Vaping
Safer does not mean safe

Vasilios Tzilas,
Demosthenes Bouros

First Academic Department of Pneumonology,
Hospital for Thoracic Diseases, "Sotiria",
Medical School, National and Kapodistrian
University of Athens,
Athens, Greece

In recent years there has been a dramatic increase regarding the use of electronic nicotine delivery systems (eNDS). This increase was heavily based on the premise that eNDS are safer in comparison to combustible cigarettes. This comparison is problematic and misleading. Smoking is one of the deadliest addictions on earth. Comparing vaping to smoking may lead to a false sense of safety. First of all, safer does not mean safe, especially taking into consideration the enormous mortality and morbidity associated with smoking. Second the long term effects of vaping are largely unknown. It took decades to establish the detrimental effects of smoking. Claiming that vaping is safe is premature and irresponsible. Third, it is now well established that vaping can lead to potentially lethal acute lung injury known as e-cigarette associated lung injury (EVALI). The 2.290 reported cases of EVALI with 47 deaths prove that vaping is not a safe option. eNDS are an extremely profitable market with 11.3 billion dollars in the U.S. in 2018. Their sales are expected to surpass combustible cigarettes by 2023[1]. Marketing of eNDS is quite aggressive and the increase in vaping is particularly disturbing among adolescences. In 2017, 11% of U.S. students in the 12th grade (age 17-18 years) reported vaping in the last month. The prevalence sky-rocketed to 20.9% in 2018 and 25.4% in 2019[2].

eNDS are devices of various designs consisting of 3 parts, the atomizer, the battery and the mouthpiece. The atomizer consists of the e-liquid reservoir, the wick and a metal coil that is wrapped around the wick. The wick is usually made of cotton or silica and is soaked in the e-liquid that contains propylene glycol, vegetable glycerin, nicotine and various flavoring agents. When the user presses a button, the electrical circuit is closed and electric current (supplied by the battery) runs through the coil resulting in high temperatures. This causes the aerosolization of the e-liquid that is inhaled through the mouthpiece. Thus, the term vaping is actually is misnomer. Vapor is a substance in the gas phase. People using eNDS do not inhale a vapor and actually they do not vape. eNDS users inhale a solution and specifically an aerosol, a suspension of tiny particles of liquid, solid, or both within a gas.

While, the long term effects of vaping are largely unknown there is increasing data proving that vaping can cause acute lung injury. In the U.S. 2.290 cases of EVALI have been reported and 47 deaths. EVALI is a serious complication of vaping as the vast majority of the cases (95%) were hos-

Correspondence to:
Prof. Demosthenes Bouros MD, PhD, FERS, FAPSR, FCCP
FirstAcademic Department of Pneumonology,
Hospital for Diseases of the Chest, "Sotiria",
Medical School, National and Kapodistrian University
of Athens, Athens, Greece,
152 Messogion Av., Athens 11527, Greece
E-mail: debouros@med.uoa.gr, debouros@gmail.com

pitalized. Most of the EVALI cases were young patients, under 35 years old (77%), with a median age of 24 years and age range from 13 to 78 years. Common symptoms are cough, dyspnea or chest pain of acute or subacute onset. Fever and fatigue can also be seen. Some patients complain for nausea, vomiting, diarrhea or abdominal pain. According to CDC (Centers for Disease Control and Prevention) a confirmed case of EVALI requires: using an eNDS in 90 days prior to symptom onset, pulmonary infiltrates on chest X-ray or computed tomography (CT), and exclusion of alternative diagnoses (infection, cardiac, rheumatologic, or neoplastic process). Minimum criteria to exclude infection on initial work-up are: i) a negative respiratory viral panel, ii) a negative influenza PCR or rapid test and iii) other clinically indicated respiratory infectious disease testing (e.g., urine Antigen for *Streptococcus pneumoniae* and *Legionella*, sputum culture, if productive cough, BALF culture is done, blood culture, HIV-related opportunistic respiratory infections if appropriate) are negative[3]. If infection is identified but the clinical team believes it is not the sole cause of the underlying lung injury or when the above mentioned tests to rule out pulmonary infection are not performed and the clinical team believes infection is not the sole cause of the underlying lung injury, the case is characterized as probable[3]. These case definitions are not clinical guidelines but were designated for surveillance reasons.

From a pathological point of view, various patterns have been reported. Initially, it was thought that EVALI was a form of acute exogenous lipoid pneumonia caused by the lipids within the inhaled aerosol. However, typical findings of exogenous lipoid pneumonia are rarely reported[4]. Furthermore, in computed tomography no areas of fat density (around -50 Hounsfield Units) are identified[5]. Several forms of pathology patterns have been reported as diffuse alveolar damage (DAD), acute fibrinous pneumonitis (AFOP), organizing pneumonia (OP), giant cell interstitial pneumonia (GIP)[6] and diffuse alveolar hemorrhage (DAH)[7]. Butt et al reviewed lung biopsies from 17 patients with EVALI (9 transbronchial biopsies, 1 cryobiopsy, and 7 surgical lung biopsies). There were no specific histological findings. Foamy macrophages and pneumocyte vacuolization were seen in all cases. Pigmented macrophages were never a dominant feature and granulomas were not seen. No cases of exogenous lipoid pneumonia were identified in this series[6]. Thus, a negative oil red O staining on BALF does not exclude the diagnosis of EVALI. The surgical lung biopsies and cryobiopsy cases allowed assessment of the distribution of disease that was predominantly centrilobular (75%). The wide variety of histology patterns is reflected on the imaging characteristics as well. Many radiological patterns have been described as ill-defined centrilobular nodules with upper lobe predominance, consolidation, ground glass opacities, septal thickening and an organizing pneumonia pattern with subpleural and perilobular pattern[5,8]. In every young patient with bilateral pulmonary infiltrates it is important to ask for any vaping history.

