# VAPING RELATED LUNG DISORDERS

DM SEMINAR

# Outline

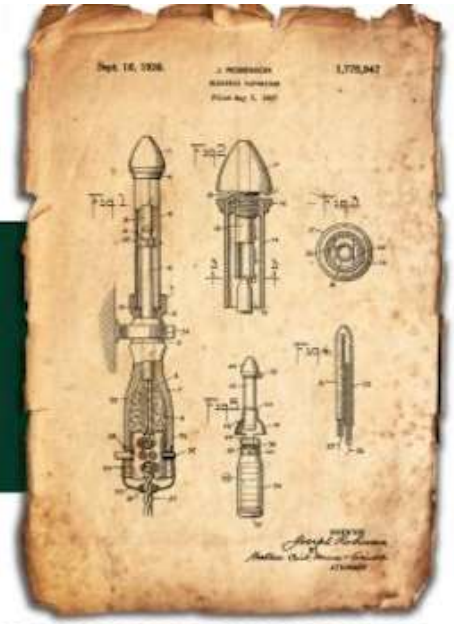
- History
- E-cigarette – Nicotine and Cannabis, constituents
- E-cigarette use – prevalence, patterns, reasons
- E-cigarette – smoking cessation, gateway drug
- E-cigarettes and health – Asthma, COPD
- EVALI
- Role of Vitamin E acetate in EVALI
- CDC updates and recommendations

# 1927

Joseph Robinson filed a patent for the first "Electric Vaporizer" in 1927 and was approved in 1930.

*My invention relates to vaporizing devices for holding medicinal compounds which are electrically heated to produce vapors for inhalation, and to provide a device for individual use which may be freely handled without any possibility of being burned.*

**JOSEPH ROBINSON**
*May 3, 1927 New York*



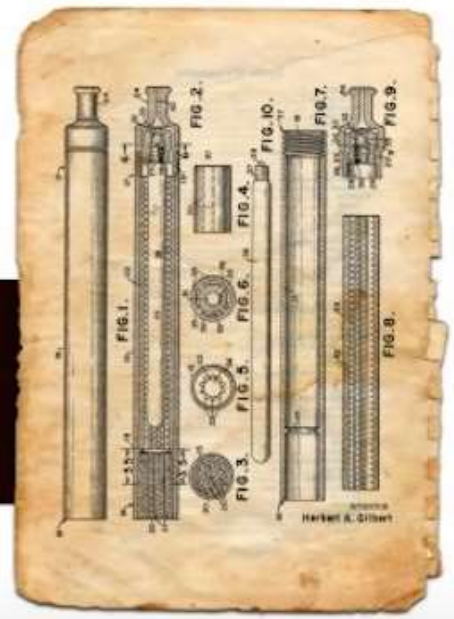
Although not actually made for vaporizing tobacco, the device has similar capabilities to a modern electronic cigarette.

# 1963

Herbert A. Gilbert files a US Patent for the first smokeless cigarette.

*The present invention relates to a smokeless non tobacco cigarette and has for an object to provide a safe and harmless means for and method of smoking by replacing burning tobacco and paper with heated, moist, flavored air.*

**GILBERT HERBERT A**
*Apr 17, 1963 Pennsylvania*




Unfortunately, he was way ahead of his time and his ideas wouldn't be revisited for almost 30 years.

# 1990'S

A number of new patents are issued for cigarette substitutes, including several novel electronic cigarette designs.

In 1998, Philip Morris begins selling Accord, a battery-powered "heat not burn" device as a cigarette substitute.

# 2004

The first commercial e-cigarettes were introduced in China in 2004.


APR
2006
Electronic cigarettes become available for sale and use in Europe.
2007
Electronic cigarettes quickly enter the U.S. after being a hit in Europe.

# 2009

**OCT**

California Governor Arnold Schwarzenegger protects adult consumer rights by rejecting a bill to ban e-cigarettes in California.

amazon

Amazon bans the sale of electronic tobacco products on their website.

ash.

The United Kingdom Action on Smoking and Health expresses initial support for electronic cigarettes as a possible harm reduction product, saying that products should be made available that deliver nicotine in a safe way, without the harmful components found in tobacco.

# History of E-cigarettes

- Herbert A. Gilbert, 1965 - First smokeless, non-tobacco cigarette
- Replaced burning tobacco and paper with heated, moist, flavored air
- Safe and harmless method of smoking

3,200,819

# SMOKELESS NON-TOBACCO CIGARETTE

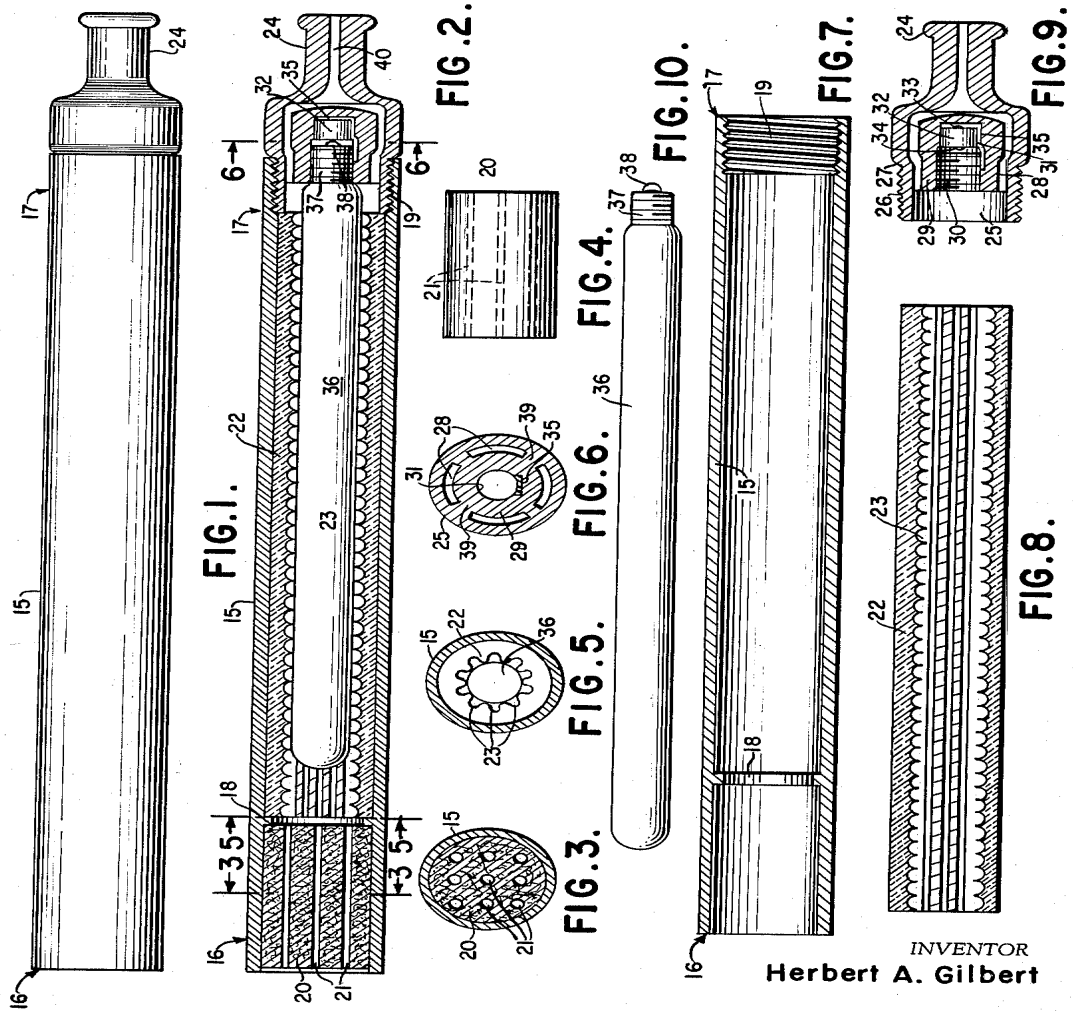
Herbert A. Gilbert, 278 McKinley Road, Beaver Falls, Pa.

Filed Apr. 17, 1963, Ser. No. 273,624
10 Claims. (Cl. 128—208)

Aug. 17, 1965 H. A. GILBERT 3,200,819

SMOKELESS NON-TOBACCO CIGARETTE

Filed April 17, 1963




INVENTOR
Herbert A. Gilbert

BY Mawhinney & Mawhinney
ATTORNEYS

Some of the advantages of the invention are:

(a) There is no open flame or fire and fire hazard is therefore eliminated.

(b) Nothing is consumed so that there is no smoke, ashes or dirt.

(c) Since the air which enters the lungs of the user comes into contact with only inert materials, there is nothing of an injurious nature being placed into the respiratory system of the user.

(d) Heated medication for respiratory ailments may be induced into the lungs of a user of this invention should a physician feel the same desirable.

(e) Persons who wish to smoke but have been advised against such a practice by their doctor may use this invention to maintain the satisfaction of smoking without any of its disadvantages.

(f) By changing the liquid employed to moisten the cartridge **20**, a variety of tastes may be imparted to the warm moist air which serves to duplicate the smoking sensation.

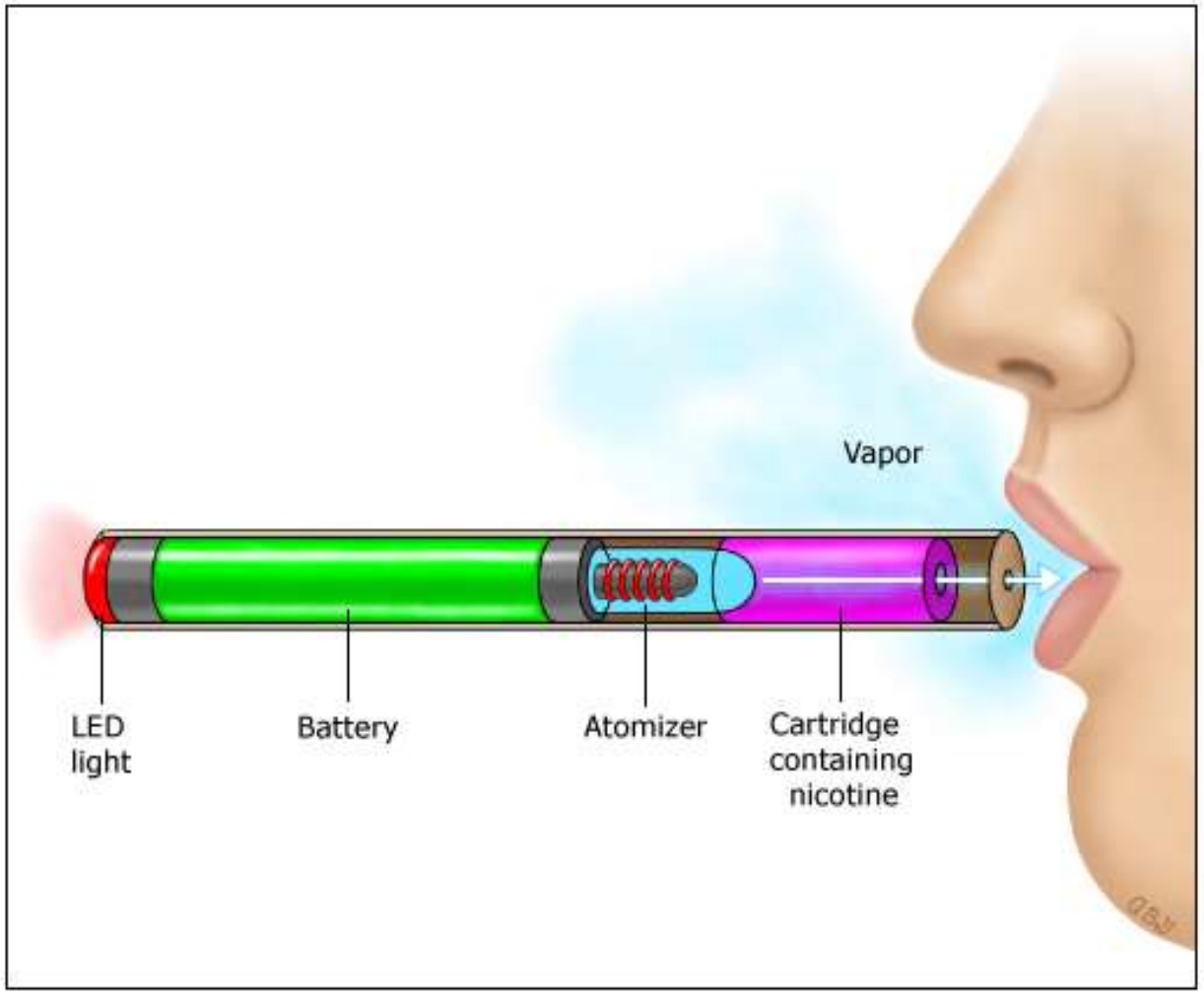
(g) The size and shape of the device according to this invention may approximate the size and shape of a cigarette; therefore its use will not call undue attention to the user. A white coloration of the basic tube **15** and mouthpiece will further add to this illusion.

