CLINICAL PRACTICE GUIDELINES

2021 **MOH/P/PAK/xxxxxx**

MANAGEMENT OF E-CIGARETTE OR VAPING PRODUCT USE ASSOCIATED-LUNG INJURY (EVALI)

DRAFT

Ministry of Health Malaysia

Academy of Medicine Malaysia

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STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

UPDATING THE CPG

These guidelines were issued in 2021 and will be reviewed in a minimum period of four years (2025) or sooner if new evidence becomes available. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.

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LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II -1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

FORMULATION OF RECOMMENDATION

In line with the current development in CPG methodology, the CPG Unit of MaHTAS is in the process of adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG Development Group as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

a. Diagnosis

- Relevant laboratory investigations should be done to rule out other probable diagnoses before diagnosis of e-cigarette or vaping product use associated-lung injury (EVALI) can be made.
- Chest X-ray should be done in all suspected EVALI cases.
  - Computed tomography scan of the chest should be performed if chest X-ray is normal.
- Bronchoscopy may be performed if clinically indicated to exclude alternative diagnosis and not to confirm EVALI.
- The diagnosis of EVALI should be made based on case definitions as outlined by the United States Centers for Disease Control and Prevention.

b. Treatment

- For patients suspected or confirmed of diagnosis of EVALI, these treatments may be initiated:
  - supplemental oxygen
  - antibiotics when there is diagnostic uncertainty
  - systemic corticosteroids based on the severity of the illness

c. Referral/Follow-up

- A physician should be consulted for any case suspected of EVALI at the emergency department or primary care facility.
- Patients with EVALI should only be discharged when they fulfil the discharge criteria.
  - Upon discharge, hospital prescription should be given.
  - Follow-up should be done by the treating physician.

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GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these Clinical Practice Guidelines (CPG) were from the Ministry of Health (MoH) and the Ministry of Higher Education. There was active involvement from a multidisciplinary Review Committee (RC) during the process of the CPG development.

This is the first edition of an evidence-based CPG on the Management of E-Cigarette or Vaping Product Use Associated-Lung Injury (EVALI). Literature search was carried out using the following electronic databases: mainly Medline via Ovid and Cochrane Database of Systemic Reviews and others e.g. Pubmed and Centers for Disease Control and Prevention (refer to **Appendix 1** for **Example of Search Strategy**). The search was limited to literature published on humans and in English. In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. Experts in the field were also contacted to identify further studies. All searches were conducted from 27 August 2020 to 1 September 2020. Literature searches were repeated for all clinical questions at the end of the CPG development process, allowing any relevant papers published before 28 February 2021 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

There was no relevant evidence-based CPG used as a reference in developing the MoH CPG on EVALI. A total of seven clinical questions were developed under three sections (diagnosis, treatment and referral/follow-up). Members of the DG were assigned individual questions within the sections (refer to **Appendix 2** for **Clinical Questions**). The DG members met 12 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist when applicable, presented in evidence tables and further discussed in DG meetings. All statements and recommendations subsequently formulated were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. There were only a few published articles on EVALI and all were of low level evidence. This CPG is based largely on the findings of reviews and observational studies, with local practices taken into consideration.

The literature used in these guidelines were graded using the US/Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was done using the principles of GRADE as much as possible (refer to the preceding page). The writing of the CPG strictly follows the requirement of Appraisal of Guidelines for Research and Evaluation (AGREE) II.

Upon completion, the draft of the CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the Health Technology Assessment and Clinical Practice Guidelines Council MoH Malaysia for review and approval. Details on the CPG development methodology by MaHTAS can be obtained from the Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at http://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf?mid=634).

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OBJECTIVES

The objective of this CPG is to provide evidence-based recommendations on the management of EVALI on the following aspects:

a) diagnosis
b) treatment
c) referral and follow-up

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

a. Inclusion Criteria

- All vape and e-cigarette users

TARGET GROUP/USERS

This document is intended to guide health professionals and relevant stakeholders in primary and secondary/tertiary care in the management of EVALI, including:

i. doctors
ii. allied health professionals
iii. trainees and medical students
iv. policymakers
v. patients and their advocates
vi. professional societies

HEALTHCARE SETTINGS

Primary and secondary/tertiary care settings

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The draft guidelines were reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

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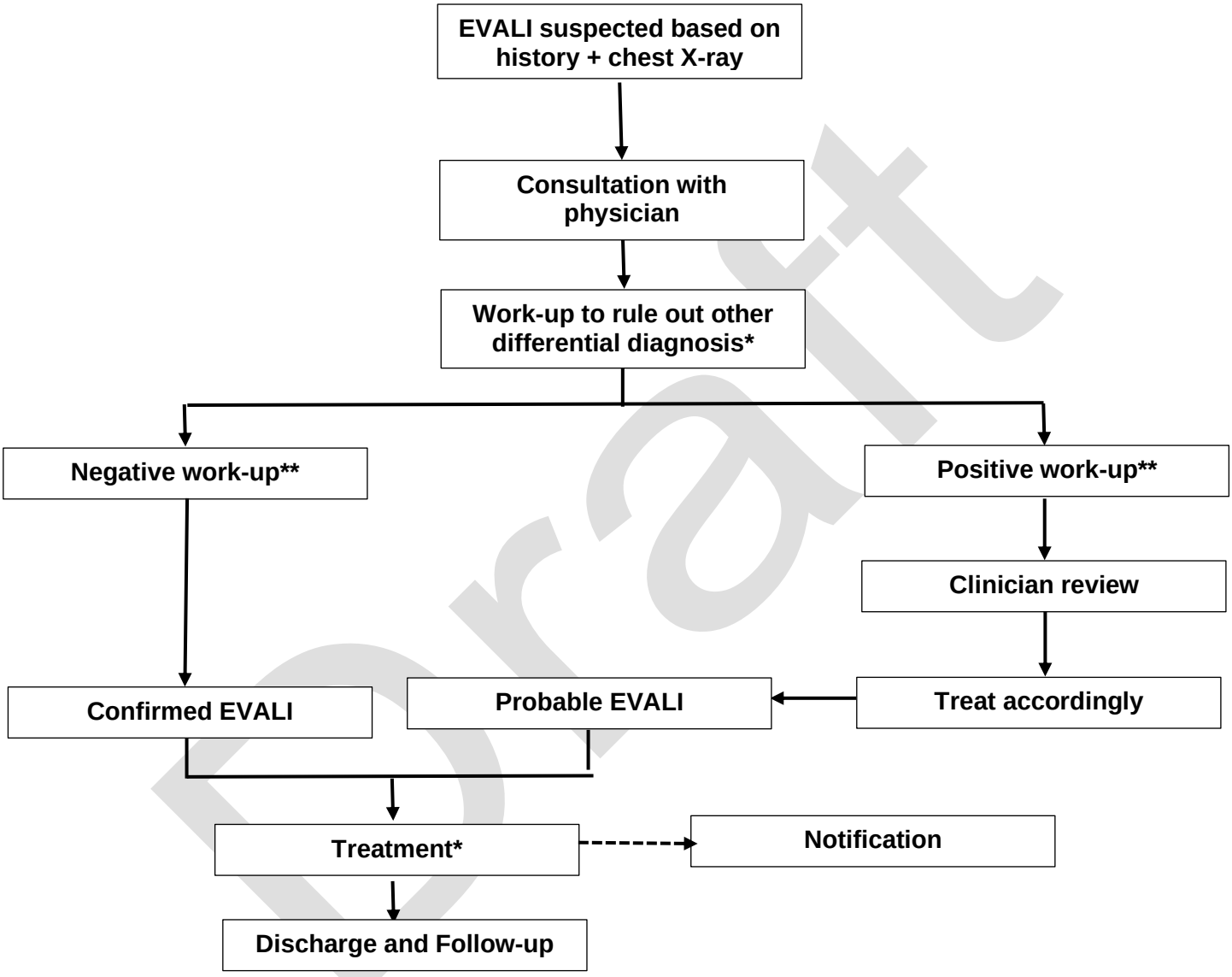
ALGORITHM ON MANAGEMENT OF E-CIGARETTE OR VAPING PRODUCT USE ASSOCIATED-LUNG INJURY (EVALI)



