Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

arise during the daily care of patients with COVID-19-associated ARDS, it is imperative that high-quality clinical investigation proceeds, despite the inherent challenges of implementing research protocols in the uncertain and risky environment of a pandemic.

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Autopsy insights from the EVALI epidemic

The first recorded autopsy was that of Julius Caesar in 44 BCE to establish which knife wound had caused his death; the wound that ruptured his aorta was the culprit. Autopsies have been the foundation of medical advancement over the subsequent centuries, and were done in 40–60% of all hospital deaths as recently as the 1950s.[1,2] With increasingly sophisticated imaging and diagnostic advancements, autopsy rates have declined substantially to less than 1%.[3] Despite these advancements, clinically missed diagnoses involving a primary cause of death are found at autopsy about 8–24% of the time.[4]

Given the frequency of misclassification when clinicians diagnose familiar diseases; e-cigarette, or vaping, product use-associated lung injury (EVALI), a new syndrome whose definition is evolving, is expected to result in similar or even greater diagnostic error. Initial reports were based on a non-specific clinical case definition of vaping, imaging opacities, and exclusion of alternative explanatory diagnoses.[5]

In *The Lancet Respiratory Medicine*, Sarah Reagan-Steiner and colleagues[6] present the first systematic characterisation of EVALI using autopsy and lung biopsy findings, which help to improve the understanding of what EVALI is, and is not. In addition to lung biopsy samples from 10 patients, the report includes autopsy findings from 13 individuals, representing a quarter of patients who were reported to have died from EVALI (52 as of Dec 10, 2019).[7] Three (23%) of 13 individuals who died from suspected EVALI had pulmonary pathology suggesting an alternative or concomitant disease. In retrospect, given the pathological findings of bronchopneumonia, bronchoaspiration, or interstitial lung disease, these patients would not have met the definition of EVALI that required exclusion of alternative diagnoses. Clinicians face this diagnostic challenge daily, with inadequate data, and they need to decide how invasive an evaluation should be to exclude alternative causes of respiratory failure.

The findings generated from this pathological case series reveal how heterogenous a lethal syndrome such as EVALI can be. Severe diseases often manifest with multiple organ dysfunction regardless of the original injury. Some patients with EVALI had microthrombi in the renal glomeruli, and other studies have characterised patients with gastrointestinal symptoms.[5,8] Additionally, the presence of fibrosis, aspiration, infection, heart failure, and asthma all suggest alternative or additional diagnoses in up to


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30% of deceased patients who used e-cigarettes or vaping products.

In 2019, the US Centers for Disease Control and Prevention added a negative viral panel and a negative influenza test to the definition of a confirmed EVALI case, but even this updated definition requires revision. As of 2020, a new cause of pulmonary infiltrates and respiratory failure has been added to the differential; arguably, a negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test is also required for making a diagnosis of EVALI in 2020. This definition will probably continue to evolve for as long as EVALI remains a diagnosis of exclusion without a specific diagnostic test. Although the presence of diffuse alveolar damage and pathological findings consistent with acute lung injury were taken to be diagnostic of EVALI by Reagan-Steiner and colleagues in this study, such findings are hardly specific to EVALI. One explanation for EVALI is that vitamin E acetate adversely affects lung surfactant, or that terpenes cause direct lung irritation, as most patients (48 of 51) have been shown to have vitamin E acetate in bronchoalveolar-lavage fluid,[9] including one patient from this autopsy case series. However, another possibility is that EVALI might have multiple causes. Not all samples in patients with EVALI have recovered vitamin E acetate. Furthermore, e-cigarette and vaping product use has been shown to cause other well-characterised diseases, including lipoid pneumonia and bronchiolitis obliterans, which are not EVALI.[10]

When an epidemic or pandemic disease receives recognition in the press, avoiding exposure suspicion bias is difficult, because disease prominence leads to a more intense search to find the exposure. Diagnostic suspicion bias, conversely, occurs when perception or knowledge of the exposure affects the diagnosis. In 2019, physicians in the USA considered EVALI in patients who presented with acute lung injury and had a vaping history. The more severe the acute lung injury appeared, the more likely the clinician might be to ask about vaping history. Similarly, a patient with viral pneumonia and a history of vaping might have been characterised erroneously as EVALI. The findings from this study suggest that these biases occurred in diagnosing EVALI. Lessons learned from EVALI can be applied to the current COVID-19 pandemic to recognise how clinician biases can result in widespread variability in the evaluation and diagnosis of a disease. The autopsy data are a humbling reminder of how often clinicians err in diagnosing a complex disease. Cases where clinicians were confident of an EVALI diagnosis sometimes turned out to be asthma, heart failure, or streptococcal infection instead.

Despite including a substantial proportion of patients who died with EVALI, this study represents a small number of patients with limited generalisability. These pathological findings are representative of only the sickest patients with EVALI. In the end stage of acute lung injury, pathological findings are consistent, but it remains to be seen whether at earlier stages of EVALI more specific or informative patterns might be observed.

The EVALI epidemic has not ended. Our understanding of EVALI continues to evolve and a single causative agent now seems less likely. Individuals will continue to vape, and nicotine and THC adulterants still persist. Understanding the pathology of lung injury in EVALI remains important, and perhaps the most crucial insight from these findings is to keep an open mind and search for alternative diagnoses, even in patients we are confident have EVALI.

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