# Modern E-cigarette

- Electronic Nicotine Delivery System (ENDS)
- Hon Lik, Chinese research pharmacist, 2004
- He quit smoking after his father who was a heavy smoker, died of lung cancer
- Consists of a cartridge, an atomizer (vaporization chamber with a heating element), and a battery

# E-cigarette parts

- “RUYAN” - 2004
- Activation – by inhaling or pressing a button
- Atomizer – heats and aerosolizes the liquid creating “vapor”
- Vaping – smoking an E-cigarette



| Product | Description | Some Brands |
|---|---|---|
| **Disposable e-cigarette**  | Cigarette-shaped device consisting of a battery and a cartridge containing an atomizer to heat a solution (with or without nicotine). Not rechargeable or refillable and is intended to be discarded after product stops producing aerosol. Sometimes called an e-hookah. | NJOY OneJoy, Aer Disposable, Flavorvapes |
| **Rechargeable e-cigarette**  | Cigarette-shaped device consisting of a battery that connects to an atomizer used to heat a solution typically containing nicotine. Often contains an element that regulates puff duration and /or how many puffs may be taken consecutively. | Blu, GreenSmoke, EonSmoke |
| **Pen-style, medium-sized rechargeable e-cigarette**  | Larger than a cigarette, often with a higher capacity battery, may contain a prefilled cartridge or a refillable cartridge (often called a clearomizer). These devices often come with a manual switch allowing to regulate length and frequency of puffs. | Vapor King Storm, Totally Wicked Tornado |
| **Tank-style, large-sized rechargeable e-cigarette**  | Much larger than a cigarette with a higher capacity battery and typically contains a large, refillable cartridge. Often contains manual switches and a battery casing for customizing battery capacity. Can be easily modified. | Volcano Lavatube |

Circulation. 2014;129:1972-1986.

# E-Liquid Constituents

| Constituents | Concentration/type | Comments |
|---|---|---|
| Nicotine | 6mg/ml, 12mg/ml, 18mg/ml, 24mg/ml | 0 to 30ug per puff (30 puffs - 1mg)<br>1 conventional cigarette – 1mg nicotine |
| Humectants | Propylene glycol / glycerol / ethylene glycol<br><br>80% of liquid | Propylene oxide – carcinogen<br>Acrolein – upper respiratory tract irritation<br>Formaldehyde, acetaldehyde |
| Flavors | Candy, fruit, soda, alcohol | To attract youth |
| Metals | Tin, lead, nickel, chromium, arsenic, manganese, cobalt | From - Metallic coil, device and liquid |

J Thorac Dis 2019;11(12):5572-5585

# Vaping - Cannabis

## Cannabis concentrates (THC based oils, wax)

| Constituents | Comment | Limitation / AE |
|---|---|---|
| Pesticides | Used to grow cannabis | May not be eliminated completely even after processing |
| Solvents | Butane, hexane | Case reports of severe pneumonitis (butane hash oil) |
| Flavors | Diacetyl, acetoin | Popcorn Lung (BO) |
| Cutting agents | Vitamin E acetate | Surfactant disruption |

Addiction, 115: 587– 588

**Table 1.** Electronic Cigarette (E-Cigarette) Use Patterns Among US Adults by Demographics and Smoking Status, 2014 National Health Interview Survey ($n$ = 36 697)[a]

| | Never user | Former trier[b] | Someday[c] | Daily |
|---|---|---|---|---|
| | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) |
| Sex | | | | |
| Male (48.2%) | 85.8 (84.8–86.7) | 10.1 (9.4–10.7) | 2.9 (2.3–3.5) | 1.3 (1.1–1.6) |
| Female (51.8%) | 88.9 (88.1–89.6) | 7.8 (7.3–8.3) | 2.4 (1.9–2.9) | 1.0 (0.8–1.3) |
| Age group | | | | |
| 18 to 24 (12.6%) | 78.4 (75.9–80.7) | 16.5 (14.7–18.6) | 4.3 (2.9–6.1) | 0.9 (0.5–1.4) |
| 25 to 44 (34.2%) | 83.4 (82.4–84.4) | 11.9 (11.1–12.8) | 3.2 (2.8–3.7) | 1.5 (1.2–1.8) |
| 45 to 64 (34.5%) | 89.8 (88.9–90.7) | 6.6 (6.1–7.3) | 2.3 (1.8–2.9) | 1.2 (1.0–1.5) |
| ≥65 (18.7%) | 96.3 (95.8–96.8) | 2.2 (1.9–2.7) | 0.8 (0.6–1.2) | 0.6 (0.4–0.9) |
| Race/ethnicity | | | | |
| White, NH (66.3%) | 85.2 (84.3–86.0) | 10.3 (9.7–10.9) | 3.1 (2.7–3.7) | 1.4 (1.2–1.7) |
| Black, NH (12.0%) | 92.4 (91.5–93.2) | 5.6 (4.9–6.4) | 1.5 (1.1–2.1) | 0.4 (0.3–0.7) |
| Hispanic (15.3%) | 91.4 (90.2–92.4) | 6.5 (5.6–7.5) | 1.7 (1.2–2.3) | 0.5 (0.3–0.7) |
| Other, NH (6.4%) | 91.5 (89.9–92.9) | 6.1 (5.0–7.4) | 1.4 (0.9–2.0) | 1.0 (0.5–1.9) |
| Cigarette smoking status | | | | |
| Daily smoker (12.8%) | 50.9 (48.5–53.3) | 32.8 (30.9–34.8) | 12.7 (10.9–14.8) | 3.5 (2.7–4.4) |
| Some day smoker (3.9%) | 57.4 (53.6–61.1) | 27.7 (24.4–31.4) | 11.5 (9.2–14.2) | 3.4 (2.2–5.2) |
| Recent quitter—quit 1 year ago or less (2.9%) | 52.0 (47.2–56.8) | 29.9 (25.8–34.4) | 5.0 (3.2–8.0) | 13.0 (10.5–16.1) |
| Former smoker—quit 2 to 3 years ago (1.7%) | 66.6 (61.5–71.4) | 23.0 (18.7–27.9) | 3.8 (2.4–6.2) | 6.5 (4.2–9.9) |
| Former smoker—quit 4+ years ago (17.2%) | 95.8 (94.9–96.5) | 3.5 (2.9–4.1) | 0.6 (0.2–1.3) | 0.2 (0.1–0.4) |
| Never-smoker (61.1%) | 96.8 (96.4–97.2) | 2.8 (2.5–3.2) | 0.3 (0.2–0.5) | 0.1 (0.0–0.1) |
| Region | | | | |
| Northeast (17.3%) | 90.3 (89.0–91.4) | 7.3 (6.4–8.4) | 1.5 (1.1–1.9) | 0.9 (0.6–1.5) |
| Midwest (23.0%) | 84.9 (83.5–86.2) | 10.6 (9.8–11.5) | 3.2 (2.4–4.3) | 1.2 (0.9–1.7) |
| South (37.2%) | 87.7 (86.6–88.7) | 8.4 (7.7–9.2) | 2.7 (2.1–3.4) | 1.2 (1.0–1.5) |
| West (22.5%) | 87.2 (86.2–88.2) | 9.0 (8.2–9.9) | 2.7 (2.2–3.2) | 1.1 (0.8–1.4) |
| Overall | 87.4 (86.8–88.0) | 8.9 (8.5–9.3) | 2.6 (2.3–3.0) | 1.1 (1.0–1.3) |

CI = confidence interval; NH = non-Hispanic.
[a]Prevalence estimates used weighted data.
[b]Have ever tried an e-cigarette but currently use "not at all".
[c]Currently use e-cigarettes "some days".

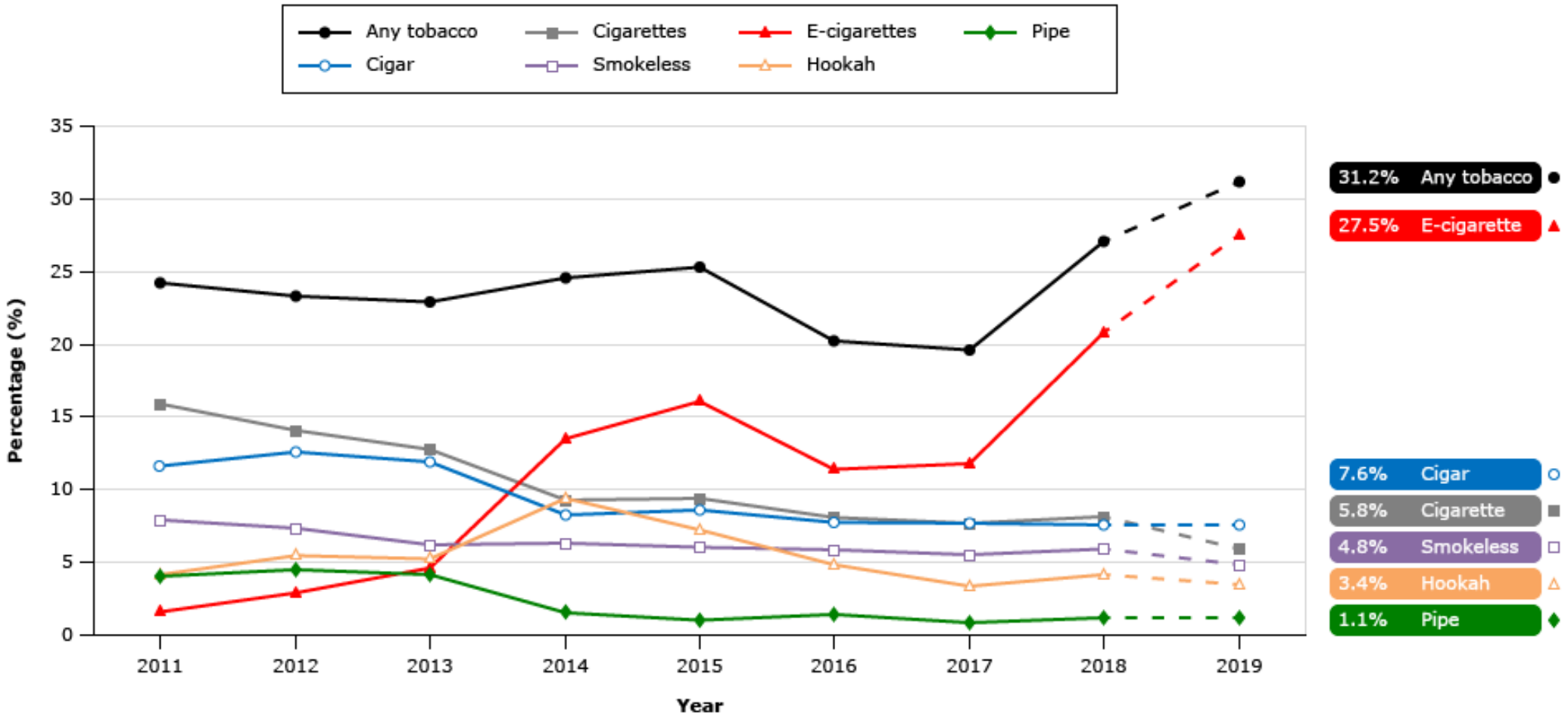
NHIS, cross-sectional survey – 2014
Computer based personal interview - 36,697 subjects

E-cigarette use highest in

- Males
- 18-24 years
- Whites
- Recent quitter

Nicotine & Tobacco Research, 2016, Vol. 18, No. 5

# Current tobacco product use among high school students (NYTS, 2011-2019)




MMWR Surveill Summ 2019; 68:1.

# Reasons for E—cigarette use

**TABLE 6. Reasons for e-cigarette use* among middle and high school students who reported using e-cigarettes and other tobacco products during the past 30 days — National Youth Tobacco Survey, United States, 2019**

| Reason | Use e-cigarettes only† | | Use e-cigarettes and other tobacco products§ | |
|---|---|---|---|---|
| | % (95% CI) | Estimated no.¶ | % (95% CI) | Estimated no. |
| I was curious about them | 56.1 (53.4–58.7) | 1,900,000 | 38.4 (35.1–41.7) | 730,000 |
| Friend or family member used them | 23.9 (21.7–26.3) | 810,000 | 22.2 (19.6–25.1) | 420,000 |
| They are available in flavors, such as mint, candy, fruit, or chocolate | 22.3 (20.3–24.5) | 760,000 | 26.6 (23.8–29.6) | 500,000 |
| I can use them to do tricks | 22.0 (20.0–24.2) | 740,000 | 29.0 (25.6–32.7) | 550,000 |
| They are less harmful than other forms of tobacco, such as cigarettes | 17.2 (15.3–19.3) | 580,000 | 19.1 (16.7–21.9) | 360,000 |
| I can use them unnoticed at home or at school | 14.5 (12.9–16.3) | 490,000 | 22.9 (19.4–26.8) | 430,000 |
| I was peer pressured into using them | 8.9 (7.7–10.3) | 300,000 | 7.5 (5.8–9.8) | 140,000 |
| They are easier to get than other tobacco products, such as cigarettes | 3.9 (3.0–5.0) | 130,000 | 9.7 (7.9–11.8) | 180,000 |
| I've seen people on TV, online, or in movies use them | 3.8 (3.1–4.6) | 120,000 | 5.4 (3.9–7.4) | 100,000 |
| To try to quit using other tobacco products, such as cigarettes | 2.8 (1.8–4.2) | 90,000 | 17.0 (14.0–20.5) | 320,000 |
| They cost less than other tobacco products, such as cigarettes | 2.5 (1.9–3.3) | 80,000 | 11.6 (9.4–14.3) | 220,000 |
| I used them for some other reason** | 15.9 (14.0–18.0) | 540,000 | 22.2 (17.9–27.3) | 420,000 |

**Abbreviations:** CI = confidence interval; e-cigarettes = electronic cigarettes; TV = television.

* Assessed by the question, "What are the reasons why you have used electronic cigarettes or e-cigarettes? (Check all that apply.)" Responses were not mutually exclusive.

