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Electronic cigarettes' effects on respiratory health

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ABSTRACT

BACKGROUND. Electronic cigarettes (ECs) are electronic nicotine delivery systems (ENDS). ECs have been sold as a safer alternative to traditional cigarettes due to the lack of tobacco combustion since 2006. Their use has risen dramatically not only among current smokers willing to quit, but even among never-smokers and adolescents. Anyway, few data are available on the effects of ECs' use on respiratory health. This article aims to summarize the available evidence on this matter.
MATERIALS AND METHODS. We collected on PubMed relevant studies and case reports on electronic cigarette use and its effects on respiratory health.
RESULTS. Electronic cigarettes' structure includes several sources of toxicity. Its constituents are rich in heavy metals, founded in various concentrations in the aerosolized vapor. E-liquid used to refill EC's cartridge is made of propylene glycol (PG) and vegetable glycerin (VG), which irritate the respiratory system. Moreover, e-liquid taste is often ameliorated with a wide range of commercial or homemade flavors, whose safety is uncertain. Several studies revealed that ECs vapor induces harmful effects at different levels of the respiratory tract, from airways to lung parenchyma, altering the pulmonary homeostasis. E-cigarette, or vaping, product use-associated lung injury" (EVALI) is a pulmonary disease described for the first time in 2019, characterized by the presence of bilateral ground-glass opacities on chest imaging, affecting people with a history of ECs in the previous 90 days. Moreover, current literature suggests a potential carcinogenic role of ECs and describes vaping as a risk factor from asthma developing and exacerbations.
CONCLUSIONS. From available data, ECs should not be considered a harmless alternative to tobacco cigarettes. There is an urgent need for further studies to establish the long-term effects of vaping.

BACKGROUND

Electronic cigarettes (ECs) are battery-operated nicotine delivery devices touted as a safer alternative to conventional combustible cigarettes and as an aid to quit smoking. Their use has widely expanded in the last decade, above all among young people and adolescents, mostly because the absence of tobacco combustion contributes to the spread of the idea that vaping is harmless. The diffusion of ECs among young people has exceeded tobacco cigarettes since 2014[1]. In 2015, the Center for Disease Control and Prevention conducted a National Youth Tobacco Survey, revealing that 5.3% of US middle school students and 16% of US high school students were current users of EC[2]. The term vaping reminds to vapor and may induce to underestimate the potential risks associated with ECs; conversely, the vapor produced by ECs has a complex chemical composition, and even though its toxicity is undoubtedly lower than traditional cigarettes, there is not enough data on long-term effects in humans, particularly on respiratory health.
This work aims to sum up the available data on ECs and their effect on respiratory health, allowing physicians and whoever will read it to understand the potential risks of vaping. Firstly, we will describe the e-cigarette's structure and its potential sources of toxicity.

KEYWORDS

ELECTRONIC CIGARETTES
VAPING
ACUTE LUNG INJURY
PULMONARY TOXICITY

Then, we will focus on the currently described effects of ECs on the respiratory system, considering both *in vitro* and *in vivo* models and clinical case reports. In a separate section, we will deepen Electronic Cigarettes, or Vaping, Product Use-Associated Lung Injury (EVALI), and other patterns of lung injuries associated with ECs use. Lastly, we will analyze the potential role of ECs in the development of respiratory diseases and lung cancer.

MATERIALS AND METHODS

Pertinent studies or case reports on electronic cigarette use and their effects on respiratory health were identified through PubMed, typing "Electronic cigarettes and lung injury" or "Electronic cigarettes' effects on the respiratory system" or "Electronic cigarettes' pulmonary toxicity".

RESULTS

Structure of EC and its potential toxicity

Electronic cigarettes (ECs) are battery-operated devices that aerosolize a liquid containing nicotine and produce a vapor that the user inhales. The first electronic cigarette was produced in China in 2003 by a pharmacist (Hon Lik). He aimed to allow smoking in prohibited areas[2]. In 2006, ECs were launched in USA and Europe as a "safer alternative to combustible cigarettes". The advertisements explicitly stressed the benefit of the lack of tobacco combustion, and the potential role as a device to quit smoking[3].