The actual causes of EVALI have not been determined yet. Both **propylene glycol** and **vegetable glycerin** have been designated by the FDA as "generally recognized as safe" (GRAS) for oral intake. Propylene glycol is extensively used as an antifreeze agent and in the food, plastics, perfume and pharmaceutical industries. However, it must be emphasized that safe to ingest does not mean safe to inhale. There is a paucity of data regarding the long term effects of inhaling heated glycol and vegetable glycerin. **Vitamin E** is one such example. Vitamin E is found in many foods, including vegetable oils, cereals, meat, fruits, and vegetables. It is also available as a dietary supplement and in many cosmetic products, like skin creams. However, Vitamin E is used as a thickening agent in eNDS containing tetrahydrocannabinol (THC). Bronchoalveolar lavage fluid (BALF) from 29 patients with EVALI was tested by the CDC. All of the samples tested positive for Vitamin E. This was the first time that a chemical of concern was detected in biologic samples from patients with EVALI. In the above study, THC was identified in 82% of the samples representing another risk factor. In a case series from Illinois and Wisconsin 84% of the patients reported vaping THC products[3]. Another characteristic example is diacetyl. **Diacetyl** is used as a buttery flavor agent in microwave popcorn and is designated as GRAS by the FDA. Nevertheless, when inhaled it can cause bronchiolitis obliterans, widely known as popcorn lung. Interestingly, diacetyl can be found in e-liquids[1]. Finally, when heated, propylene glycol and glycerin can form **acrolein** and other toxic **aldehydes**[9]. Public is strongly advised not to modify or add any substances to eNDS that are not intended by the manufacturer and are home-made, purchased illegally or through retail establishments.

There is also amisconception that eNDS are not related to second hand exposure[10]. The 24 hour time weighted average (TWA) concentration of **PM_{10} particles** at a vaping convention was **12-fold increased** above the regulation of the U.S. Environmental Protection Agency (150 μg/m^3). Maximum concentration of PM_{10} exceeded 10.000 μg/m^3 for more than 50% of the time during the vap-

ing convention[11]. There is also the problem of children ingesting e-liquids with several reports coming from the U.K. and the U.S.[10]

Vaping is more than just inhaling vapor. It is actually an inhalation of several solid and liquid particles suspended in gas. Substances deemed to be safe for intake can have deleterious effects when inhaled. Furthermore, it is worth noting that the generated heat that is fundamental for the aerosolization of the e-liquid can lead to production of substances (as acrolein and other toxic aldehydes) that were not present initially. Finally, the eNDS give the opportunity of experimentation by adding various substances, adjusting coil resistance and thus the heat generated and so on. It took a lot of decades to finally realize the lethal results of smoking. Easy and premature conclusions regarding the safety of vaping can lead to detrimental results. The lungs were evolved through thousands of years based on the inspiration of atmospheric air. Inspiration of any other substance is potentially dangerous. As pneumonologists it is important to stand at the first line of defense raising awareness and passing on responsible information.

REFERENCES

1. Chun LF, Moazed F, Calfee CS, Matthay MA, Gotts JE. Pulmonary toxicity of e-cigarettes. Am J Physiol Lung Cell Mol Physiol 2017; 313:L193-L206.
2. Miech R, Johnston L, O'Malley PM, Bachman JG. Trends in adolescent vaping, 2017-2019. N Engl J Med 2019; 381:1490-1.
3. Layden JE, Ghinai I, Pray I, et al. Pulmonary illness related to e-cigarette use in Illinois and Wisconsin - Preliminary Report. N Engl J Med 2019. DOI: 10.1056/NEJMoa1911614.
4. Viswam D, Trotter S, Sherwood Burge P, Walters GI. Respiratory failure caused by lipoid pneumonia from vaping e-cigarettes. Case Report. BMJ 2018; 2018:bcr-2018-224350.
5. Henry TS, Kanne JP, Kligerman SJ. Imaging of vaping-associated lung disease. N Engl J Med 2019; 381:1486-7.
6. Butt YM, Smith ML, Tazelaar HD, et al. Pathology of vaping-associated lung injury. N Engl J Med 2019; 381:1780-1.
7. Agustin M, Yamamoto M, Cabrera F, Eusebio R. Diffuse alveolar hemorrhage induced by vaping. Case Rep Pulmonol 2018; 2018:9724530.
8. Henry TS, Kligerman SJ, Raptis CA, Mann H, Sechrist JW, Kanne JP. Imaging findings of vaping-associated lung injury. Am J Roentgenol 2019; 1-8. doi: 10.2214/AJR.19.22251.
9. Sleiman M, Logue JM, Montesinos VN, et al. Emissions from electronic cigarettes: Key parameters affecting the release of harmful chemicals. Environ Sci Technol 2016; 50:9644-51.
10. Larcombe AN. Early-life exposure to electronic cigarettes: cause for concern. Lancet Respir Med 2019; 7:985-92.
11. Chen R, Aherrera A, Isichei C, et al. Assessment of indoor air quality at an electronic cigarette (Vaping) convention. J Expo Sci Environ Epidemiol 2018; 28:522-9.