† Reported use of only e-cigarettes on ≥1 day during the past 30 days (n = 2,361).

§ Reported use of e-cigarettes and at least one other tobacco product (e-cigarettes and cigarettes, cigars, smokeless tobacco, hookahs, pipe tobacco, or bidis [small brown cigarettes wrapped in a leaf]) on ≥1 day during the past 30 days (n = 1,267).

¶ Estimated weighted total number of users was rounded down to the nearest 10,000 persons.

** Respondents could subsequently specify a reason through a write-in option (n = 465).

MMWR / December 6, 2019 / Vol. 68 / No. 12

# E-cigarettes for smoking cessation

- Cochrane review, 2016
- 2 RCTs, EC vs Placebo (non-nicotine), n=662
- 1 RCT, EC vs Nicotine patch, n=584

Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.:

# E-cigarettes for smoking cessation

**Electronic cigarettes (EC) for smoking cessation**

**Patient or population:** people defined as current smokers at enrolment into trials, motivated or unmotivated to quit
**Intervention:** nicotine-containing electronic cigarettes
**Comparison:** placebo electronic cigarettes or nicotine replacement therapy (or for adverse events, uncontrolled)

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk[1] | Corresponding risk | | | | |
| | Control | Electronic cigarettes | | | | |
| **Cessation: Nicotine EC versus placebo EC**[2] assessed with exhaled CO<br>Follow-up: 6 - 12 months | 40 per 1000 | 93 per 1000<br>(42 to 201) | RR 2.29<br>(1.05 to 4.96) | 662<br>(2 studies) | ⊕⊕◯◯<br>**low**[3,4] | Only RCTs reported here. Some cohort data also available (see full review) but only RCTs provide efficacy data |
| **Cessation: Nicotine EC versus nicotine replacement therapy** assessed with exhaled CO<br>Follow-up: 6 months | 58 per 1000 | 73 per 1000<br>(39 to 135) | RR 1.26<br>(0.68 to 2.34) | 584<br>(1 study) | ⊕◯◯◯<br>**very low**[3,5] | As above |

Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.:

# E-cigarettes for smoking cessation

**Analysis 1.1. Comparison 1 Smoking cessation, Outcome 1 Nicotine EC versus placebo EC.**

Review: Electronic cigarettes for smoking cessation

Comparison: 1 Smoking cessation

Outcome: 1 Nicotine EC versus placebo EC

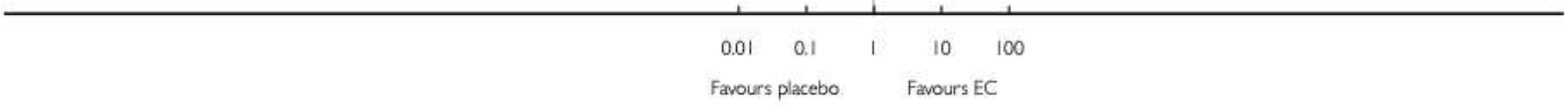
| Study or subgroup | Experimental n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Bullen 2013 | 21/289 | 3/73 | | 47.3 % | 1.77 [ 0.54, 5.77 ] |
| Caponnetto 2013a | 22/200 | 4/100 | | 52.7 % | 2.75 [ 0.97, 7.76 ] |
| **Total (95% CI)** | **489** | **173** | | **100.0 %** | **2.29 [ 1.05, 4.96 ]** |

Total events: 43 (Experimental), 7 (Control)

Heterogeneity: $Chi^2 = 0.30$, df = 1 (P = 0.58); $I^2 = 0.0\%$

Test for overall effect: Z = 2.09 (P = 0.037)

Test for subgroup differences: Not applicable




Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.:

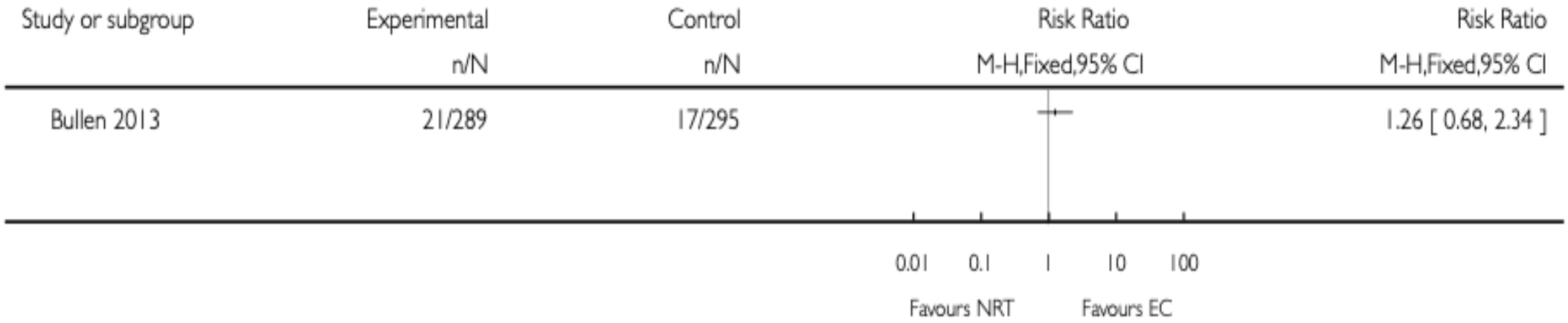
# E-cigarettes for smoking cessation

**Analysis 1.2. Comparison 1 Smoking cessation, Outcome 2 Nicotine EC versus nicotine replacement therapy.**

Review: Electronic cigarettes for smoking cessation

Comparison: 1 Smoking cessation

Outcome: 2 Nicotine EC versus nicotine replacement therapy




Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.:

# Authors conclusion

- ECs help smokers to stop smoking in the long term compared with placebo ECs
- Evidence – “LOW” GRADE
- The long-term safety of ECs is unknown

# EC vs NRT

| Study | Population | Intervention | Comparator | Outcome |
|---|---|---|---|---|
| Hajek, 2019<br><br>Pragmatic, RCT<br>multi-center - UK<br>NHS funded<br>May 2015 to Feb 2018 | N = 886<br>Smokers<br>1:1 randomization<br><br>Both groups – behaviour therapy (4 weeks) | E-cigarette ("ONE KIT" – ASPIRE company)<br><br>18mg/ml nicotine conc | NRT (patch, gum, etc) | Primary –<br>1-yr sustained abstinence rate:<br>18% - EC<br>9.9% - NRT<br><br>80% were using E-cig at 1 yr vs<br>9% were using NRT at 1 yr<br><br>Long term use of E-cig - dependence |

N Engl J Med 2019;380:629-37

# Smoking Cessation

- E-cigarettes replace or reduce conventional cigarette use
- However risk remains uncertain
- If an adult smoker is not willing for NRT, e-cigarettes can be advised as an alternative, as long as the smoker is informed about the safety and efficacy

# Gateway Effect

- Studies that evaluated the association between e-cigarette use among **never cigarette smokers** at baseline and **cigarette smoking initiation** between baseline and follow-up

- 9 longitudinal studies

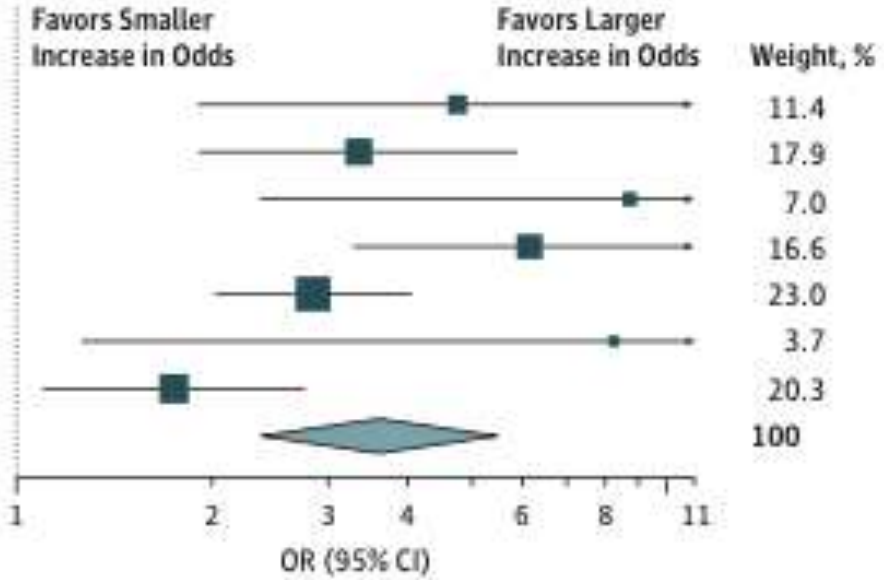
- 16,621 adolescents and young adults

JAMA Pediatr. 2017;171(8):788-797

Figure 2. Meta-analysis of Adjusted Odds of Cigarette Smoking Initiation Among Never Cigarette Smokers at Baseline and Ever e-Cigarette Users at Baseline Compared With Never e-Cigarette Users at Baseline

| Source | Probability of Cigarette Smoking Initiation, % | | Unadjusted OR (95% CI) | Adjusted OR (95% CI) | Weight, % |
|---|---|---|---|---|---|
| | Ever e-Cigarette Users | Never e-Cigarette Users | | | |
| Miech et al,[10] 2017 | 31.1 | 6.8 | 6.23 (1.57-24.63) | 4.78 (1.91-11.96) | 11.4 |
| Spindle et al,[9] 2017 | 29.4 | 10.6 | 3.50 (2.41-5.09) | 3.37 (1.91-5.94) | 17.9 |
| Primack et al,[22] 2016 | 37.5 | 9.0 | 6.06 (2.15-17.10) | 8.80 (2.37-32.69) | 7.0 |
| Barrington-Trimis et al,[8] 2016 | 40.4 | 10.5 | 5.76 (3.12-10.66) | 6.17 (3.29-11.57) | 16.6 |
| Wills et al,[7] 2016 | 19.5 | 5.4 | 4.25 (2.74-6.61) | 2.87 (2.03-4.05) | 23.0 |
| Primack et al,[6] 2015 | 37.5 | 9.6 | 5.66 (1.99-16.07) | 8.30 (1.19-58.00) | 3.7 |
| Leventhal et al,[5] 2015 | 31.8 | 5.6 | 7.78 (6.15-9.84) | 1.75 (1.10-2.78) | 20.3 |
| Total | 30.4 | 7.9 | 5.12 (4.41-5.95) | 3.62 (2.42-5.41) | 100 |

Heterogeneity: $\tau^2 = 0.15$; $Q_6 = 15.04$; $P = .02$; $I^2 = 60\%$
Test for overall effect: $z = 6.25$; $P < .001$




The odds ratios (OR) for the studies[5-10,22] are adjusted for a study-specific set of demographic, psychosocial, and behavioral risk factors. The size of the point estimate (black square) is proportional to the weight of the study in the random-effects meta-analysis model. The weights add to 99.9% and not 100% because of rounding. Q indicates Cochrane Q.

E-Cigarette use was associated with greater risk for subsequent cigarette smoking initiation

JAMA Pediatr. 2017;171(8):788-797

# E-cigarettes and health

# Pro-inflammatory effects of E-cigarettes – vapor condensate or flavorants

| Cells tested/systems affected | Treatment/type of lung fluid tested | Main findings |
|---|---|---|
| *In vitro* tests | | |
| Isolated neutrophils | EC vapor extract | Increased expression/activity of: (I) CD11b & CD66b; (II) release of MMP9, neutrophil elastase and IL-8 and (III) activation of p38 MAPK |
| Alveolar macrophage culture | EC vapor condensate | Reduction in cell viability. Sub-lethal concentrations increased generation of ROS, cytokines (IL-6, TNFα, IL-8, MCP-1) and MMP9 |
| Monocytic cell types MM6 and U937 | Exposed to EC flavorants e.g., diacetyl, cinnamaldehyde, pentanedione, o-vanillin, maltol, coumarin; doses 10–1,000 μM | Increased generation of IL-8; certain flavorants were cytotoxic at relatively high concentrations |
| *Ex vivo* test | | |
| Isolated neutrophils from EC users | Activated with 25 nM PMA | Isolated peripheral neutrophils demonstrated increased NET formation upon PMA stimulation |
| *In vivo* tests | | |
| Effects of EC use on airways | Induced sputum samples | Elevated levels of elastase and MMP9. Increases in NET-related proteins (e.g., MPO, azurocidin, protein arginine deiminase 4) |
| Effects of EC use on airways | Bronchoalveolar lavage fluid | Neutrophil elastase, MMP2 & MMP9 equally elevated in vapers and smokers |
| Effects of use of EC, containing only PG & VG, on airways | Bronchoalveolar lavage fluid | No changes in inflammatory cell counts or cytokines, however, changes in urinary PG correlated with change in cell counts and cytokines (although changes were small) |