EC's structure consists of three principal elements: a battery, a heating element known as "atomizer", and a cartridge holding the liquid; other secondary components are: an airflow sensor, a microchip that controls the heating element, and (in some models) a LED light simulating a burning cigarette. The atomizer is a chamber with a resistance coil, that heats the liquid producing a vapor the user inhales through a mouthpiece whenever he/she switches on the device. The heating process may be activated either manually, by pressing a switch on the device, or by inhaling (only for models with an integrated air flow sensor). Both the atomizer and the battery include metal components such as nickel, chrome, and lithium[3].

E-liquid is a complex flavored mixture of glycols, nicotine, and particles. The most common constituents of e-liquid are propylene glycol (PG) and vegetable glycerin (VG), which are organic humectants[3]. Cutaneous application and ingestion of PG and VG are considered "Generally Recognized as Safe" (GRAS) by Food and Drug Administration (FDA), but few details are available regarding their safety when inhaled[4]. PG and VG generate toxic compounds when heated, such as acetaldehyde, formaldehyde, and acrolein, all substances with well-known irritant effects on respiratory airways and lung epithelia[4]. The nicotine added to e-liquid is usually isolated from the tobacco plant in variable concentrations. It is important to emphasize that several other compounds, such as tobacco-specific nitrosamines (TSNAs), are extracted with nicotine. TSNAs are known carcinogenic agents, whose concentration in e-liquid may vary from traces to consistent. Moreover, nicotine concentration is extremely variable among different devices, and some studies demonstrated that even e-liquids sponsored as "nicotine-free" contain nicotine[2,4,5]. Although ECs are sponsored as aids in smoking cessation, nicotine's concentration is often superior to traditional cigarettes[6]. Besides nicotine, flavors are added to ameliorate the taste, increasing the appeal to consumers, above all young generations. Some flavors, such as cinnamon, and additives, such as diacetyl (2,3-butanedione) have been associated with cytotoxic effects and acute bronchiolitis obliterans, also known as "popcorn lungs"[5,7]. Furthermore, consumers can create a homemade mixture, evading health institutions' control. In addition to standard, nicotine-added or nicotine-free ECs, an increasing number of smokers consumes ECs containing marijuana or tetrahydrocannabinol (THC). THC vaping is called "dabbing", is far more common among younger consumers, and often involves a homemade mixture of conventional e-liquid and various THC-containing products (e.g., cannabis oil, prefilled cannabis-cartridges, etc.). Dabbing is associated with acute lung injury[4], as discussed below.

As mentioned above, a standard EC contains several metal parts; therefore, an additional source of toxicity may consist of the heavy metal-enriched aerosol created by the interactions among e-liquid, atomizer, and EC's metal components. In particular, compounds such as nickel-chromium, chromium-aluminum-iron, copper, silver, zinc, and manganese have been isolated in EC's vapor, as well as higher (2-100 times) nickel concentrations than regular cigarettes[2].

Electronic cigarette's evolution

EC structure has significantly evolved since the first prototype's launch. Currently, there are four generations of EC-devices. The first generation comprises devices that most resemble to traditional cigarettes and are named "cig-a-like" or "vape sticks". The typical product consists of a slender non-refillable electronic device with a LED light that simulates tobacco burning.

The second-generation devices are called "tank systems" or "vape pens" and are characterized by a bulkier design with a more powerful battery than the previous generation. This kind of EC has a clearomizer, a specific atomizer in which the cartridge may be refilled with a larger quantity of e-liquid.
Third-generation ECs, named "mods", are more technologically advanced devices allowing the user to modify battery's voltage and refill the cartridge with commercial or homemade formulations.
The fourth generation EC is an updated version of mod. The main difference is the increased capacity, allowing the user to inhale more with a single recharge. The most known and sold model of fourth generation device is JUUL, developed in 2016 by Pax Labs., Inc. (San Francisco, CA USA), and is characterized by a compact and discrete design and a wide range of flavors, for which is very popular among younger consumers[4].