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***May require admission**

Refer to **Subchapter 2.5 on **Case Definitions**

1. INTRODUCTION

Electronic cigarette or e-cigarette (e-cig) is a handheld device equipped with aerosol generator, battery and solution storage area. Its purpose is delivery of nicotine or other chemicals via aerosolisation.[Brown CJ, et al., 2014] It was developed in 2003 and since then marketed worldwide.[NCCDPHP (US), 2016.] It is believed that e-cig entered the Malaysian market in mid-2000s and gained popularity in 2010s.

The first local study in 2016 showed an estimated figure of 600,000 e-cig users.[Ab Rahman J et al., 2019] The number had increased to 1.1 million as reported in the Malaysian National Health and Morbidity Survey 2019 with the highest prevalence among those aged 20 to 24.[IPH, 2020] In addition, the Tobacco & E-Cigarette Survey Among Malaysian Adolescents (TECMA) 2016 reported 300,000 e-cig users among Malaysian youth aged 10 to 19. The highest prevalence was among those in the age group 16 to 19.[IPH, 2016] In 2018, a cross-sectional study among secondary school students ever used of any smoking products in the last 30 days in Kuala Lumpur showed a prevalence of 73% of e-cig users.[Nur Atikah AH et al., 2019]

The Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems reported that exposure to nicotine and toxicants from the aerosolisation of e-cig ingredients was dependent on usage and characteristics of the device which influenced the variability of potentially toxic substances emitted.[National Academies of Sciences, Engineering, and Medicine, 2018]

Inhalation of e-cig aerosol could potentially cause:[NCCDPHP (US), 2016.]

- adverse effects due to acute administration of nicotine, flavourants, chemicals, other particulates
- accidental overdose of nicotine
- developmental effects on the brain from nicotine exposure
- uptake of subsequent illicit drug use
- gateway to conventional cigarettes and dual use of both types of cigarette
- negative psychosocial health
- battery explosion

Health Effects of E-Cigarette Use Among U.S. Youth and Young Adults reported that delivery of nicotine from e-cig was in doses range from negligible to larger than conventional cigarettes, while its second-hand nicotine exposure was comparable to conventional cigarettes.[NCCDPHP (US), 2016]

E-cig can induce negative cardiovascular effects through various mechanisms e.g. oxidative stress, inflammation, DNA damage, arterial stiffness and, altered haemodynamics and platelet activity.[Buchanan ND et al., 2020] Daily e-cig use is associated with increased odds of having myocardial infarction (OR=1.79, 95% CI 1.20 to 2.66).[Alzahrani T et al., 2018] E-cig aerosol exposure is also associated with respiratory symptoms in healthy individuals and increased symptoms of patients with asthma, cystic fibrosis and chronic obstructive pulmonary disease.[Thirión-Romero I et al., 2019]

In July 2019, a large case series of pulmonary illnesses were reported in Illinois and Wisconsin, United States of America (USA). These were patients with history of e-cig use within 90 days of the onset of symptoms and had pulmonary infiltrate on imaging with no other contributable cause of the illness. They were termed as E-cigarette or Vaping Product Use Associated Lung Injury (EVALI).[Layden JE et al., 2020, level III]

A total of 2,807 cases of EVALI with 68 deaths had been reported to the Centers for Disease Control and Prevention, USA until 18 February 2020. Laboratory data suggested a strong link between vitamin E acetate and the outbreak of the disease in the country.[CDC (Outbreak of EVALI)] In

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addition, analysis of THC-containing cartridges e-liquid and vapour had shown the presence of potential toxicants e.g. solvent-derived hydrocarbons, silicon conjugated compounds, etc.[Muthumalage T et al., 2020]

Based on experience of CPG DG, several cases of probable EVALI have been highlighted among the clinicians in Malaysia. However, the number of cases maybe underreported due to lack of awareness. The development of this first evidence-based CPG on the Management of EVALI is timely with the emergence of this novel medical condition. It will guide the healthcare providers locally on the best practice in the management of EVALI.

2. DIAGNOSIS

2.1 Clinical Presentation

EVALI is a disease that may be missed due to lack of awareness among healthcare providers. In a nationwide study based on cases reported to Centers for Disease Control (CDC) and Prevention of USA, there were patients who initially presented to outpatient setting with EVALI-related symptoms but not admitted. From this cohort, out of those who were later admitted, 46% were fatal while 21% were non-fatal. The risk of mortality was higher among patients with co-morbidities i.e. respiratory disease, cardiac disease, mental health condition and obesity.[Werner AK et al., 2020, level III]

Although CDC case definition stated 90 days, evidence showed that patients used e-cig up to the onset of illness and seek medical attention acutely soon after symptoms appeared.[Aberegg SK et al., 2020, level III]

Symptoms commonly presented in EVALI are:[Layden JE et al., 2020, level III; Kalininskiy A et al., 2019, level III; Blagev DP et al., 2019, level III:]

- respiratory symptoms
  - shortness of breath
  - cough
  - chest pain
- gastrointestinal symptoms
  - nausea
  - vomiting
  - diarrhoea
  - abdominal pain
- constitutional symptom
  - fever

Signs of EVALI that commonly observed are:[Layden JE et al., 2020, level III; Kalininskiy A et al., 2019, level III; Blagev DP et al., 2019, level III]

- hypoxia
- tachycardia
- tachypnoea

2.2 History of e-Cig or Vaping Product Use for Patients with Suspected EVALI

Patient presented with EVALI symptoms should be asked on the use of e-cig or vaping products.