J Thorac Dis 2019;11(12):5572-5585

# E-cigarette use – epidemiological surveys

| Cross sectional studies | N | EC use | Outcome |
|---|---|---|---|
| Hong Kong, 2016 | 45,000 adolescents | EC use in previous month | Increased **Cough or sputum** production (OR 2.1, 95% CI – 1.8 to 2.5) |
| South California, 2017 | 2000 high school students` | Past and current use of EC | 2 fold increase in the risk of **cough, sputum** compared to never users |
| Health eHeart study, 2018 | 40,000 subjects | Current EC use | Higher self ratings of **dyspnea** |

BMJ 2019;366:l5275

# Spirometric study

| Study | N | Intervention | Outcome |
|---|---|---|---|
| Meo SA, 2019 | 30 (EC)<br>30 (controls) | EC use and spirometry after a period of abstinence (at least 1 hr) | EC –<br>Lower $FEV_1$ (4.6L vs 5.2L; P=0.007)<br>Lower $FEV_1$/FVC (77.4 vs 83.4; P=0.001)<br><br>Can reflect acute bronchospasm rather than lasting changes |

Am J Mens Health 2019;13:155

# Conventional Asthmatic smokers on switching to EC

| Study | N | Primary outcome | Limitations |
|---|---|---|---|
| Polosa, 2014<br>Retrospective study | 18 mild to moderate Asthmatic smokers | Improvement in<br><br>$FEV_1$ and<br><br>Performance in methacholine challenge test | No change in Asthma exacerbations<br><br>Small sample |

Int. J. Environ. Res. Public Health 2014, 11, 4965-4977

# EC use and Asthma

- Pooled data of Behavioral risk factor surveillance system (BRFSS) 2016 and 2017
- Cross sectional, self reported, telephonic survey in USA
- 4,02,822 adults aged > 18 years, lifetime smoking < 100 cigarettes
- 3103 (0.7%) were current e-cigarette users
- 34,074 (8.5%) with asthma

Osei et al. BMC Pulmonary Medicine (2019) 19:180

# EC use and Asthma

The odds ratio of self-reported asthma

- 1.39; (95% confidence interval: 1.15, 1.68) in **current EC users**
- 1.31 (95% confidence interval: 1.05, 1.62) in **occasional EC users**
- 1.73 (95% confidence interval: 1.21, 2.48) in **daily EC users** compared to never e-cigarette users

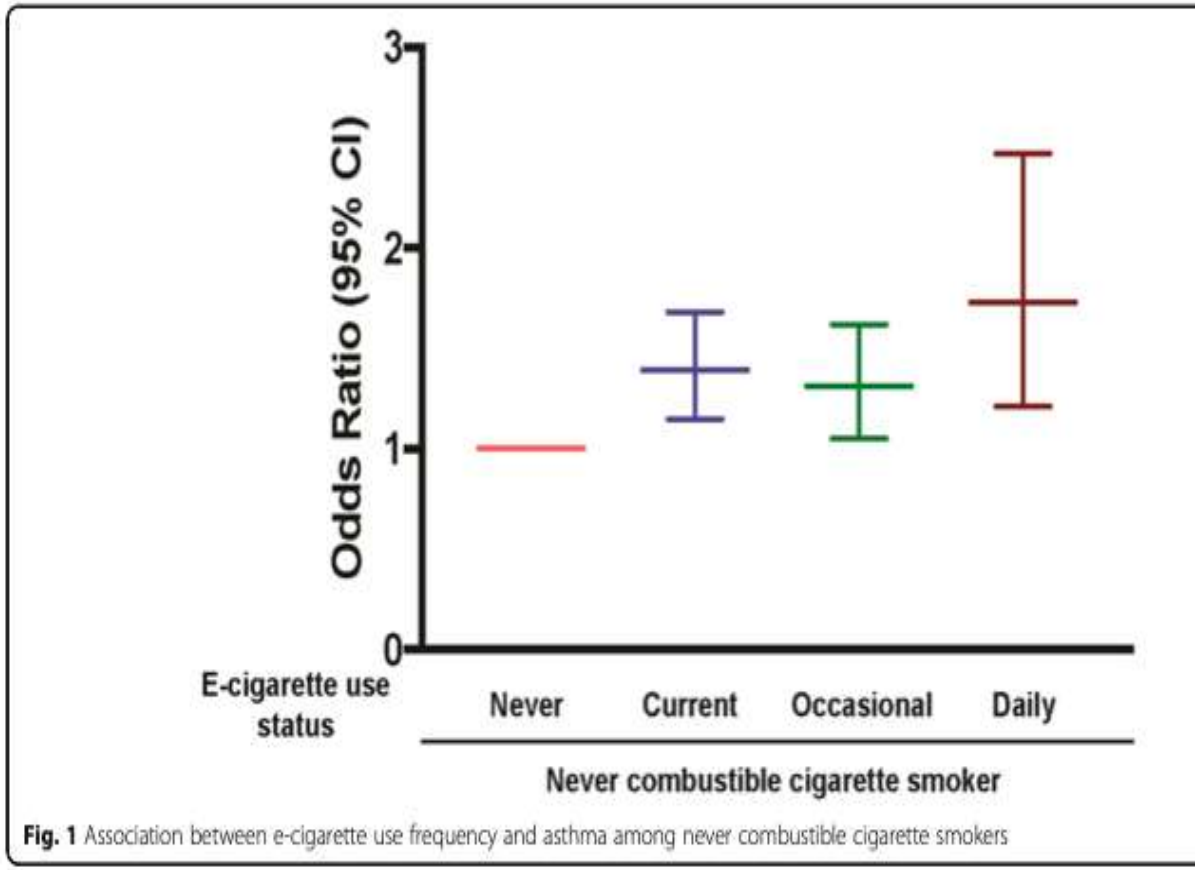


**Fig. 1** Association between e-cigarette use frequency and asthma among never combustible cigarette smokers

Osei et al. BMC Pulmonary Medicine (2019) 19:180

# Conventional smokers with COPD switching to EC

- Retrospective study
- Four Italian hospitals in the outpatient setting
- September 2013 to December 2015
- 48 COPD patients, 1 year follow up
- Those who continued to smoke CC versus those who switched to EC

CC – conventional cigarette

Polosa et al. Respiratory Research (2016) 17:166

**Table 1** Baseline demographics of the subjects on the study

| | COPD Controls | COPD E-Cig users | Baseline *P*-value between groups |
|---|---|---|---|
| Age[c] | 65.3 (±5.5) | 66.9 (±6.7) | 0.350 |
| Sex | 21 M, 3 F | 20 M, 4 F | - |
| COPD GOLD stage | | | |
| Stage 1 | 3 | 2 | - |
| Stage 2 | 5 | 6 | - |
| Stage 3 | 11 | 10 | - |
| Stage 4 | 5 | 6 | - |
| post-BD FEV1[b] (L) | 1.47 (1.13, 1.72) | 1.25 (0.94, 1.78) | 0.298 |
| post-BD FVC[b] (L) | 2.39 (2.1, 2.64) | 2.37 (2, 2.65) | 0.902 |
| %FEV1/FVC[c] | 56.2 (±10.3) | 59.4 (±8.4) | 0.244 |
| Pack years of smoking[c] | 51.7 (±9.9) | 52.4 (±10.7) | 0.365 |
| Cig/day[c] | 20.5 (±3.3) | 21.8 (±4.4) | 0.228 |
| CAT score[b] | 20.5 (17.8, 24.3) | 21.5 (17.8, 25.3) | 0.710 |
| COPD Exacerbations[a, c] | 2.1 (±1.1) | 2.3 (±1) | 0.440 |

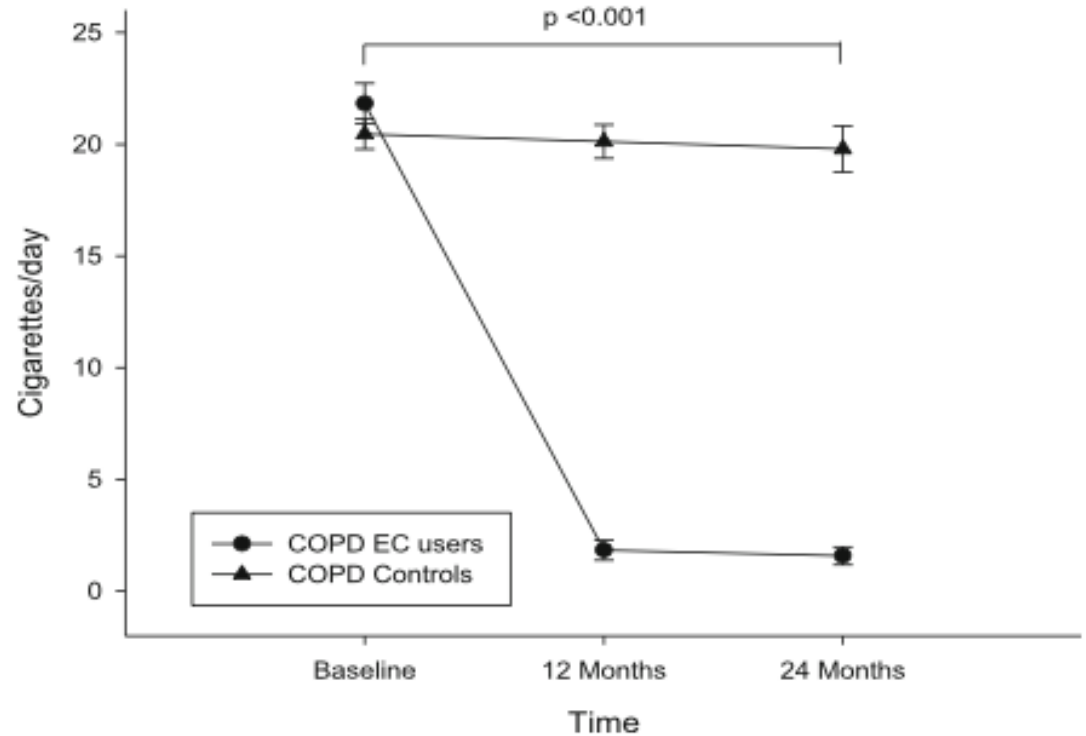



**Fig. 1** Changes in the number of cigarettes smoked in a day from baseline, at follow-up visit 1 (12 ± 1.5 months) and visit 2 (24 ± 2.5 months) separately for electronic cigarettes users (*closed circles*) and controls (*closed triangles*). All data expressed as mean and error bars are standard deviation of the mean. The p value is an overall comparison of both groups over the 24-month period

Polosa et al. Respiratory Research (2016) 17:166

**Table 2** Comparison of controls and e-Cigarette users at baseline, 12-month and 24-month follow-up visits

| | Baseline | 12-Month Follow-up | Within group p value vs Baseline[Ω] | 24-Month Follow-up | Within group *P* value vs Baseline[Ω] | Overall between group *p* value from Baseline[k] |
|---|---|---|---|---|---|---|
| COPD Controls (*n* = 24) | | | | | | |
| post-BD FEV1[a] (L) | 1.47 (1.13, 1.72) | 1.43 (1.12, 172) | 0.538 | 1.45 (1.17, 1.66) | 0.657 | 0.223 |
| post-BD FVC[a] (L) | 2.39 (2.1, 2.64) | 2.35 (2.2, 2.74) | 0.065 | 2.35 (2.19, 2.83) | 0.141 | 0.977 |
| %FEV1/FVC[b] | 56.2 (±10.3) | 55.9 (±10.1) | 0.328 | 56.3 (±10.1) | 0.277 | 0.033 |
| Cig/day[b] | 20.5 (±3.3) | 20.1 (±3.7) | 0.371 | 19.8 (±5) | 0.296 | <0.001 |
| CAT score[a] | 20.5 (17.8, 24.3) | 20 (17.5, 24.3) | 0.075 | 20 (15.8, 24) | 0.361 | 0.001 |
| COPD Exacerbations[b] | 2.1 (±1.1) | 2.2 (±1) | 0.906 | 2.1 (±1.1) | 0.819 | 0.005 |
| 6MWD[a, c] | 267.3 (195, 351.5) | 270 (210.3, 372) | 0.056 | 270.5 (220.8, 373.9) | 0.096 | 0.002 |
| COPD EC users (*n* = 24) | | | | | | |
| post-BD FEV1[a] (L) | 1.25 (0.94, 1.78) | 1.23 (0.93, 1.73) | 0.102 | 1.29 (0.92, 1.67) | 0.153 | |
| post-BD FVC[a] (L) | 2.37 (2, 2.65) | 2.45 (1.92, 2.73) | 0.081 | 2.46 (1.84, 2.86) | 0.252 | |
| %FEV1/FVC[b] | 59.4 (±8.4) | 58.3 (±8.6) | 0.457 | 57.9 (±8.5) | 0.483 | |
| Cig/day[b] | 21.8 (±4.4) | 1.8 (±2.2) | <0.001 | 1.58 (±2) | <0.001 | |
| CAT score[a] | 21.5 (17.8, 25.3) | 17.5 (15.8, 20.5) | <0.001 | 18 (15, 20) | <0.001 | |
| COPD Exacerbations[b] | 2.3 (±1) | 1.8 (±1) | 0.002 | 1.4 (±0.9) | <0.001 | |
| 6MWD[a, c] | 266.5 (187.5, 313.5) | 307 (219.5, 342) | 0.002 | 327 (239.5, 359.5) | 0.002 | |