Effects of vaping on the respiratory system

In the last few years, there was a tremendous increase of EC's consumers, as we discussed above. Therefore, health authorities and scientific societies raised several concerns about the effects of vaping on the respiratory system. Ireri Thirión-Romero defined vaping as "a source of high exposure of the human respiratory system to fine particles" with a pattern of deposition in the lungs comparable to that of tobacco cigarettes[2]. Vaping exposure induces damage at different levels of the respiratory system, from airway epithelium to lung parenchyma[8]. In the next paragraphs, we will deepen this statement.

Airway epithelium damage

When heated, PG and VG generate toxic compounds such as formaldehyde and acrolein. These substances induce mucus hypersecretion, neutrophils' recruitment, activation, and subsequent degranulation and apoptosis, impairing antimicrobial response; moreover, the exposure of airways to these compounds increases oxidative stress, leading to a pro-inflammatory state. *In vitro* models of human bronchial cells exposed to EC vapor, or PG and VG solutions, showed a decreased airway barrier function, as a result of impaired mucociliary clearance, and mitochondrial oxidative stress, as demonstrated by lower levels of reduced glutathione[9-11].

Effects on gas exchange

EC vapor inhalation modifies the alveolar surfactant's composition, leading to a gas exchange impairment. This effect has been demonstrated in a murine model with both nicotine-added and nicotine-free e-liquid[12]. This study proved that PG causes the disruption of the surfactant layer, altering the alveolar gas exchange. Besides, gas exchange impairment was confirmed in a randomized clinical trial that recruited fourth-generation EC's consumers, who manifested changes in transcutaneous oxygen tension after e-vapor inhalation[13].

Lung parenchyma damage

Several *in vivo* and *in vitro* studies revealed EC vapor's cytotoxic effect. *In vitro* models assessed cytotoxicity by lactic acid dehydrogenase (LDH) release, which is independent of nicotine concentration. Human cells exposed to EC vapor show apoptosis's impairment, alterations into DNA repair mechanisms, increased oxidative stress, and membrane dysfunction[14]. Increased levels of epithelial membrane proteins have been detected in the serum of ECs users, supporting the existence of a direct mechanism of lung injury[8]. As a consequence of exposure to EC vapor, lung cells of *in vitro* models (murine, human primary alveolar type II-cells, and alveolar macrophages) showed a dysregulation between pro- and anti-inflammatory cytokines in favor of pro-, such as interleukin 8 (IL-8), IL-6, tumor necrosis factor-alpha (TNF-α)[14]. As described by Gerloff and colleagues, the wide variety of e-liquids potentially leads to different inflammatory effects on exposed cells[15].

Immunity dysregulation

The inhalation of ECs vapor was proved to induce oxidative stress in airway epithelium as well as alveolar epithelium[16]. As previously discussed, ECs vapor exposure alters the airway mucosa by reducing muco-ciliary function and, therefore, increases airway susceptibility to infections. Vaping exposure causes hypersecretion of a transmembrane platelet-activating receptor (PAFR), which is co-opted by pneumococci to adhere to the host cells. PAFR overexpression enhances microbial virulence and consequently the risk of respiratory infections[8]. Moreover, PG and VG exposures determine a lipid accumulation in alveolar macrophages, altering the innate immunity in animal models[12]. Bronchoalveolar lavage fluid (BALF) of mice exposed to ECs presented an increased bacterial load, especially methicillin-resistant *Staphylococcus aureus* (MRSA), pneumococci with increased adhesion to host cells, and alveolar macrophages with damaged phagocytosis[2]. Madison et al demonstrated that mice exposed to e-vapor and infected with the influenza virus had significantly delayed immune response[12].