Healthcare providers should employ non-judgemental, open-ended and private questioning sessions with patients.[Belok SH et al., 2020, level III] Confidentiality should be practised according to local guidelines.

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- Questions on e-cig or vaping product use in patients with suspected EVALI:[Aldy K et al., 2020, level III, Belok SH et al., 2020, level III; Jatlaoui TC et al., 2019, level III]
  - e-cig use
    - time of last use
    - duration
    - method (aerosol, dabbing or dripping)
    - frequency
    - concomitant smoking products use or substances abuse
  - devices and e-liquids
    - product brand name
    - delivery system (open or closed - refer to **Appendix 3** on **Types of Vaping Products in Malaysia**)
    - types of substances use (tetrahydrocannabinol/THC, cannabis, nicotine, modified products, additional substances)
    - product source

2.3 Laboratory Investigation

EVALI is a diagnosis of exclusion. Thus, laboratory investigations need to be done to rule out other probable diagnosis.

There were no laboratory abnormalities specific for the diagnosis of EVALI. Several observational studies showed that most EVALI patients had elevated inflammatory markers. The patients had leucocytosis with neutrophil predominance and, high erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and procalcitonin. There was also mild elevation of liver enzymes.[Layden JE et al., 2020, level III; Werner AK et al., 2020, level III; Cherian SV et al., 2020, level III; Kalininsky A et al., 2019, level III]

In a cross-sectional study, none of the EVALI patients had a microbiologically-confirmed infectious pneumonia. Additional inflammatory serologies (antinuclear antibody, antiglomerular basement membrane and antineutrophil cytoplasmic antibodies) were also negative.[Blagev DP et al., 2019, level III]

- Laboratory investigations for EVALI work-up will include:
  - full blood count
  - ESR
  - CRP
  - culture and sensitivity study - blood, sputum, urine
  - urinalysis
  - respiratory panel for influenza and other possible infectious pathogens
  - autoimmune screening
- In local setting, tuberculosis and COVID-19 work-up

Recommendation 1

- Relevant laboratory investigations* should be done to rule out other probable diagnoses before diagnosis of e-cigarette or vaping product use associated-lung injury can be made.

*Refer to the yellow box above.

2.4 Imaging

- Abnormal chest imaging, either chest X-ray (CXR) or computed tomography (CT) scan, is mandatory for the diagnosis of EVALI.
- While CXR is often abnormal in EVALI cases, a normal CXR does not exclude the diagnosis. In the setting of a normal CXR in a high clinical suspicion of EVALI, a CT scan should be performed to better assess for lung injury.

In a cross-sectional study involving 98 patients from Illinois and Wisconsin, chest imaging findings were positive in all cases of EVALI. These were based on either CXR or CT scan.[Layden J et al., 2020, level III]

Findings in CXR of EVALI patients include ground-glass opacities and consolidation which are usually bilateral and almost symmetric in distribution.[Artunduaga M et al., 2020, level III] The abnormalities are lower lobe predominant or diffuse in most cases with sparing of the heart border and subpleural region. Septal thickening manifesting as Kerley B lines can also be seen.[Kligerman S et al., 2020, level III]

Imaging findings of EVALI are better seen on CT scan compared with CXR. The common patterns seen on CT scan are those of acute lung injury (ALI), in the spectrum of diffuse alveolar damage (DAD) and organising pneumonia (OP) with bilateral relatively symmetrical multifocal ground-glass opacities with or without consolidation.[Kligerman S et al., 2020, level III; Panse PM et al., 2020, level III]. Conspicuous lobular and/or subpleural sparing is common as well as sparing around the peribronchovascular interstitium.[Kligerman S et al., 2020, level III; Panse PM et al., 2020, level III] Ill-defined centrilobular nodules, representing foci of airway-centered organising pneumonia on biopsy, are common and usually occur in conjunction with lower lobe or diffuse parenchymal opacity which can mimic the CT findings of acute hypersensitivity pneumonitis. Less commonly, centrilobular nodules may be diffuse with little or no associated ground-glass opacity. Septal thickening is a common finding and in some instances, a crazy paving can occur. Reverse halo or atoll signs are less common but may also be seen.[Panse PM et al., 2020, level III]

Apart from DAD or OP, other less commonly described patterns of ALI in EVALI are diffuse alveolar haemorrhage (DAH) and acute eosinophilic pneumonia-like pattern (AEP). On CT scan, DAH may be seen as multifocal ground-glass opacities, with or without consolidation and often with poorly defined centrilobular nodules. The AEP-like pattern has findings that overlap with the OP and DAD pattern but is associated with pronounced smooth interlobular septal thickening and pleural effusions secondary to increased vascular permeability.[Panse PM et al., 2020, level III]

Mild and symmetrical hilar and mediastinal lymphadenopathy are common findings of EVALI.[Panse PM et al., 2020, level III, Kalininsky A et al., 2019, level III] However, necrotic or calcified lymphadenopathy is not a feature. Although uncommon, patients with EVALI can present with pneumomediastinum and/or pneumothorax. Lung cysts/bullae are uncommon early injury but can occur during the reparative phase.[Kligerman S et al., 2020, level III, Layden J et al., 2020, level III] Pulmonary embolism can occur in conjunction with EVALI but is uncommon.[Artunduaga M et al., 2020, level III]

Refer to **Appendix 4** on **Imaging Features in EVALI**.

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Recommendation 2

- Chest X-ray should be done in all cases suspected of e-cigarette or vaping product use associated-lung injury.
  - Computed tomography scan of the chest should be performed if chest X-ray is normal.