*Abbreviations*: *COPD* Chronic obstructive pulmonary disease, *EC* e-Cigarette, *n* number, *BD* bronchodilator, *L* litre, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *Cig* conventional cigarettes, *CAT* COPD assessment tool, *6MWD* 6 min walk distance

[a] Median (interquartile range); [b] Mean (± standard deviation)

[c] 13 subjects in the COPD E-Cig user group and 14 in the COPD control group

[Ω] Statistical analyses conducted using Mann Whitney *U* Test (as data non-parametric) except for Cig/day and COPD exacerbations which were analysed using student *T* test (parametric data)

[k] Statistical analyses conducted using repeated measures ANOVA with Bonferroni adjustment

Decreased exacerbations
Improved CAT scores

No improvement in $FEV_1$
Retrospective study
Small sample

Polosa et al. Respiratory Research (2016) 17:166

# RCT, CC to EC switch

| Study | Population | Intervention | Comparator | Outcome |
|---|---|---|---|---|
| Cravo, 2016<br>RCT, parallel group<br><br>Safety profile<br><br>CC smokers switching to EC for 12 weeks | N = 408<br><br>Age:21-65 years<br><br>5-30 cig/day for at least 1 year | EC (n=306) | CC (n=102) | Adverse events in EC group (total – 1515 events)<br><br>• more common in 1st week after switching – “nicotine withdrawal” (495 events) |

A.S. Cravo et al. Regulatory Toxicology and Pharmacology (2016) 81:114

Very common AEs (frequency of ≥10%) in the EVP group, by system organ class, and frequency of these AEs in the CC group.

| | EVP (N = 306) | | CC (N = 102) | |
|---|---|---|---|---|
| | Number of subjects | % of subjects | Number of subjects | % of subjects |
| *Respiratory, thoracic and mediastinal disorders* | | | | |
| Sore Throat | 85 | 27.8% | 9 | 8.8% |
| Cough | 52 | 17.0% | 8 | 7.8% |
| *Nervous system disorders* | | | | |
| Headache | 145 | 47.4% | 34 | 33.3% |
| *Infection and infestation* | | | | |
| Nasopharyngitis | 34 | 11.1% | 8 | 7.8% |
| *Psychiatric disorders* | | | | |
| Desire to smoke | 84 | 27.5% | 13 | 12.7% |
| *General disorders and administration site conditions* | | | | |
| Irritability | 33 | 10.8% | 1 | 1.0% |
| *Metabolism and nutrition disorders* | | | | |
| Increased appetite | 43 | 14.1% | 1 | 1.0% |

A.S. Cravo et al. Regulatory Toxicology and Pharmacology (2016) 81:114

# Summary

- In healthy adults smoking EC causes increase in cough, sputum production and dyspnea
- EC smokers have higher rates of self reported asthma
- Insufficient evidence of benefit  in CC smokers with COPD on switching to EC
- Nicotine withdrawal symptoms are the most common adverse events in COPD patients switching from CC to EC

The Journal of Emergency Medicine, Vol. ■, No. ■, pp. 1–3, 2013
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0736-4679/$ - see front matter

http://dx.doi.org/10.1016/j.jemermed.2013.09.034

## Clinical Communications: Adults

# CASE REPORT OF ELECTRONIC CIGARETTES POSSIBLY ASSOCIATED WITH EOSINOPHILIC PNEUMONITIS IN A PREVIOUSLY HEALTHY ACTIVE-DUTY SAILOR

Darshan Thota, MD and Emi Latham, MD

Emergency Department, Naval Medical Center San Diego, San Diego, California
*Reprint Address:* Darshan Thota, MD, Emergency Department, Naval Medical Center San Diego, 34800 Bob Wilson Drive, San Diego, CA 92134

☐ **Abstract—Background: Electronic cigarettes (e-cigarettes) are a technology that has been touted as a safe and effective alternative to traditional cigarettes. There is, however, a paucity of literature showing the adverse outcomes of e-cigarettes and a correlation with acute eosinophilic pneumonia (AEP). Objective: To present a possible association between e-cigarettes and AEP. Case Report: A 20-year-old previously healthy man was found to develop AEP after smoking an e-cigarette. He was treated with antibiotics and steroids and his symptoms improved. Conclusion: Though an alternative to traditional cigarettes, e-cigarettes can have unpredictable and potentially serious adverse effects. More research needs to be conducted to determine their safety. If seeing a patient in the ED with pulmonary symptoms after use of e-cigarettes, AEP should be considered in the differential. Published by Elsevier Inc.**

August 2013
BAL – 74% eosinophils
Improved with oxygen, IV Abx, Steroids

# Bilateral Pneumonia and Pleural Effusions Subsequent to Electronic Cigarette Use

**Kendall Moore, Henry Young II, Matthew F. Ryan***

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Received 8 July 2015; accepted 1 September 2015; published 7 September 2015





September 2015

Improved with conservative Rx
No specific cause identified

## Abstract

**Electronic nicotine delivery systems also known as electronic cigarettes (or e-cigarettes) are marketed by their manufactures as a safer alternative to tobacco cigarettes because of potentially reduced delivery of toxins. However, the scientific evidence and the long-term health effects of e-cigarettes are limited. We describe a case of a 43-year-old man who had been smoking electronic cigarettes excessively for three days and presented with acute dyspnea, increased work of breathing and tachycardia. Subsequent chest x-ray revealed bilateral pleural effusions. In addition, the patient had a new oxygen requirement and was thus admitted with a diagnosis of pneumonia and bilateral pleural effusions. The case and the potential harmful effects of electronic cigarettes are discussed herein.**

Open Journal of Emergency Medicine, 2015, 3, 18-22

# Hypersensitivity Pneumonitis and Acute Respiratory Distress Syndrome From E-Cigarette Use

Casey G. Sommerfeld, MD, Daniel J. Weiner, MD, Andrew Nowalk, MD, PhD, Allyson Larkin, MD

June 2018

BAL
26% neutrophils
13% lymphocytes
22% eosinophils

Electronic cigarette (e-cigarette) use, or "vaping," is gaining widespread popularity as an alternative to conventional cigarettes among adolescents. Little is known of the health risks of e-cigarette use, especially in children and adolescents. We present a Case Report of a previously healthy 18-year-old woman who presented with dyspnea, cough, and pleuritic chest pain after e-cigarette use. She developed respiratory failure with hypoxia and was intubated, and ultimately met diagnostic criteria for acute respiratory distress syndrome. Chest tubes were placed to drain worsening pleural effusions. Computed tomography of the chest revealed dependent opacities in both lung bases, superimposed smooth interlobular septal thickening, and pleural effusions. Bronchoalveolar lavage revealed cellular debris and reactive mononuclear cells, and cell counts were remarkable for elevated mononuclear cells and eosinophilia. After the results of a workup for an infectious etiology came back negative, the patient was diagnosed with hypersensitivity pneumonitis and intravenous methylprednisolone therapy was initiated. After this the patient rapidly improved, was weaned off vasopressor support, and was extubated. This is the first reported case of hypersensitivity pneumonitis and acute respiratory distress syndrome as a risk of e-cigarette use in an adolescent, and it should prompt pediatricians to discuss the potential harms of vaping with their patients. Hypersensitivity pneumonitis, lipid pneumonia, and eosinophilic pneumonia should be included in the differential diagnosis of patients who exhibit respiratory symptoms after the use of an e-cigarette.

Pediatrics. 2018;141(6):e20163927

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin — Preliminary Report

Jennifer E. Layden, M.D., Ph.D., Isaac Ghinai, M.B., B.S., Ian Pray, Ph.D., Anne Kimball, M.D., Mark Layer, M.D., Mark Tenforde, M.D., Ph.D., Livia Navon, M.S., Brooke Hoots, Ph.D., Phillip P. Salvatore, Ph.D., Megan Elderbrook, M.P.H., Thomas Haupt, M.S., Jeffrey Kanne, M.D., Megan T. Patel, M.P.H., Lori Saathoff-Huber, M.P.H., Brian A. King, Ph.D., M.P.H., Josh G. Schier, M.D., Christina A. Mikosz, M.D., M.P.H., and Jonathan Meiman, M.D.

- July 10, 2019 – August 27, 2019
- Wisconsin Department of Health Services (WDHS) – 28 cases
- Illinois Department of Public Health (IDPH) – 25 cases
- Received reports of pulmonary disease of unclear cause associated with the use of e-cigarettes and related products

# Timeline

- July 10, 2019 - Children's Hospital of Wisconsin - Notified 5 previously healthy adolescents admitted with dyspnea and respiratory failure to WDHS
- History and w/u – inconclusive, except for a history of recent EC use

- July 25, 2019 – WDHS issued an alert of the clinical syndrome
- July 31, 2019 - IDPH – contacted WDHS for clinical treatment guidance for a similar patient
- August 1, 2019 - Joint WDHS and IDPH – initiated public health investigation
- August 20, 2019 - CDC – deployed epidemiological assistance field team (Epi-Aid)

**Table 1. Outbreak Surveillance Case Definitions of Severe Pulmonary Disease Associated with E-Cigarette Use — August 30, 2019.***

**Confirmed case**

Use of an e-cigarette (vaping) or dabbing in 90 days before symptom onset; and

Pulmonary infiltrate, such as opacities on plain-film radiograph of the chest or ground-glass opacities on chest CT; and

Absence of pulmonary infection on initial workup: the minimum criteria include negative respiratory viral panel and influenza PCR or rapid test if local epidemiology supports testing. All other clinically indicated testing for respiratory infectious disease (e.g., urine antigen testing for *Streptococcus pneumoniae* and legionella, sputum culture if productive cough, bronchoalveolar-lavage culture if done, blood culture, and presence of HIV-related opportunistic respiratory infections if appropriate) must be negative; and

No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process)

**Probable case**

Using an e-cigarette (vaping) or dabbing in 90 days before symptom onset; and

Pulmonary infiltrate, such as opacities on plain film chest radiograph or ground-glass opacities on chest CT; and

Infection identified by means of culture or PCR, but the clinical team caring for the patient believes that this is not the sole cause of the underlying respiratory disease process; or as the minimum criteria, to rule out pulmonary infection not met (testing not performed) and clinical team caring for the patient believes that this is not the sole cause of the underlying respiratory disease process; and

No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process)

These surveillance case definitions are from the Centres for Disease Control and Prevention and are meant for surveillance purposes and not for clinical diagnosis

**Table 2. Demographic Characteristics, Symptoms, Evaluation, and Clinical Course of 53 Case Patients.***

| Characteristic | Values |
|---|---|
| Median age (range) — yr | 19 (16–53) |
| Male sex — no./total no. (%) | 44/53 (83) |
| Race or ethnic group — no./total no. (%)† | |
| White | 37/45 (82) |
| Black | 4/45 (9) |
| Hispanic | 4/45 (9) |
| Medical history documented in medical record — no./total no. (%) | |
| Asthma | 16/53 (30) |
| Mood or anxiety disorder | 18/53 (34) |
| E-cigarette use in the previous 90 days — no./total no. (%)‡ | |
| Reported nicotine use | 25/41 (61) |
| Reported only nicotine use | 7/41 (17) |
| Reported THC use | 33/41 (80) |
| Reported only THC use | 15/41 (37) |
| Reported nicotine and THC use | 18/41 (44) |
| Reported CBD use | 3/41 (7) |

| | |
|---|---|
| **Symptoms reported at presentation** | |
| Median duration of symptoms before presentation (range) — days | 6 (0–61) |
| Any respiratory symptom — no./total no. (%)§ | 52/53 (98) |
| Shortness of breath | 46/53 (87) |
| Any chest pain | 29/53 (55) |
| Pleuritic chest pain | 20/53 (38) |
| Cough | 44/53 (83) |
| Hemoptysis | 6/53 (11) |
| Any gastrointestinal symptom — no./total no. (%)§ | 43/53 (81) |
| Nausea | 37/53 (70) |
| Vomiting | 35/53 (66) |
| Diarrhea | 23/53 (43) |
| Abdominal pain | 23/53 (43) |
| Any constitutional symptom – no./total no. (%)§ | 53/53 (100) |
| Subjective fever | 43/53 (81) |
| Chills | 31/53 (58) |
| Weight loss | 14/53 (26) |
| Fatigue or malaise | 24/53 (45) |
| Headache — no./total no. (%) | 21/53 (40) |
| **Vital signs at presentation** | |
| Temperature ≥38°C — no./total no. (%) | 15/51 (29) |
| Heart rate >100 beats/min — no./total no. (%) | 34/53 (64) |
| Respiratory rate >20 breaths/min — no./total no. (%) | 22/51 (43) |
| Oxygen saturation while breathing ambient air — no./total no. (%) | |
| ≥95% | 16/52 (31) |
| 89–94% | 20/52 (38) |
| ≤88% | 16/52 (31) |