Passive vaping

Current literature on the possible risk of passive vaping is limited, but there is an increasing concern about the potential danger of ECs aerosol exhaled by users for non-users. Whereas passive exposure from traditional cigarettes derives mainly from combustion, EC aerosol

derives totally from the user's exhalation. In 2014, a study by Czogala et al demonstrated that secondhand aerosol (SHA) isolated from human breath differs from aerosol generated by a machine due to biological processes occurring in the user's respiratory tract: interestingly, in SHA particulate matter's concentration is 4.5 times higher than in aerosol produced by a machine[17]. SHA also depends on the characteristics of the e-liquid used, and the voltage applied to the EC device. Many studies have investigated indoor air quality after vaping, demonstrating an increased concentration of particulate matter, carbon dioxide, nicotine, and volatile organic compounds. A study by Balbè et al demonstrated that volunteers exposed to passive EC aerosol have a salivary and urinary nicotine concentration comparable to those exposed to passive tobacco smoking[18]. Passive vaping has been associated with an increased frequency of respiratory irritation symptoms[19].

E-cigarette, or vaping, product use-associated lung injury (EVALI)

In August 2019, the Center for Disease Control and Prevention (CDC) identified a new clinical condition, named "E-cigarette, or vaping, product use-associated lung injury" (EVALI), after a public health investigation, promoted by the Wisconsin Department of Health Service (WDHS) and the Illinois Department of Public Health (IDPH), based upon several case reports of acute lung injury possibly related to ECs use[20].

EVALI is a pulmonary disease associated with the use of ECs in the 90 days before clinical onset, characterized by a combination of symptoms usually affecting respiratory and/or gastrointestinal tract, as well as constitutional symptoms. A high percentage of EVALI has been associated with the use of ECs containing THC, especially vitamin E acetate, the most commonly used additive in THC-containing products, strongly linked to lung injury[21]. The diagnostic workup of EVALI requires the exclusion of infections or other potential causes of acute lung injury, and a temporal correlation between the use of ECs and the onset of symptoms. Whether it was not possible to exclude pulmonary infections, but the clinician team believed that the respiratory condition could not be explained by the sole infection, a probable diagnosis of EVALI should be considered. Current definitions of confirmed and probable EVALI, purposed by the CDC, are listed in Table 1.

Clinical presentation and laboratory findings

EVALI may have an acute or subacute onset. Patients, often young and without relevant comorbidities, may suffer from a mild disease and develop a severe condition, needing hospital admission and, sometimes, intensive care.

Among a total of 53 cases analyzed between July and August 2019 meeting the criteria for probable or confirmed EVALI, the most common respiratory signs and symptoms were reduced oxygen saturation, hypoxemia, dyspnea, tachypnea, cough, chest pain, and hemoptysis. Gastrointestinal symptoms reported were nausea, vomiting, diarrhea, and abdominal pain. Constitutional symptoms observed were fever, chills, fatigue, and weight loss. The most frequent laboratory alteration was leukocytosis, with neutrophilic predominance. A mild increase of aminotransferase and erythrocytes sedimentation rate values were described in some cases, as well as hyponatremia and hypokalemia. EVALI patients should be thoroughly investigated for potential infections, including respiratory viruses, influenza, community-acquired pneumonia's both common and uncommon

Table 1. Centers for Disease Control and Prevention surveillance case definitions for EVALI[20].

EVALI confirmed case	**EVALI probable case**
Vaping or dabbing in 90 days before symptom onset	Vaping or dabbing in 90 days before symptom onset
Presence of pulmonary infiltrates, such as opacities on chest-XR or Ground glass opacities on thorax CT scan	Presence of pulmonary infiltrate, such as opacities on chest-XR or Ground glass opacities on thorax CT scan
Absence of infections confirmed by negative tests (respiratory viral panel including influenza virus, urinary antigen test for Streptococcus pneumoniae and Legionella, sputum or bronchoalveolar lavage culture if available, blood culture) and exclusion of HIV-related opportunistic infections if appropriate	Identification of an infection, but the clinical team believes this is not the sole cause of the underlying respiratory condition or infection tests not performed
Absence of plausible alternative diagnosis (cardiac, rheumatologic, or neoplastic conditions)	Absence of plausible alternative diagnosis (cardiac, rheumatologic, or neoplastic conditions)

Abbreviations: EVALI = E-cigarette, or vaping, product use-associated lung injury; CT = Computed Tomography; HIV = Human Immunodeficiency Virus.

bacteria (e.g., *Streptococcus pneumoniae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, opportunistic infections, fungal pneumonia). More than 50% of cases had a severe illness characterized by respiratory failure requiring intensive care unit admission, with non-invasive or invasive mechanical ventilation[20].