2.5 Bronchoscopy

There is no clear role of bronchoscopy in the diagnosis of EVALI. Based on current evidence, there is no specific bronchoscopic findings that can confirm the diagnosis of EVALI. Bronchoscopy may be performed to exclude specific suspected alternative diagnosis where non-invasive methods are inadequate. It should be guided by clinical pre-test probabilities of the EVALI.[Aberegg SK et al., 2020, level III]

Several observational studies showed predominance of macrophages and neutrophils, and scant eosinophils in cytology of bronchoalveolar lavage (BAL) in EVALI patients. Lipid-laden macrophages (LLMs) in BAL had been reported in most EVALI patients as well as asymptomatic persons who were e-cig users. Although LLMs were not specific for EVALI, their absence should prompt reconsideration of diagnosis. A diverse patterns of diffuse lung injury and inflammation were seen in histopathology examination of lung biopsy of EVALI patients but none were pathognomonic. Thus, cytology and histopathology examination of lung biopsy specimens from bronchoscopy were nonspecific and could not confirm the diagnosis of EVALI.[Aberegg SK et al., 2020, level III]

Findings of vitamin E acetate in BAL provided direct evidence of its existence at the primary site of injury among EVALI patients.[Blount BC et al., 2019, level III.]

Recommendation 3

- Bronchoscopy may be performed if clinically indicated to exclude alternative diagnosis and not to confirm e-cigarette or vaping product use associated-lung injury.

2.6 Case Definitions

The case definitions of EVALI recommended by Centers for Disease Control and Prevention of USA is shown below:[2019 CDC]

- 2019 Lung Injury Surveillance Primary Case Definitions:[2019 CDC]
  - **Confirmed Case:**
    Using an e-cig ("vaping") or dabbing* in 90 days prior to symptom onset
    AND
    Pulmonary infiltrate, e.g. opacities, on plain film chest radiograph or ground-glass opacities on chest CT
    AND
    Absence of pulmonary infection on initial work-up. Minimum criteria are:
    1. A negative respiratory viral panel
    AND
    2. A negative influenza polymerase chain reaction (PCR) or rapid test, if local epidemiology supports influenza testing
    AND
    All other clinically-indicated respiratory infectious disease testing (e.g. urine antigen for *Streptococcus pneumoniae* and *Legionella*, sputum culture if productive cough,

BAL culture if done, blood culture, human immunodeficiency virus-related opportunistic respiratory infections if appropriate) are negative
AND
No evidence in medical record of alternative plausible diagnoses (e.g. cardiac, rheumatologic, or neoplastic process).

- **Probable Case:**
  Using an e-cig ("vaping") or dabbing* in 90 days prior to symptom onset
  AND
  Pulmonary infiltrate, e.g. opacities, on plain film chest radiograph or ground-glass opacities on chest CT
  AND
  Infection identified via culture or PCR, but clinical team** believes this infection is not the sole cause of the underlying lung injury **OR minimum criteria** to rule out pulmonary infection not met (testing not performed) and clinical team** believes infection is not the sole cause of the underlying lung injury.
  AND
  No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process).

Footnotes
*Using an electronic device (e.g. electronic nicotine delivery system (ENDS), electronic cigarette, e-cig, vaporiser, vape(s), vape pen, dab pen or other device) or dabbing to inhale substances (e.g. nicotine, marijuana, THC, THC concentrates, cannabidiol (CBD), synthetic cannabinoids, flavourings or other substances)

**Clinical team caring for the patient

Notes: These case definitions are meant for surveillance and not clinical diagnosis. The case definitions are subject to change and will be updated as additional information becomes available if needed.

In USA, confirmed and probable EVALI cases are reported by the clinicians to the local health authorities.[Layden JE et al., 2020, level III; Aldy K et al., 2020, level III]

In our local setting, as EVALI is a new entity with an increasing trend of e-cig use, there is a need to report EVALI cases for surveillance purpose to MoH, Malaysia. The surveillance data can be used to plan for policy and guidance in clinical management.

Recommendation 4
- The diagnosis of e-cigarette or vaping product use associated-lung injury should be made based on case definitions as outlined by United States Centers for Disease Control and Prevention.

3. AETIOLOGY/CHEMICAL PROFILING

E-cig is a device that produces an aerosol by heating a liquid which contains a solvent in one or more flavourings, with or without nicotine (also known as e-liquid). It is composed of an atomiser that uses electrical current from a battery to heat a metal coil. This aerosolises an e-liquid, which is conducted from a reservoir to the coil by a wick. Aerosol from e-cig may contain different chemical composition subject to device type, voltage used and e-liquid content.[Belok SH et al., 2020, level III]

Generally, e-liquid constitutes varying ratios of vegetable glycerin (VG), propylene glycol (PG), nicotine, and flavouring agents. However, some studies detected more than 60 compounds in e-liquid, this includes chemicals which is not stated by the manufacturer.[Traboulsi H et al., 2020, level III] As e-cig metal components undergo repeated cycles of heating and cooling, traces of toxic metal can leach into the e-liquid and emitted through e-cig aerosol.[Traboulsi H et al., 2020, level III; Chun LF et al., 2017, level III]

Chemicals in e-liquid (e.g. PG and VG) and flavouring agent are considered to be "generally recognised as safe (GRAS)" by United States Food and Drug Administration (FDA) for oral consumption but not through inhalation. They will be converted to toxicant when heated during e-cig smoking.[Chun LF et al., 2017, level III]

Recent evidence showed that vitamin E acetate had been detected in a high proportion of THC-containing products associated with EVALI cases.[Taylor J et al., 2019, level III]

Contribution of chemicals of concerns in EVALI cases has been studied. This include chemicals in either THC- or non-THC-containing products. Thus, chemical profiling is important for ongoing surveillance of the potential toxicants that can be associated with EVALI.

In a nationwide study of hospitalised EVALI patients in USA, the self-reported substance use in e-cig were 53% on both THC- and nicotine-containing product, 33% exclusive THC-containing product and 14% exclusive nicotine-containing product.[Krishnasamy VP et al., 2020, level III]

A small study on EVALI patients in Minnesota tested selected products because of available product volume and features that physically differentiated the cartridges showed that vitamin E acetate was the most common compound detected in THC-containing product. Issues faced in doing chemical profiling in the study include:[Taylor J et al., 2019, level III]

- poor cooperation of the patients in providing product for testing
- insufficient amount of material to be tested
- toxicant of concern did not cover flavouring agents

In a systematic review of case reports on e-cig-related illness and injury, 56% of patients who had respiratory symptoms reported using CBD/THC. Another 40% of patients used unknown/unspecified liquid while 3% used nicotine. Further scientific research was warranted to study on the causal role of each of the e-liquid ingredients, their thermolysis byproducts, potential interactions and additive effects.[Tzortz A et al., 2020, level III]

Toxicology testing has been recommended to assess aetiologies of lung diseases instigated by substances of abuse. This need to done with proper patient consent.[Belok SH et al., 2020, level III]

- Potential toxicants in e-liquid include PG, VG, flavouring agents, vitamin E acetate, CBD, THC and nicotine.
- More strong evidence is warranted before proper chemical profiling can be recommended in cases of EVALI.