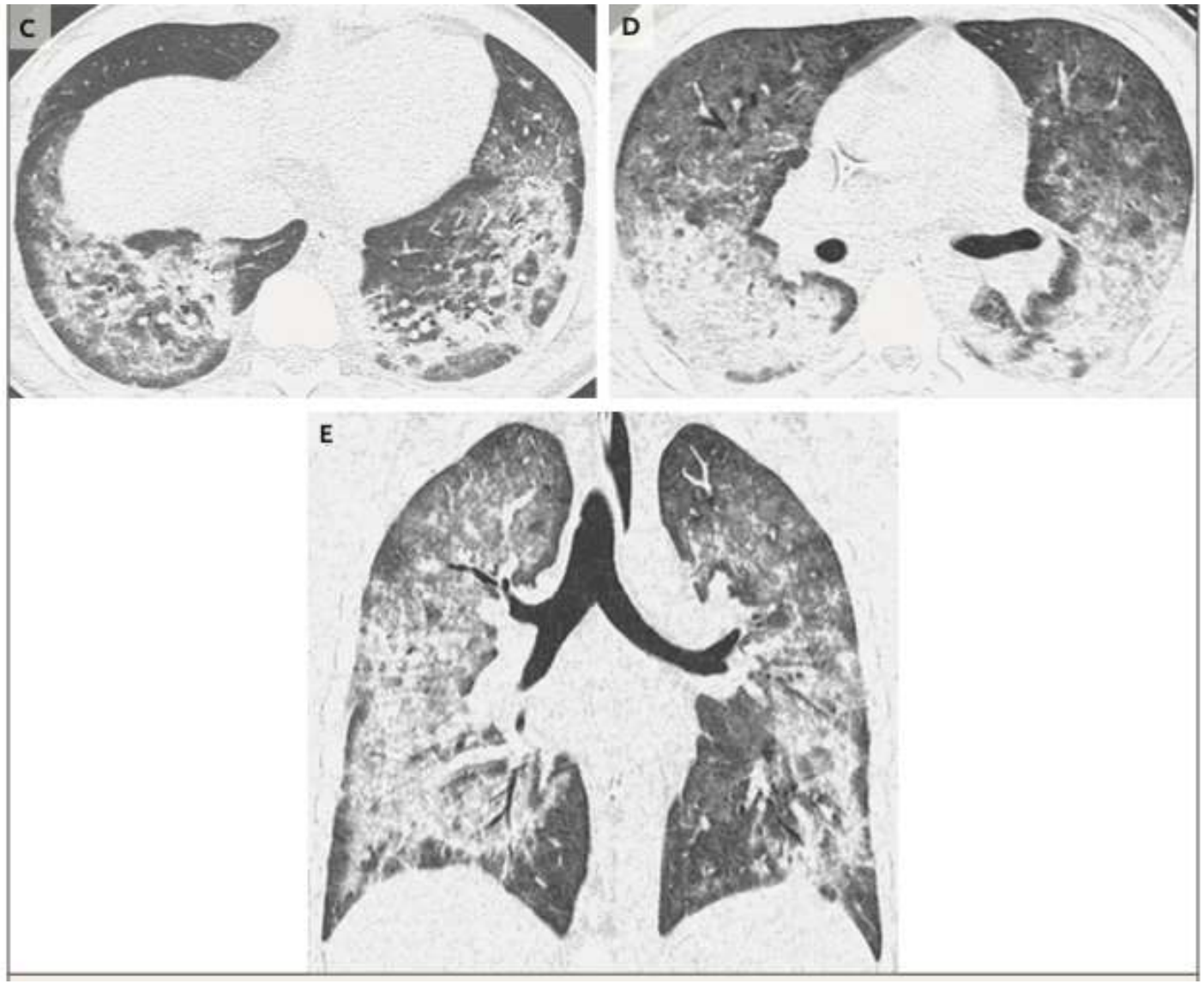
| | |
|---|---|
| **Initial radiographic findings** | |
| Abnormal chest radiograph — no./total no. (%) | 48/53 (91) |
| Abnormal chest CT — no./total no. (%) | 48/48 (100) |
| Bilateral infiltrates identified on chest radiograph or CT — no./total no. (%) | 53/53 (100) |
| **Treatment** | |
| Antibiotics for lower respiratory tract infection — no./total no. (%) | |
| As outpatient | 24/53 (45) |
| During hospitalization | 45/50 (90) |
| Glucocorticoids — no./total no. (%) | |
| Systemic glucocorticoids, oral or intravenous, during hospitalization | 46/50 (92) |
| Intravenous glucocorticoids | 38/46 (83) |
| Had clinical improvement documented with use of systemic glucocorticoids | 30/46 (65) |
| **Clinical course** | |
| Hospitalization — no./total no. (%) | 50/53 (94) |
| Outpatient or ED visit before hospitalization — no./total no. (%) | 36/50 (72) |
| Median duration of hospitalization (range) — days | 6 (1–25) |
| Receipt of supplemental oxygen — no./total no. (%) | 46/53 (87) |
| Receipt of noninvasive positive-pressure ventilation — no./total no. (%) | 19/53 (36) |
| Intubation and mechanical ventilation — no./total no. (%) | 17/53 (32) |
| Admission to intensive care unit — no./total no. (%) | 31/53 (58) |
| Death — no./total no. (%) | 1/53 (2) |

9 cases met Berlin criteria of ARDS
2 cases underwent ECMO, 1 died

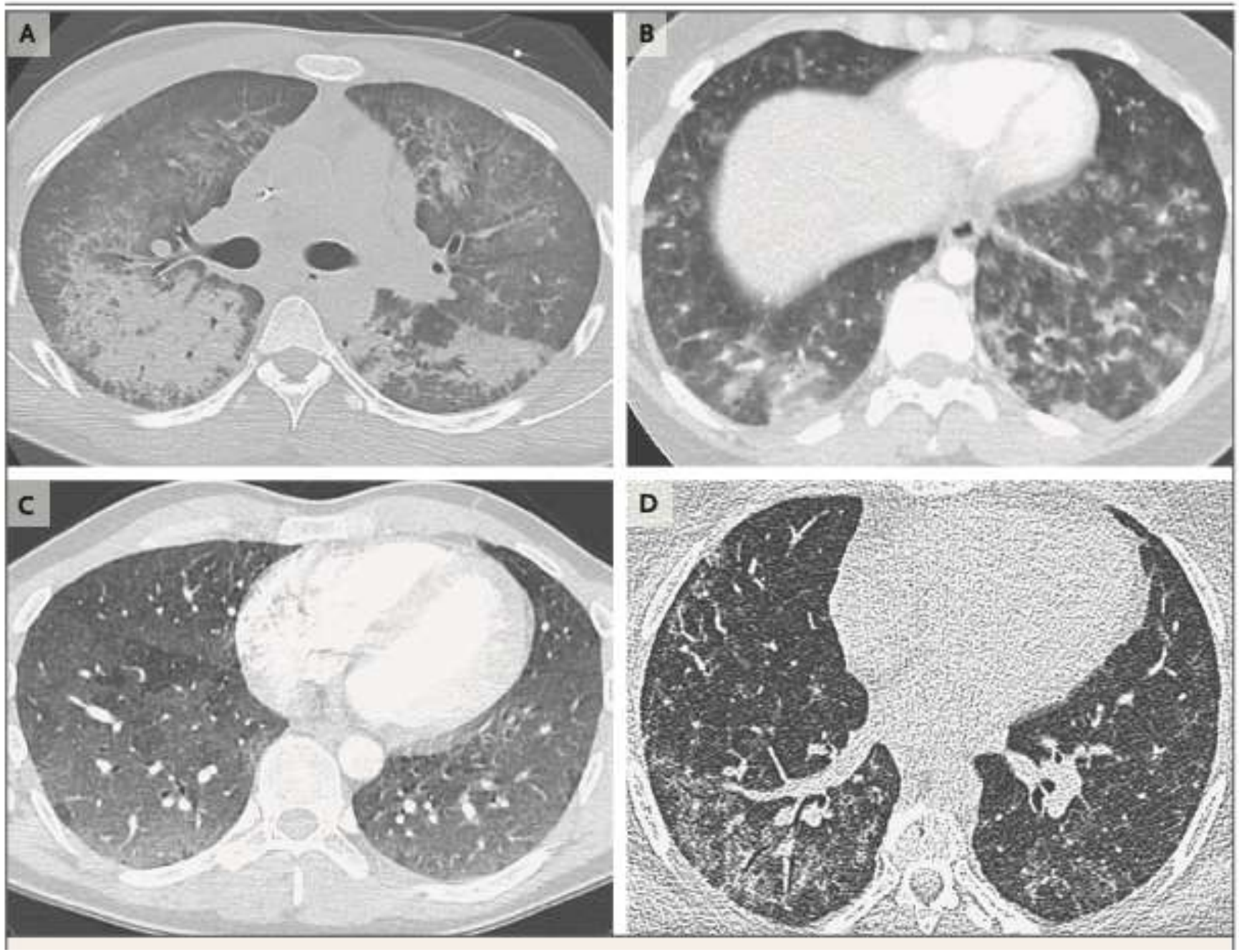
Of the 48 patients who underwent CT imaging
4 cases of pneumomediastinum
5 pleural effusions
1 case of pneumothorax

One patient had both pneumomediastinum and a pneumothorax

one patient had both pneumomediastinum and pleural effusion


C
D
E

| Test | N/Comments |
| --- | --- |
| BAL | 24 patients |
| BAL – DC | 14 patients<br>Median<br>E – 0% (0-6)<br>N - 65% (10-91)<br>L – 7% (1-40)<br>M – 21% (2-68) |
| Lipid laden macrophages with Oil red O stain | 7/14 |
| TBLB | 3 patients |
| OLB | 2 patients |
| HPE | DAD and foamy macrophages<br>Non-specific inflammation<br>Interstitial and peribronchiolar GI |




A – DAD
B – AEP
C – HP
D –Giant cell pneumonitis (cobalt)

N ENGL J MED 381;15

Morbidity and Mortality Weekly Report

# Outbreak of Electronic-Cigarette–Associated Acute Lipoid Pneumonia — North Carolina, July–August 2019

Kevin Davidson, MD[1]; Alison Brancato, MS[1]; Peter Heetderks, MD[1]; Wissam Mansour, MD[1]; Edward Matheis, MD[1]; Myra Nario, MS[1]; Shrinivas Rajagopalan, MD, PhD[2]; Bailey Underhill, MS[1]; Jeremy Wininger, MS[1]; Daniel Fox, MD[1]

- 5 patients with respiratory failure
- All – recent use of marijuana oils in EC
- BAL on day 3-5 – extensive lipid laden macrophages

Diagnosis of Acute lipoid pneumonia was made:

- EC containing oils
- Consistent radiology
- Lipid laden macrophages in BAL

- All five patients improved with IV steroids

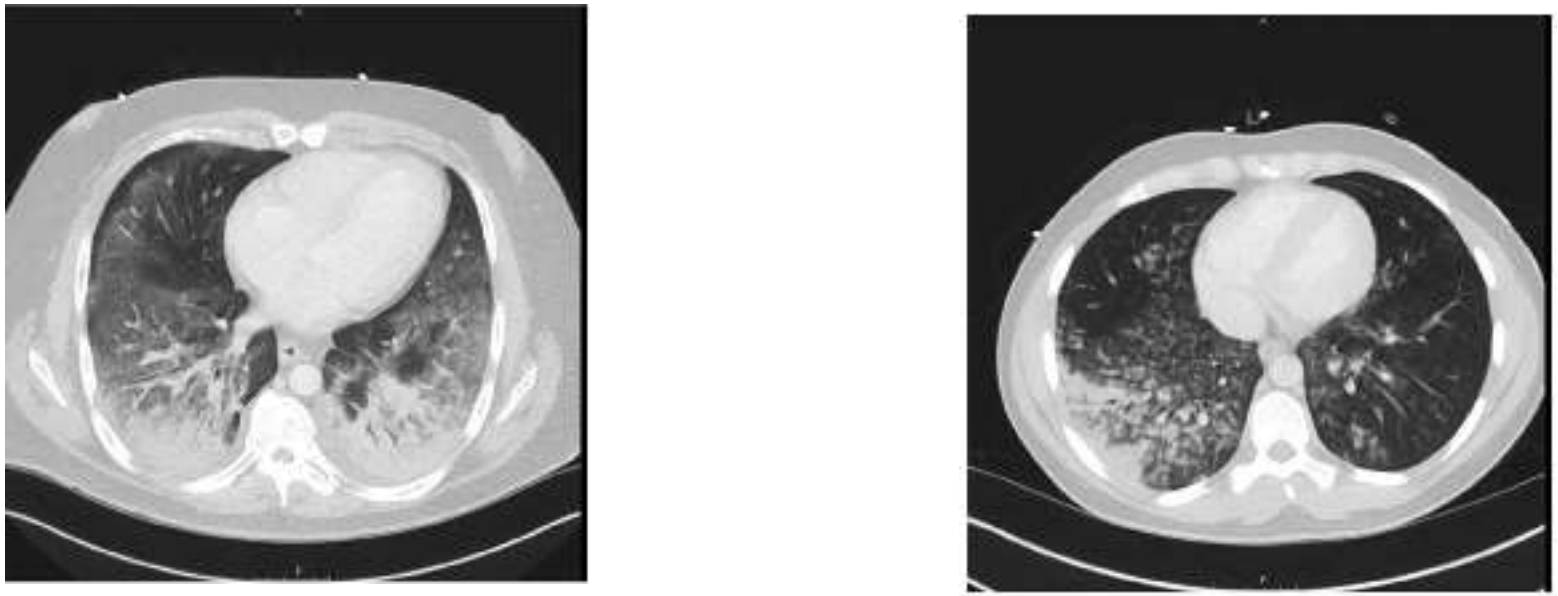
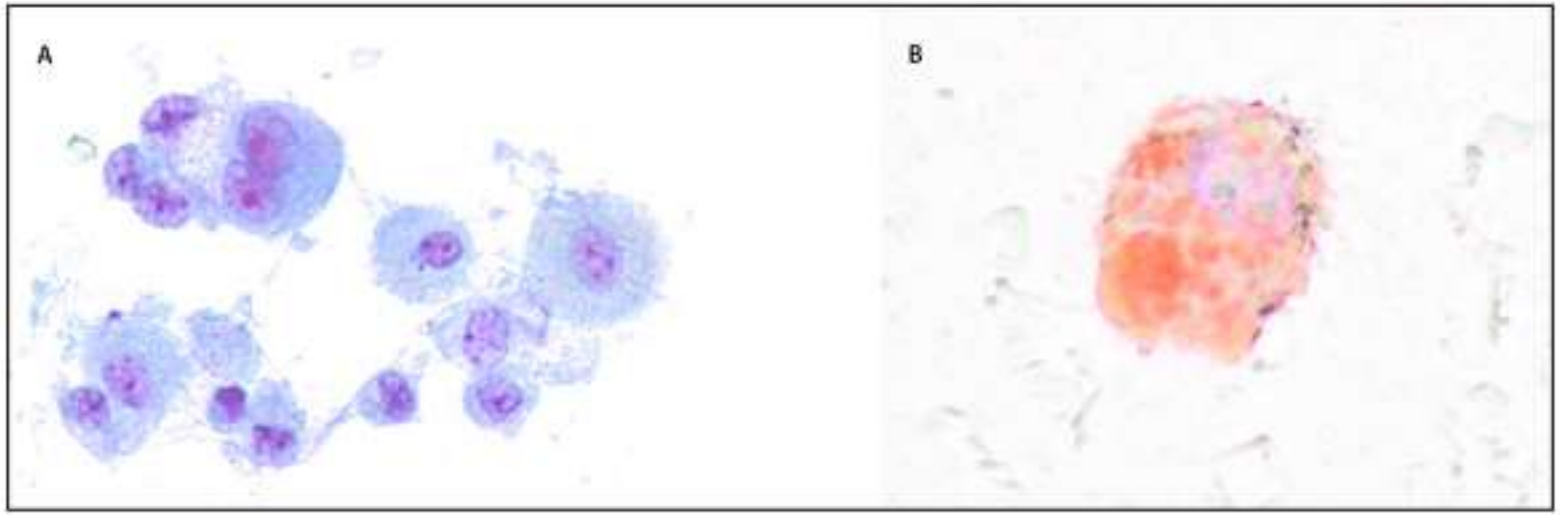