Radiological features

Radiological evaluation of EVALI revealed bilateral opacities on the chest radiograph. On CT scan EVALI common alterations were bilateral ground-glass opacities (GGOs), both patchy and/or confluent, with or without subpleural sparing and with a gravitational-dependent gradient[4].

Pathological findings

The precise pathological process of EVALI is still unclear. Almost all patients who underwent to bronchoalveolar lavage (BAL) had a neutrophilic or macrophage predominance, whereas in some cases, an eosinophilic dominance was observed. When available, oil-red-O staining revealed lipid-laden macrophages. Lung biopsies did not show a specific pathological pattern, but a spectrum of acute to subacute lung injury ones: non-specific inflammation, acute diffuse alveolar damage, foamy macrophages, organizing pneumonia, and in most severe cases, hyaline membranes[4,21].

Management and treatment

As we exposed above, the clinical spectrum of EVALI varies from a mild disease to a severe, intensive care-needing condition. An accurate evaluation should be done to determine whether a patient suffering/suspected to suffer from EVALI can be a candidate for outpatient management. The decision for inpatient versus outpatient management should be based on the oxygen saturation level of room air. If SpO_2 is >95% on room air, outpatient management can be considered. SpO_2 represents a crucial criterion, but other parameters should be taken into account: absence of respiratory distress, hemodynamic stability, absence or relevant comorbidities that may compromise cardiopulmonary reserve, reliable access to care in case of respiratory decline, appropriate social support, scheduled short- and long-term follow-up[22].

EVALI's treatment is above all supportive. Although a standardized treatment is not available yet, dueto the lack of randomized controlled clinical trials, systemic corticosteroids are suggested because of the role inflammation plays in disease development[4]. Furthermore, e-cigarette or vaping cessation is mandatory[22].

Other forms of vaping-associated lung injuries

Apart from EVALI, which undoubtedly represents the most common vaping-associated lung disease with acute or subacute onset, other forms of vaping-associated lung injuries have been reported. The definition of vaping-associated lung injury is based on the presence of radiological abnormalities, observed on chest-Xray and/or HRCT scans. Henry and colleagues identified four different imaging patterns related to ECs use: acute eosinophilic pneumonia (AEP), diffuse alveolar damage (DAD), organizing pneumonia (OP), and lipoid pneumonia[23]. These different patterns may share a common pathophysiological pathway, which includes airway and alveolar inflammation and edema[24]. These radiological patterns are usually characterized by the presence of consolidations and ground-glass opacities, with a predominant basal distribution and subpleural sparing. The onset could be acute or even subacute (e.g., organizing pneumonia). Other rarer patterns are giant-cell interstitial pneumonia, hypersensitivity pneumonitis (HP), and diffuse alveolar hemorrhage[23].

Acute eosinophilic pneumonia (AEP) is an inflammatory disease of unknown origin, probably triggered by inhaled antigens exposure. Patients complain of non-specific symptoms (fever, cough, dyspnea). Chest x-ray and HRCT show diffuse infiltrates and consolidations; BALF is mostly eosinophilic. ECs vapor-triggered inflammation may lead to increased levels of cytokines as IL-5, IL-6, IL-7, and TNF-α, which may determine the typical eosinophilic exudate within the alveoli; tobacco cigarettes may activate a similar pathway[25].

Thota and Latham, and Zhaohui and co-workers described two cases of AEP in healthy, young ECs-consumers. In both cases, the symptoms developed in a few days; thoracic imaging showed bilateral, patchy ground-glass opacities, and BAL revealed eosinophilia. Both patients improved with systemic steroid treatment[25,26].