4. DIFFERENTIAL DIAGNOSIS

The most common differential diagnoses of EVALI are infectious pneumonia and other inflammatory lung diseases due to its flu-like illness as listed below:[Aberegg SK et al., 2020, level III]

- infectious pneumonia -
  - bacterial
  - fungal

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    - viral
    - pneumocystis jirovecii
- diffuse parenchymal lung diseases -
    - acute hypersensitivity pneumonitis
    - acute eosinophilic pneumonia
    - organising pneumonia
    - cellular non-specific interstitial pneumonia
- other diffuse lung diseases -
    - acute respiratory distress syndrome
    - diffuse alveolar haemorrhage

- Testing or empirical treatment for usual infectious pneumonia based on the probability of the illness is recommended.
- Probability of alternative diagnosis increases when either:
    - absence of typical demographic and clinical features of EVALI
    - presence of atypical presentations
    - presence of predisposition for other illness
- EVALI can be considered a leading or provisional diagnosis if none other illness is probable based on the above evaluation.[Aberegg SK et al., 2020, level III]

5. TREATMENT

The treatment of EVALI is symptomatic based on the presenting symptoms which can be respiratory, gastrointestinal or constitutional in nature.

For respiratory symptoms, the following are done:

- **Oxygenation**

Ensure adequate oxygenation via nasal cannula, non-invasive or invasive ventilation. In a cross-sectional study of 36 patients in Pittsburgh, 64% patients required supplemental oxygen therapy during admission with 20% on mechanical ventilation.[Zou RH et al., 2020, level III]

- **Antimicrobials**

In a multicentre cross-sectional study involving 60 patients, 90% of EVALI patients were given antibiotics due to overlapping presentation and diagnostic uncertainty.[Blagev DP et al., 2019, level III] As community-acquired pneumonia is a more common cause for hypoxaemic respiratory failure, antibiotics are strongly recommended with sequential de-escalation if no evidence of pulmonary or bloodstream infection is found.[Cherian SV et al., 2020, level III]

Antibiotics coverage are recommended to be given empirically for at least 48 hours if history is unclear, if patient is intubated or has severe hypoxaemia despite supplemental oxygen.[Kalininskiy A et al., 2019, level III]

Alternative diagnosis of concomitant EVALI with infections may be considered when laboratory evidences of infections are positive but in whom clinicians feel that microbiologic diagnoses alone are incompatible with the clinical course or severity of the illness.[Zou RH et al., 2020, level III]

- Treatment with empiric antimicrobials, including antivirals, should be considered in accordance with established local guidelines and microbiology pattern.[Jatlaoui TC et al., 2019, level III]

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- **Corticosteroids**

A multicentre cross-sectional study showed a rapid improvement within days in 95% of EVALI patients received corticosteroids therapy. The initial corticosteroids dosing and duration of therapy varied with severity of illness at presentation. Patients admitted to the intensive care unit (ICU) were given higher doses and longer courses of corticosteroids while outpatients had short bursts of oral corticosteroids.[Blagev DP et al., 2019, level III]

In a narrative review, systemic corticosteroids and antibiotics were started immediately in severe cases. Majority of patients showed excellent response (either in clinical, radiological or pulmonary function) to methylprednisolone.[Cherian SV et al., 2020, level III]

In less severe cases, infections were ruled out prior to initiation of corticosteroids.[Cherian SV et al., 2020, level III] Oral prednisolone had also been administered in less severe hospitalised cases and outpatients.[Blagev DP et al., 2019, level III]

Most patients responded within a week of treatment. Thus, corticosteroids should be tapered down based on clinical improvement. There were no established guidelines on the duration of steroids in EVALI, but given good response and unfavourable side effects of corticosteroids, it was recommended no longer than two weeks.[Cherian SV et al., 2020, level III]

- Documented corticosteroids treatment in EVALI are:[Blagev DP et al., 2019, level III]
  - initial daily dose for:
    - intravenous methylprednisolone is 125 mg/day (IQR 120 - 240)
    - oral prednisolone is 40 mg/day (IQR 40 - 60)
  - duration before tapering dose or stopping: 2 days (IQR 1 - 4)
  - total duration of therapy: 11 days (IQR 6 - 18)

*There is no evidence on the use of hydrocortisone, dexamethasone and inhaled corticosteroids in EVALI.

Treatment of gastrointestinal or constitutional symptoms are treated accordingly based on severity of the symptoms.

Recommendation 5

- In patients suspected or confirmed of diagnosis of e-cigarette or vaping product use associated-lung injury, these treatments may be initiated:
  - supplemental oxygen
  - antibiotics when there is diagnostic uncertainty
  - systemic corticosteroids based on the severity of the illness

Tobacco cessation

- Smoking of tobacco and tobacco products (cigarette, electronic cigarette/vape, shisha, pipe, cigar etc.) can lead to various non-communicable diseases (NCDs). Worldwide, more than eight million people die every year because of this habit.[WHO Tobacco Fact Sheet, 2020]

- Hence, the decision to integrate smoking treatment with NCDs is important to reduce the prevalence of NCDs and their complications. This decision was made during the World Health Organization Framework Convention on Tobacco Control (WHO FCTC) Steering Committee Meeting in December 2019 chaired by the Honourable Health Minister of Malaysia.

- The treatment for smoking should be initiated by the treating doctor based on the assessment and treatment of tobacco use disorder as in **Table 1**. Details on this can be found in the CPG on Treatment of Tobacco Use Disorder 2016, available at: https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Respiratory/CPG_TobacoDisorder.pdf

Table 1. Assessment and treatment of tobacco use disorder

ASSESSMENT AND TREATMENT	
1.	Ask and document smoking status for all patients.
2.	Provide brief advice on quit smoking at every visit to all smokers.
3.	Assess level of nicotine addiction using Modified Fagerström Test for Cigarette Dependence Questionnaire (**COMPULSORY**) and verify smoking status using carbon monoxide breath analyser (**IF AVAILABLE**).
4.	Offer pharmacotherapy to all smokers who are attempting to quit, unless contraindicated.
5.	If selected, use nicotine replacement therapy (NRT) for at least eight to twelve weeks, whereas varenicline should be used for at least twelve weeks.
6.	Combination therapy (e.g. two NRTs, a non-NRT, e.g. bupropion with an NRT) is better than monotherapy in smoking cessation treatment and may be most useful for those smokers at highest risk of relapse.
7.	Use smoking cessation medications with caution in special populations (e.g. children and adolescents, pregnant, breastfeeding women, psychiatric and substance abuse disorder patients).
8.	Arrange a minimum of six to eight face to face follow-up sessions for smoking cessation interventions in six months through counselling support team (health education officer, pharmacists or any officer trained for quit smoking services).

