about the use of e-cigarettes as a routine element of the interview among patients with respiratory symptoms [32],
* educating patients about the harmfulness of vaping, in particular cartridges of suspicious origin [10][24],
* educating patients not to add any substances to previously purchased cartridges, even in small quantities [9]
* tightening the policy of conducting the sale of e-cigarettes by, among others, increasing the minimum purchase age from 18 to 21 in countries that have not yet done so, reducing the attractiveness of e-cigarettes by completely banning flavoured e-cigarette cartridges, restricting online sales, and taxing e-cigarette products to reduce youth initiation [33]

However, the CDC cautions against encouraging patients to return to smoking classic cigarettes as a method of preventing EVALI. Instead, such patients should be helped in quitting completely using smoking addiction treatments [9].

**Conclusions**

The impact of e-cigarettes on the health of users may be much more complex than originally thought, challenging their widely promoted image as a safer alternative to traditional cigarettes [3][4].

A key finding in the pathogenesis of EVALI was the association of the syndrome with the presence of vitamin E acetate (VEA) in illegal e-cigarette cartridges containing THC, which highlights the role of the illegal market in the development of the epidemic [10][11]. Heating VEA in e-cigarettes leads to the formation of toxic substances that disrupt lung function on multiple levels, causing inflammation in the mechanism of lipoid pneumonia or other forms of lung damage [16][17][18]. Although the clinical symptoms of EVALI remain rather nonspecific, similar to those of viral infections of the lower respiratory tract, the use of appropriate diagnostic methods, such as radiological imaging and BALF studies, allows for more effective differentiation of cases [9][20][24][25][26].

Treatment, mainly based on the use of glucocorticosteroids and antimicrobial therapy, shows promising results, although it requires individual adjustment due to the risk of complications, especially in the presence of co-occurring infections [9][27][28][29][30][31]. The prognosis is good, but the high rate of relapses, especially with continued use of e-cigarettes, emphasizes the importance of health education and abandoning their further use [32].

To prevent recurrence of EVALI epidemics and similar incidents, it is crucial to increase physicians' awareness of this disease, routinely ask patients about the use of e-cigarettes, and educate them about the harmfulness of vaping, especially cartridges from unreliable sources. Patients should also be warned against adding substances to cartridges [9][10][24][32]. Additionally, it is necessary to tighten e-cigarette sales policies, including by raising the minimum purchase age, banning flavored cartridges, and limiting online sales [33]. The CDC recommends avoiding recommending a return to smoking traditional cigarettes and instead offering assistance in quitting smoking [9].

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Conceptualization: JB, MB

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Software: PK, KA

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Formal analysis: KA, PK

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