A case of organizing pneumonia related to ECs use was described by Khan et al in 2018[27]. A case of BALF analysis confirmed diffuse alveolar hemorrhage (DAH) associated with ECs use, confirmed after BAL analysis, was reported by Agustin et al[28].

Some cases of acute lung injuries associated with ECs vaping and dabbing showed 50% or even more lipid-laden macrophages positive to oil red O staining on BALF, suggesting vaping-related lung injury[29]. Regardless of the specific pattern, most of these patients needed hospital admission and sometimes intensive care.

ECs use and chronic respiratory diseases

As mentioned above, ECs were sponsored as a safer alternative to conventional cigarette, and as useful smoking cessation devices. The ECs use prevalence is increasing among adults with a history of traditional smoking. Nevertheless, studies on ECs effects on people suffering from chronic respiratory diseases, or at risk of developing them, are still limited. This population

includes people at risk of developing respiratory diseases strongly linked to the smoking habit, such as Chronic Obstructive Pulmonary Disease (COPD), and people already affected by COPD. A prospective observational study by Bowler and colleagues suggested that ECs users had an increased prevalence of chronic bronchitis, COPD exacerbations, and a more rapid decline in lung function; intriguingly, this study found no evidence of either traditional cigarette smoking cessation or change of smoking habit[30].

Similarly, asthmatic patients who use ECs may have: increased airway resistances and decreased forced expiratory volume in 1 second to forced vital capacity ratio (FEV_1/FVC) at pulmonary function tests[31,32]; an increased fraction of exhaled nitric oxide (FeNO); increased levels of inflammatory cytokines (e.g., IL-4, IL-13, IL-1β, TNF-α) in exhaled breath condensate[32].

Several studies suggested that ECs use may increase the risk of developing asthma and might increase both asthma severity and exacerbations[33]. As we explained above, the exposure to vaporized e-liquid seems to create a pro-inflammatory environment in the lung.A respiratory immune dysregulation characterizes asthma itself, so we may hypothesize that ECs use may enhance such phenomenon, impacting on asthma severity and risk of exacerbations[34]. A South Korean study revealed that asthma was more prevalent among ECs users in a high school population, suggesting that ECs use should be considered as a risk factor for asthma development[35].

The carcinogenic effect of tobacco cigarettes is well-known: cigarette smoking represents the most important risk factor for lung cancer. It is less clear whether ECs may have a similar effect. Lee et al demonstrated that the derivates of nicotine in ECs induce DNA damage and reduce DNA repair activity in the lung, bladder, and heart tissue of murine models, as well as in cultured human epithelial and urothelial cells, revealing a potential carcinogenic effect of ECs[36].

DISCUSSION

This work highlights that although ECs are touted as safer alternatives to traditional cigarettes, they are not harmless devices and may increase the risk of developing a wide range of respiratory diseases. Clinicians should consider the possibility of vaping associated-acute lung injury in patients with acute respiratory failure and a history of ECs use and investigate the use of THC-rich e-liquid or flavored e-liquids.

Moreover, the presumed ECs aiding role in tobacco cessation has not been demonstrated by randomized clinical trials. On the contrary, some studies argued an increased nicotine addiction from ECs than traditional ones; therefore, they should be considered as another addictive nicotine product rather than a helpful tool to quit smoking.

Considering the rapid diffusion of ECs, above all among young people, there is an urgent need for further studies on the long-term effects of ECs, and more studies are needed to assess the potential effects of SHA on healthy people and people suffering from respiratory diseases. Testing the substances that can be added to e-liquids is also necessary to assess their potential pulmonary toxicity.

CONCLUSIONS

ECs cannot be considered innocuous nicotine delivery systems since evidence regarding vaping long-term effects is lacking. ECs exert a strong appeal on adolescents and not-smoking persons because of their presumed safety; thus, it is necessary to regulate ECs marketing and promotion; information campaigns could be helpful, above all in the schools, to increase people's awareness about ECs use associated risks.

Conflicts of Interest. The authors declare that they have no conflicts of interest or competing financial interests.

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