6. REFERRAL/FOLLOW-UP

6.1 Indications for Referral/Admission

In view of the challenges in the diagnosis of EVALI, a diagnostic pathway to evaluate patients with suspected EVALI should be considered. This is due to the lack of a specific features for this clinical syndrome. If the history and imaging are suspicious for EVALI, patients should be admitted for thorough infectious and autoimmune work-up.[Kalininskiy A et al., 2019, level III]

In local setting, history and chest X-ray are sufficient as initial work-up at primary care level on suspected EVALI cases.

- Hospital admission is highly recommended for patients with:[Evans ME et al., 2020, level III; Jatlaoui TC et al., 2019, level III]
  - decreased oxygen saturation (<95% on room air)
  - concurrent illness especially if respiratory distress is present
  - co-morbidities that compromise pulmonary reserve
  - unreliable access to medical care especially ability for follow-up within 24 - 48 hours and promptly in the event of rapidly worsening respiratory symptoms
  - poor social support

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Early follow-up within 24 - 48 hours post-discharge is essential due to the considerable degree of rehospitalisation and death among those with co-morbidities.[Evans ME et al., 2020, level III]

6.2 Management in Emergency Department/Primary Care Facility

Determining the need for hospital admission requires careful clinical judgement by the emergency physician due to high risk of rehospitalisation and mortality among the EVALI patients.[Aldy K et al., 2020, level III]

- Criteria appropriate for outpatient management are:[Aldy K et al., 2020, level III]
  - normal oxygen saturation ≥95% with no respiratory distress on room air
  - absence of high risk co-morbidities e.g. chronic obstructive pulmonary disease or congestive cardiac failure
  - availability of support system for outpatient follow-up
  - no significant diagnostic findings on initial emergency department (ED) workup

The plan upon discharge from ED include:[Aldy K et al., 2020, level III]

i. prescription of a short course oral corticosteroids with tapering dose depending on clinical severity
ii. prescription of antibiotic/antiviral if warranted
iii. education on warning signs (refer to yellow box in **Subchapter 6.3**)
iv. follow-up in 24 - 48 hours

If patient is seen in primary care facility, the same principles as above are applicable.[Evans ME et al., 2020, level III]

In our local setting, for any suspected case of EVALI, a physician should be consulted for further management.

Recommendation 6

- A physician should be consulted for any case suspected of e-cigarette or vaping product use associated-lung injury for confirmation of diagnosis when seen at the emergency department or primary care facility.

6.3 Discharge from Hospital Admission

Due to occurrence of adverse clinical outcomes among EVALI patients shortly after discharge, it is important to ensure that patients are clinically stable for at least 24 - 48 hours before discharge. There should be no clinically significant fluctuation in vital signs and patients should have a good post-hospital care transition.[Evans ME et al., 2020, level III]

- Criteria to determine readiness for hospital discharge include:[Evans ME et al., 2020, level III]
  - patient is clinically stable for 24 - 48 hours before discharge
  - initial outpatient follow-up within 48 hours of discharge
  - instruction on discharge medication and counselling of patient is given
  - screening for mental health, substance use disorders and social support needs is established before discharge
  - counselling and offering e-cigarette and tobacco use cessation intervention, including behavioural intervention and medications have been discussed

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It is crucial to determine readiness for hospital discharge among EVALI patients as this can improve their outcomes.[Evans ME et al., 2020, level III] Patients with fatal cases are more likely than those with nonfatal cases to have a history of any respiratory disease, cardiac disease and any mental health condition.[Werner Ak et al., 2020, level III] Thus, a holistic approach of discharge plan is essential.[Aldy K et al., 2020, level III]

- Discharge from hospital prescription may include:[Aldy K et al, 2020, level III]
  - prescription of a short course oral corticosteroids with appropriate dosage, duration and tapering
  - prescription of an oral antibiotic or antiviral if necessary
  - follow-up at outpatient clinic within 24 - 48 hours
  - education on strict return-to-ED warnings (development of new or worsening respiratory symptoms, with or without fever)[Jatlaoui TC et al., 2019, level III]
  - provision of access to outpatient smoking and vaping cessation facility

In our local setting, since EVALI is not well established, the CPG DG recommends such cases to be followed–up by the treating physician.

Recommendation 7

- Patients with cigarette or vaping product use associated-lung injury should only be discharged when they fulfil the discharge criteria.*
  - Upon discharge, hospital prescription should be given.**
  - Follow-up should be done by the treating physician.

*Refer to preceding yellow box on Criteria to determine readiness for hospital discharge.
**Refer to preceding yellow box on Discharge from hospital prescription.

Refer to **Appendix 5** on **EVALI Patient Follow-Up Checklist.**

Refer to **Algorithm** on **Management of E-Cigarette or Vaping Product Use Associated-Lung Injury (EVALI)**.

7. IMPLEMENTING THE GUIDELINES

The management of EVALI should be guided by evidence-based approach in order to provide quality care to the patients. Several factors may affect the implementation of recommendations in the CPG.

7.1 Facilitating and Limiting Factors

Existing facilitators for application of the recommendations in the CPG include:

- wide dissemination of the CPG (soft- and hardcopies) to healthcare providers
- training and updates on EVALI in relevant scientific and professional meeting, seminar, conference etc.
- public awareness campaigns related to harmful effects of e-cigarette

Existing barriers for application of the recommendations of the CPG are:

- limited awareness and knowledge among healthcare providers on EVALI and its management
- lack of awareness among patients, families/carers and community on EVALI
- no surveillance system on EVALI locally

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7.2 Potential Resource Implications

EVALI is a diagnosis of exclusion. Many tests are required to be done prior to confirmation of the diagnosis. Accessibility for imaging facilities especially CT scan is limited. Besides, many laboratory tests necessary to be performed in the work-up for the diagnosis are not easily available.