**FIGURE 2. Microscopy of a bronchoalveolar lavage sample (Papanicolaou stain [A]* and oil red O stain [B]†) from a patient with acute lung injury associated with vaping — North Carolina, July–August 2019**




* Papanicolaou stain demonstrating alveolar macrophages laden with vacuoles.
† Oil red O stain showing lipid deposits staining red (400x magnification).

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 20, 2020 VOL. 382 NO. 8

# Vitamin E Acetate in Bronchoalveolar-Lavage Fluid Associated with EVALI

B.C. Blount, M.P. Karwowski, P.G. Shields, M. Morel-Espinosa, L. Valentin-Blasini, M. Gardner, M. Braselton, C.R. Brosius, K.T. Caron, D. Chambers, J. Corstvet, E. Cowan, V.R. De Jesús, P. Espinosa, C. Fernandez, C. Holder, Z. Kuklenyik, J.D. Kusovschi, C. Newman, G.B. Reis, J. Rees, C. Reese, L. Silva, T. Seyler, M.-A. Song, C. Sosnoff, C.R. Spitzer, D. Tevis, L. Wang, C. Watson, M.D. Wewers, B. Xia, D.T. Heitkemper, I. Ghinai, J. Layden, P. Briss, B.A. King, L.J. Delaney, C.M. Jones, G.T. Baldwin, A. Patel, D. Meaney-Delman, D. Rose, V. Krishnasamy, J.R. Barr, J. Thomas, and J.L. Pirkle, for the Lung Injury Response Laboratory Working Group*

N ENGL J MED 382;8

# Vitamin E acetate

- Thickening agent in illicit products (THC)
- Enhance quality and appearance
- Provide desirable taste and aroma
- Lower product cost

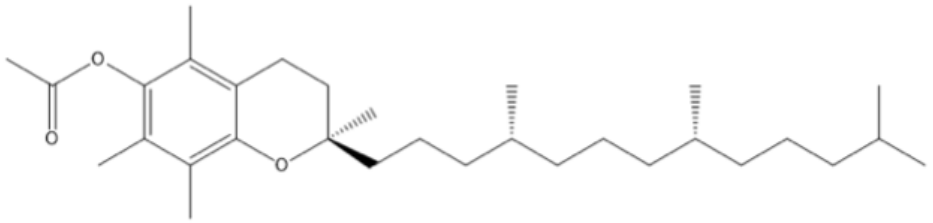
- Dietary supplement – Vitamin E
- Skin creams

- Inhalational effects – uncertain
- Viscosity – makes it undesirable as an additive to nicotine solutions

# Vitamin E acetate

- Vitamin E acetate is the ester of vitamin E (α-tocopherol) and acetic acid
- Long aliphatic tail - can penetrate a layer of surfactant to align the molecule in parallel with phospholipids

**Figure S1. Chemical structure of Vitamin E acetate.**



- Phosphatidylcholines undergo transition from a gel to a liquid crystal-line phase when exposed to increasing amounts of tocopherols
- Transitioning causes the surfactant to lose its ability to maintain the surface tension

# BAL analysis

51 patients of EVALI

- 25 – confirmed
- 26 – probable

99 healthy participants

- 52 nonusers
- 18 current nicotine EC users
- 29 current cigarette smokers

**Table 2. Characteristics of EVALI Case Patients and Healthy Comparators.***

| | EVALI Case Patients (N=51) | Healthy Comparators | | | |
|---|---|---|---|---|---|
| | | Nonusers (N=52) | E-Cigarette Users (N=18) | Cigarette Smokers (N=29) | All Comparators (N=99) |
| Median age (range) — yr | 23 (16–67) | 25 (21–37) | 27 (21–30) | 26 (21–44) | 26 (21–44) |
| Male sex — no. (%) | 35 (69) | 19 (37) | 12 (67) | 22 (76) | 53 (54) |
| Self-reported vaping — no./total no. (%) | | | | | |
| Nicotine products only | 7/43 (16) | 0/52 | 18/18 (100) | 29/29 (100) | 47/99 (47) |
| THC products only | 11/43 (26) | 0/52 | 0/18 | 0/29 | 0/99 |
| Dual use of nicotine and THC products | 22/43 (51) | 0/52 | 0/18 | 0/29 | 0/99 |

**Table 3. Frequency of Detection of Priority Toxicants in EVALI Case Patients and in Healthy Comparators.***

| Toxicant | EVALI Case Patients (N=51) | Healthy Comparators | | | |
|---|---|---|---|---|---|
| | | Nonusers (N=52) | E-Cigarette Users (N=18) | Cigarette Smokers (N=29) | All Comparators (N=99) |
| | | *number/total number (percent)* | | | |
| Vitamin E acetate | 48/51 (94) | 0/52 | 0/18 | 0/29 | 0/99 |
| Medium-chain triglyceride oil | 0/49 | 0/34 | 0/11 | 0/18 | 0/63 |
| Coconut oil | 1/48 (2) | 0/34 | 0/11 | 0/18 | 0/63 |
| Plant oil | 0/49 | 0/34 | 0/11 | 0/17 | 0/62 |
| Squalane | 0/38 | 0/52 | 0/17 | 0/29 | 0/98 |
| Squalene | 0/38 | 0/52 | 0/17 | 0/29 | 0/98 |
| $\alpha$-Pinene | 0/39 | 0/52 | 0/17 | 0/28 | 0/97 |
| $\beta$-Pinene | 0/39 | 0/52 | 0/17 | 0/28 | 0/97 |
| 3-Carene | 0/39 | 0/52 | 0/17 | 0/28 | 0/97 |
| Limonene | 1/39 (3) | 0/52 | 0/17 | 0/28 | 0/97 |
| Petroleum distillates | 0/12 | 0/52 | 0/17 | 0/29 | 0/98 |

* The listed toxicants were detected in bronchoalveolar-lavage fluid obtained from 51 patients with EVALI in 16 states from August through December 2019 and in 99 healthy comparators.

**Table 4. Exposure History and Clinical Characteristics of Three Patients with Probable Diagnosis of EVALI without Evidence of Vitamin E Acetate in BAL Fluid.***

| Variable | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| Patient-reported exposure history | Reported vaping nicotine products, denied vaping THC products | Reported daily vaping of flavored nicotine products obtained from vape shop starting 1 mo before admission, denied vaping THC products | Incomplete interview with the patient; vaping materials found at the scene by first responders; patient later reported heavy alcohol use immediately before illness |
| Symptoms | Respiratory, gastrointestinal | Constitutional, respiratory | Constitutional, respiratory |
| Medical history | Negative for chronic respiratory disease and heart disease | Negative for chronic respiratory disease and heart disease | Negative for chronic respiratory disease and heart disease |
| Presentation | Found unresponsive; on arrival at emergency department, hemoptysis and cyanosis; was intubated and admitted | Presented to urgent care on day of illness (DOI) 1 and to emergency department on DOI 3 and 5, when he was admitted | Found unresponsive; on arrival at emergency department, severe respiratory failure; was intubated and admitted |
| Admitted to intensive care unit | Yes | No | Yes |
| Respiratory support | Mechanical ventilation | None | Mechanical ventilation |
| Radiologic assessment | Hazy opacities predominantly in left lung on radiography; no CT | Bilateral patchy opacities on radiography; diffuse bilateral nodular opacities with surrounding micronodular and ground-glass opacities on CT | Bilateral infiltrates and opacities on radiography and CT |
| Infectious diseases workup | Blood cultures negative; methicillin-susceptible *Staphylococcus aureus* (interpreted by clinical team as a contaminant) in BAL fluid | Serologic analysis on admission indeterminate for coccidioides species, follow-up IgM and IgG by immunodiffusion were positive; BAL cell count, 31% eosinophils; negative results on respiratory viral panel, influenza PCR, blood cultures, legionella urinary antigen, *Streptococcus pneumoniae* urinary antigen, *Mycoplasma pneumoniae* PCR, cytomegalovirus PCR, pneumocystis antigen, fungal stain and culture, AFB smear, and mycobacterial culture | Negative results on respiratory viral panel, influenza testing, and blood cultures; methicillin-susceptible *S. aureus* (interpreted by clinical team as a contaminant) in tracheal-aspirate culture |
| Treatment | Glucocorticoids and antibiotics | Glucocorticoids, antibiotics, and antifungal agents | Glucocorticoids and antibiotics |
| Disposition | Discharged 3 days after admission | Discharged 3 days after admission | Discharged 13 days after admission |
| Discharge diagnoses | Unintentional multidrug overdose with benzodiazepines and oxycodone, active nicotinism with vaping, with suspected likely vaping-induced lung injury | Acute eosinophilic pneumonia, initially attributed to EVALI; after discharge, positive results on coccidioides serologic analysis prompted updating of diagnosis to coccidioidomycosis with or without EVALI | Acute hypoxic respiratory failure caused by vaping-associated lung injury, methicillin-susceptible *S. aureus* pneumonia, acute respiratory distress syndrome, distributive shock |

# Vitamin E acetate not seen in BAL – 3 cases

Reasons :

- Vit E acetate may have been cleared from lungs
- Inadequate processing of BAL
- Alternate diagnosis in one patient

- In Minnesota, 10 of 10 products seized by law enforcement during 2018, before the EVALI outbreak, did not contain vitamin E acetate

- 20 of 20 THC-containing products seized by law enforcement during September 2019, at the peak of the outbreak, contained vitamin E acetate

- This finding is consistent with laboratory measurements and trade websites, which suggests that the addition of vitamin E acetate to product fluid began to appear in the illicit market in late 2018 or early 2019 and gained popularity in 2019

Morbidity and Mortality Weekly Report

# Update: Characteristics of a Nationwide Outbreak of E-cigarette, or Vaping, Product Use–Associated Lung Injury — United States, August 2019–January 2020

Vikram P. Krishnasamy, MD[1]; Benjamin D. Hallowell, PhD[2,3]; Jean Y. Ko, PhD[4]; Amy Board, DrPH[1,2]; Kathleen P. Hartnett, PhD[5]; Phillip P. Salvatore, PhD[1,2]; Melissa Danielson, MSPH[6]; Aaron Kite-Powell, MS[5]; Evelyn Twentyman, MD[4]; Lindsay Kim, MD[3]; Alissa Cyrus, MPH[7]; Megan Wallace, DrPH[2,3]; Paul Melstrom, PharmD, PhD[4]; Brittani Haag, MS[5]; Brian A. King, PhD[4]; Peter Briss, MD[4]; Christopher M. Jones, PharmD, DrPH[1]; Lori A. Pollack, MD[4]; Sascha Ellington, PhD[4]; Lung Injury Response Epidemiology/Surveillance Task Force

MMWR / January 24, 2020 / Vol. 69 / No. 3

**TABLE. Demographic and product use characteristics among hospitalized patients with e-cigarette, or vaping, product use–associated lung injury (EVALI) reported to CDC — United States, August 2019–January 2020***

| Characteristic (no. with available information) | No. (%)† (N = 2,668) |
|---|---|
| **Sex (2,606)** | |
| Male | 1,731 (66) |
| Female | 875 (34) |
| **Median age, yrs (range)** | 24 (13–85) |
| **Age group (yrs) (2,619)** | |
| 13–17 | 404 (15) |
| 18–24 | 979 (37) |
| 25–34 | 631 (24) |
| 35–44 | 335 (13) |
| 45–64 | 223 (9) |
| ≥65 | 47 (2) |
| **Race/Ethnicity§ (1,856)** | |
| White | 1,360 (73) |
| Black | 64 (3) |
| American Indian/Alaska Native | 12 (1) |
| Asian/Native Hawaiian/Other Pacific Islander | 38 (2) |
| Other | 97 (5) |
| Hispanic | 285 (15) |
| **Case status (2,668)** | |
| Confirmed | 1,401 (53) |
| Probable | 1,267 (47) |
| **Substances used in e-cigarette, or vaping, products (2,022) ¶,**** | |
| Any THC-containing product | 1,650 (82) |
| Any nicotine-containing product | 1,162 (57) |
| Both THC- and nicotine-containing product use | 834 (41) |
| Exclusive THC-containing product use | 669 (33) |
| Exclusive nicotine-containing product use | 274 (14) |
| No THC- or nicotine-containing product use reported | 44 (2) |

As of Feb 18, 2020

- 2807 hospitalized,
- 68 deaths in US

**Abbreviation:** THC = tetrahydrocannabinol.

* For cases reported to CDC as of January 14, 2020.