Chemical profiling is another important factor to be addressed in identifying the probable toxicants in EVALI. However, many issues are faced in doing it which include:

- poor cooperation of patients in providing product for testing
- insufficient amount of material to be tested
- toxicant of concern did not cover flavouring agents

Currently, in local toxicology laboratories, not all toxicants can be tested due to lack of standardised testing methods and high cost involved.

Surveillance system also need to be developed to capture the data on EVALI for policy planning and guidance in clinical management. Furthermore, high level of evidence is required to improve the management of the disease.

The following is proposed as clinical audit indicator for quality management of EVALI:

$$\text{Percentage of chest radiograph done in suspected case of EVALI*} = \frac{\text{Number of chest radiograph done in suspected cases of EVALI in a period}}{\text{Number of suspected cases of EVALI in the same period}}$$

*Target of 100%

Implementation strategies will be developed following the approval of the CPG by MoH which include launching of the CPG and Training Module and training of healthcare providers in using it.

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Appendix 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: What are effective and safe treatments in EVALI?
Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to August 28, 2020>

1. Lung injury/
2. ((lung or pulmonary) adj1 injur*).tw.
3. Acute lung injury/
4. (acute adj2 lung injur*).tw.
5. 1 or 2 or 3 or 4
6. Vaping/
7. vap*.tw.
8. ((electronic cigarette or e cigarette or e cig) adj2 use*).tw.
9. Electronic Nicotine Delivery Systems/
10. (electronic adj1 cigarette*).tw.
11. e cigarette*.tw.
12. e cig*.tw.
13. electronic nicotine delivery system*.tw.
14. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 5 and 14
16. EVALI.tw.
17. 15 or 16
18. THERAPEUTICS/
19. therap*.tw.
20. treatment*.tw.
21. STEROIDS/
22. steroid*.tw.
23. corticosteroid*.tw.
24. HYDROCORTISONE/
25. hydrocortisone.tw.
26. PREDNISOLONE/
27. prednisolone.tw.
28. METHYLPREDNISOLONE/
29. methylprednisolone.tw.
30. GLUCOCORTICOIDS/
31. (glucocorticoid adj1 effect*).tw.
32. glucocorticoid*.tw.
33. CRITICAL CARE/
34. ((critical or intensive) adj1 care).tw.
35. (surgical intensive adj2 care).tw.
36. NONINVASIVE VENTILATION/
37. ((non invasive or non-invasive or noninvasive) adj2 ventilation*).tw.
38. INTUBATION/
39. intubation*.tw.
40. BRONCHODILATOR AGENTS/
41. bronchodilator*.tw.
42. (bronchodilator adj1 (agent* or effect*)).tw.
43. supportive therap*.tw.
44. supportive treatment*.tw.
45. standard therap*.tw.
46. standard treatment*.tw.
47. or/18-46
48. 17 and 47
49. limit 50 to (english language and humans)

Draft

Appendix 2

CLINICAL QUESTIONS

Diagnosis

i. What are the criteria to diagnose EVALI?
   - clinical presentation, laboratory investigations imaging, bronchoscopy

ii. What is the probable aetiology of EVALI?
   - When is chemical profiling indicated in EVALI?

iii. What are the differential diagnoses of EVALI?

Treatment

iv. What are effective and safe treatments in EVALI?

Referral and follow-up

v. What are the indications for referral/hospitalisation of EVALI patients?

vi. What are the discharge criteria for EVALI patients?
   - outpatient and inpatient

vii. What are the discharge plans for EVALI patients?
   - outpatient and inpatient

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Appendix 3

TYPES OF VAPING PRODUCTS IN MALAYSIA

Type of e-cig delivery system	Description	Picture
Open System	• Features a prominent chamber (tank) • Refillable - users can open and fill the tank with their choice of e-liquid • Allows users to modify their devices • Also known as “tanks,” “e-vapors” and “mods” • Locally also known as vape	**Device:** 
		E-liquid: 
	Other examples of open system design	
		

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<table>
<tr><td rowspan="3">Closed System</td><td rowspan="2">• Uses tanks, which come ready-filled with e-liquid
• Disposable or reloadable with prefilled cartridges
• Does not allow users to fill their devices and add other chemicals
• Also known as pods</td><td> 
</td></tr>
<tr><td> 
</td></tr>
<tr><td>Other examples of closed system design</td><td>  </td></tr>
</table>

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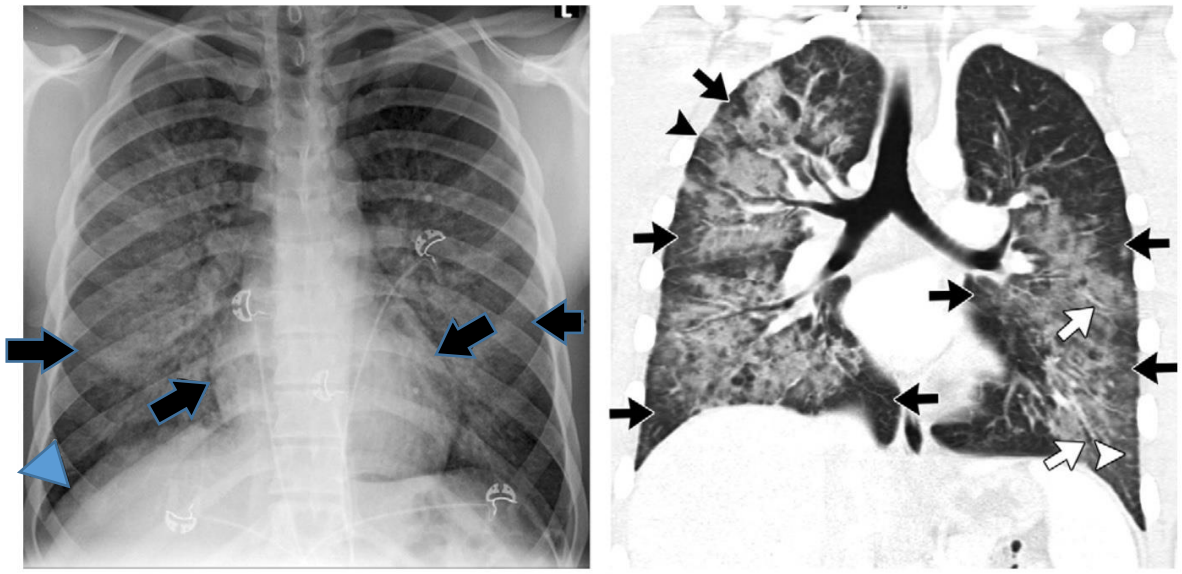
Appendix 4

IMAGING FEATURES IN EVALI



a. b.

Figure I

a. Chest radiograph shows infiltrates with sparing of subpleural region (black arrows) and interlobular septal thickening (blue arrow-head).
b. Corresponding CT image shows perihilar predominant ground-glass opacity with prominent sparing of subpleural interstitium both peripherally and centrally (black arrows) with intermixed areas of lobular sparing. In addition, there is sparing of peribronchovascular interstitium (white arrows). Septal thickening (black arrow-head) and scattered centrilobular nodules (yellow arrow-head) are present.

Source: Kligerman S, Raptis C, Larsen B, et al. Radiologic, Pathologic, Clinical, and Physiologic Findings of Electronic Cigarette or Vaping Product Use-associated Lung Injury (EVALI): Evolving Knowledge and Remaining Questions. Radiology. 2020;294(3):491-505

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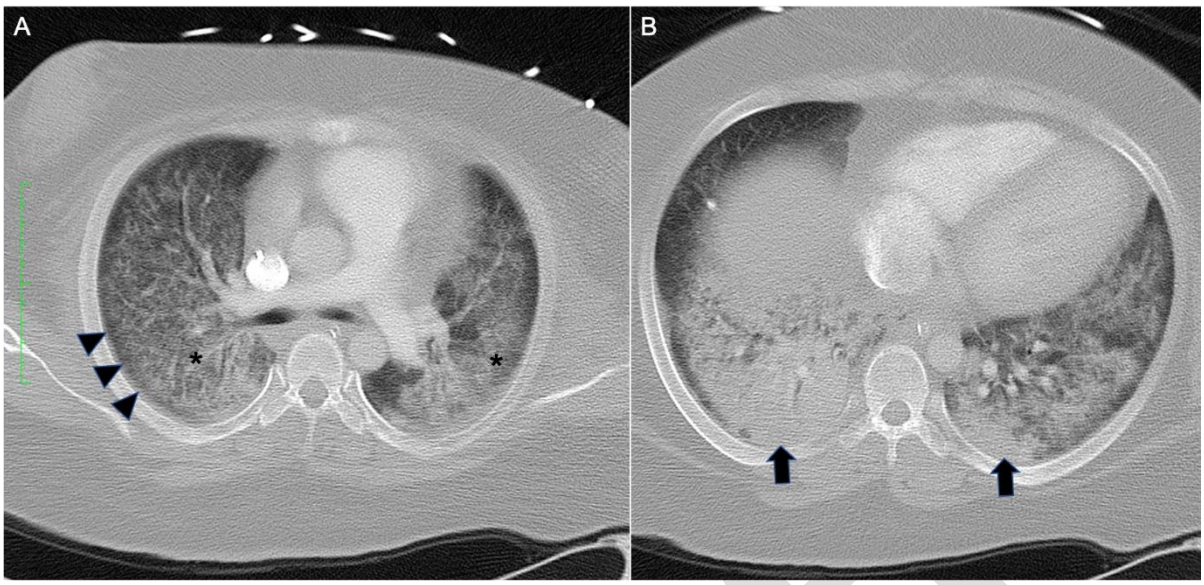

Figure II

Axial CT scan in lung window:
A - at the upper lobes showing presence of bilateral ground glass opacities (asterisks) with subpleural sparing (black arrow-heads)
B - at the lower lobes showing bilateral lung consolidation (black arrows)

Source: Radiology Department, Hospital Umum Sarawak, Kuching, Sarawak

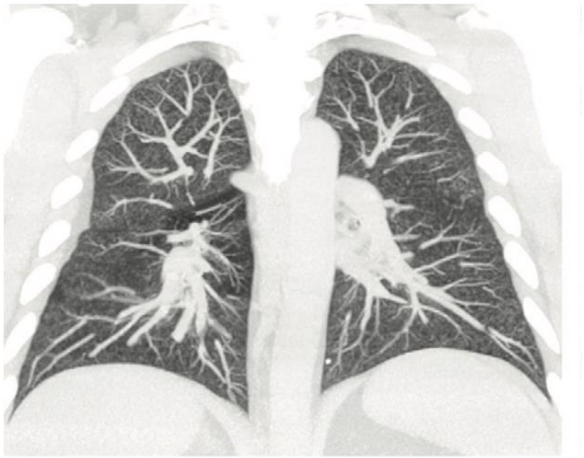

Figure III

Coronal maximum intensity projection image showing diffuse centrilobular nodularity.

Source: Kligerman S, Raptis C, Larsen B, et al. Radiologic, Pathologic, Clinical, and Physiologic Findings of Electronic Cigarette or Vaping Product Use-associated Lung Injury (EVALI): Evolving Knowledge and Remaining Questions. Radiology. 2020;294(3):491-505

Appendix 5

EVALI PATIENT FOLLOW-UP CHECKLIST

The following should be done on EVALI patients on follow-up:	
Activity	**Comment**
a. At 48 hours follow-up:	
• Continue education about EVALI	
• Assess and encourage adherence with medication regimens	
• Ask about side effects of treatment	
• Reinforce the importance of abstinence from e-cig product use	
• Facilitate referrals to other providers or services indicated by patients' medical history or conditions	
• Provide relevant resources on social, mental health and substance use disorder	
b. At 1 - 2 months follow-up	
• Repeat all the steps at 48 hours follow-up	
• Do spirometry	
• Do chest X-ray	

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LIST OF ABBREVIATIONS

AEP	acute eosinophilic pneumonia
ALI	acute lung injury
BAL	bronchoalveolar lavage
CBD	cannabidiol
CDC	Centers for Disease Control
CPG(s)	clinical practice guidelines
CRP	C-reactive protein
CT	computed tomography
CXR	chest X-ray
DAD	diffuse alveolar damage
DAh	diffuse alveolar haemorrhage
DG	development group
e-cig	electronic cigarette
ED	emergency department
ESR	erythrocyte sedimentation rate
EVALI	E-Cigarette or Vaping Product Use Associated-Lung Injury
GRADE	Grading Recommendations, Assessment, Development and Evaluation
ICU	intensive care unit
IQR	interquartile range
LLMs	lipid-laden macrophages
MaHTAS	Malaysian Health Technology Assessment Section
mg	milligramme
MoH	Ministry of Health
OP	organising pneumonia
PCR	polymerase chain reaction
PG	propylene glycol
RC	review committee
THC	tetrahydrocannabinol
US(A)	United States (of America)
VG	vegetable glycerin

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