† Percentages might not sum to 100% because of rounding.

§ These were mutually exclusive groups. Whites, blacks, American Indians/Alaska Natives, Asians/Native Hawaiians/Other Pacific Islanders, and Others were non-Hispanic. Hispanic persons could be of any race.

¶ Limited to persons who reported vaping or dabbing at least one substance in the past 3 months.

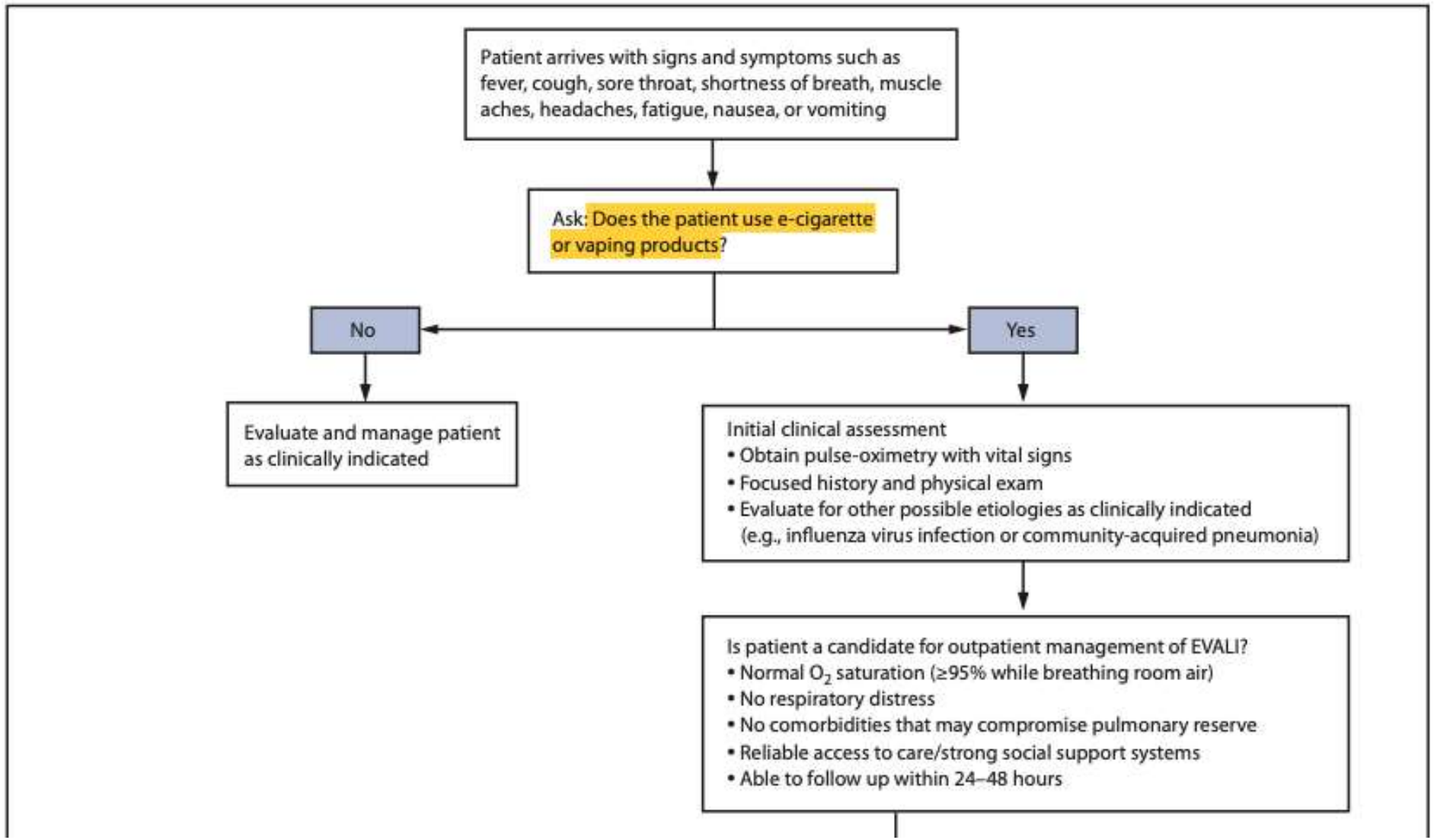
** In the 3 months preceding symptom onset.

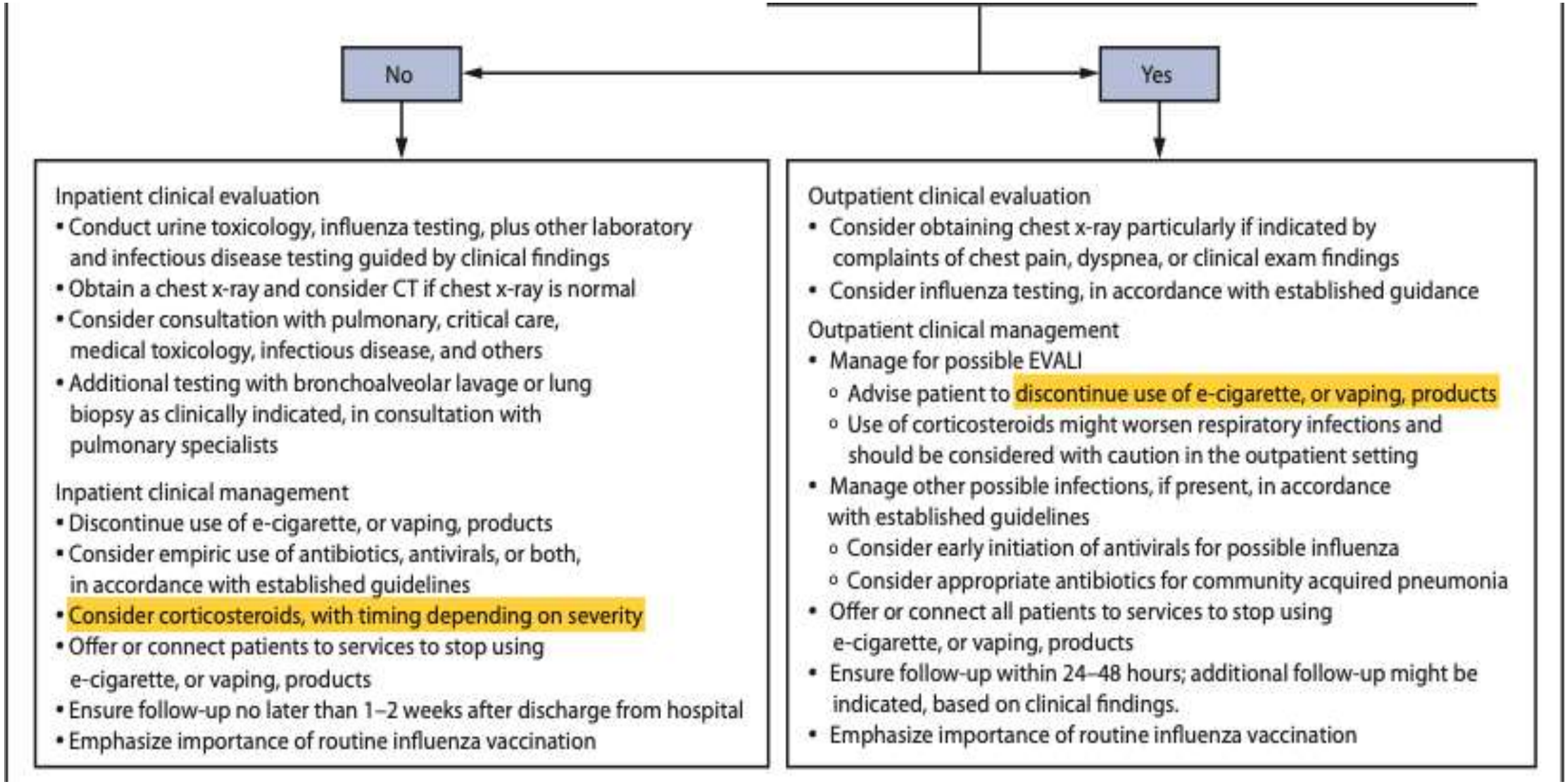
Morbidity and Mortality Weekly Report

# Update: Interim Guidance for Health Care Providers for Managing Patients with Suspected E-cigarette, or Vaping, Product Use–Associated Lung Injury — United States, November 2019

Tara C. Jatlaoui, MD[1]; Jennifer L. Wiltz, MD[1]; Sarah Kabbani MD[2]; David A. Siegel[1], MD; Ram Koppaka, MD, PhD[3]; Michele Montandon, MD[4]; Susan Hocevar Adkins, MD[5]; David N. Weissman, MD[6]; Emily H. Koumans, MD[1]; Michelle O'Hegarty, PhD[1]; Megan C. O'Sullivan, MPH[2]; Matthew D. Ritchey, DPT[1]; Kevin Chatham-Stephens, MD[7]; Emily A. Kiernan, DO[8,9]; Mark Layer, MD[9,10]; Sarah Reagan-Steiner, MD[2]; Jaswinder K. Legha, MD[11]; Katherine Shealy, MPH[1]; Brian A. King, PhD[1]; Christopher M. Jones, PharmD, DrPH[11]; Grant T. Baldwin, PhD[11]; Dale A. Rose, PhD[2]; Lisa J. Delaney, MS[6]; Peter Briss, MD[1]; Mary E. Evans, MD[11]; Lung Injury Response Clinical Working Group

**FIGURE. Algorithm for management of patients[*,†,§,¶] with respiratory, gastrointestinal, or constitutional symptoms and e-cigarette, or vaping, product use**




No
Yes
Inpatient clinical evaluation
• Conduct urine toxicology, influenza testing, plus other laboratory and infectious disease testing guided by clinical findings
• Obtain a chest x-ray and consider CT if chest x-ray is normal
• Consider consultation with pulmonary, critical care, medical toxicology, infectious disease, and others
• Additional testing with bronchoalveolar lavage or lung biopsy as clinically indicated, in consultation with pulmonary specialists
Inpatient clinical management
• Discontinue use of e-cigarette, or vaping, products
• Consider empiric use of antibiotics, antivirals, or both, in accordance with established guidelines
• Consider corticosteroids, with timing depending on severity
• Offer or connect patients to services to stop using e-cigarette, or vaping, products
• Ensure follow-up no later than 1–2 weeks after discharge from hospital
• Emphasize importance of routine influenza vaccination
Outpatient clinical evaluation
• Consider obtaining chest x-ray particularly if indicated by complaints of chest pain, dyspnea, or clinical exam findings
• Consider influenza testing, in accordance with established guidance
Outpatient clinical management
• Manage for possible EVALI
◦ Advise patient to discontinue use of e-cigarette, or vaping, products
◦ Use of corticosteroids might worsen respiratory infections and should be considered with caution in the outpatient setting
• Manage other possible infections, if present, in accordance with established guidelines
◦ Consider early initiation of antivirals for possible influenza
◦ Consider appropriate antibiotics for community acquired pneumonia
• Offer or connect all patients to services to stop using e-cigarette, or vaping, products
• Ensure follow-up within 24–48 hours; additional follow-up might be indicated, based on clinical findings.
• Emphasize importance of routine influenza vaccination

# CDC recommends

- Not to use THC containing EC
- Vitamin E acetate should not be added to any EC
- People should not add any other substances not intended by the manufacturer
- Adults using nicotine containing EC should not go back to smoking; if possible they should consider using FDA approved smoking cessation medications
- EC should not be used by youths, young adults, pregnant women

# Conclusion

- EC should not used by youth
- If an adult smoker is not willing for NRT, EC can be advised as an alternative, as long as the smoker is informed about the safety and efficacy (but not in INDIA – as we have already banned)
- THC and Vitamin E acetate are associated with EVALI

Thank you