Hématologie (GRRR-OH). Urgent chemotherapy for life-threatening complications related to solid neoplasms. *Crit Care Med* 2017;45: e640–e648.
10. Cherruault M, Le Goff M, Tamburini J, Pène F. Urgent chemotherapy in sepsis-like shock related to hematologic malignancies. *Crit Care Med* 2018;46:e465–e468.
11. Barbaro RP, Odetola FO, Kidwell KM, Paden ML, Bartlett RH, Davis MM, *et al*. Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality: analysis of the extracorporeal life support organization registry. *Am J Respir Crit Care Med* 2015;191:894–901.

ICU Resource Use in Critically Ill Patients following Chimeric Antigen Receptor T-Cell Therapy

To the Editor:

Despite favorable clinical results observed with chimeric antigen receptor T-cell therapy (CART) in B cell–related malignancies, toxicities are still relatively common and can be life threatening if not recognized and treated appropriately (1–4). Approximately 30–40% of all patients treated with CARTs require ICU admission because of treatment-related complications such as cytokine release syndrome (CRS) and neurotoxicity (immune effector cell–associated neurotoxicity syndrome [ICANS]) (3–6). Patients treated with CART incur substantial expenses as a result of the cost of treatment and associated hospitalization costs (7). In addition, clinicians worry that intensive care use by these patients will add to the already high financial burden of institutions and limit their widespread use (8). In this study, we explore resource use in patients treated with CART who were admitted to the ICU for CART-related complications. Some results of this study have been previously reported in the form of an abstract (9).

We retrospectively reviewed all adult patients with lymphoma admitted to our medical ICU between November 2017 and August 2018 to evaluate resource use with regard to imaging, interventions, and medications in addition to outcomes, including mortality up to 60 days after ICU admission. Demographics, clinical data, resource use in the ICU, and outcomes were collected. Patients with lymphoma admitted to the ICU who had not received CART were used as the comparator group and were compared with patients with lymphoma treated with axicabtagene ciloleucel CART product admitted to the ICU with CRS or ICANS. All patients treated with U.S. Food and Drug Administration–approved tisagenlecleucel were excluded as only pediatric patients were treated with this protocol during the study period. In addition, patients receiving investigational CART products were also excluded owing to restrictions from their ongoing investigational protocols. All toxicities were graded as per institutional guidelines (10). Summary statistics were used for continuous and categorical variables, Fisher's exact or chi-square test to evaluate association between categorical variables, and Wilcoxon rank sum test to evaluate the difference in a continuous variable between patient groups. To evaluate the effect of significant clinical covariates on mortality, Sequential Organ Failure Assessment (SOFA) score on ICU admission, age, and refractory disease (received $\geq$3 lines of prior chemotherapy) were included in a multivariate model. The study was approved by the institutional review board with a waiver of informed consent (PA18–0808).

During the study period, there were a total of 651 patients with lymphoma admitted to the hospital; 39 of these patients received axicabtagene ciloleucel products. One hundred thirty-six (20.9%) of these patients required ICU admission during their hospital stay; 100 (73.5%) were comparators and 20 (14.7%) were treated with CART. Age, sex, and SOFA scores were similar between groups (Table 1). Comparator patients were more commonly admitted to the ICU for respiratory failure and shock, whereas those treated with CART were primarily admitted for altered mental status; 80% of patients treated with CART were admitted for ICANS and 20% for CRS. In the CART group, 88.9% had grade $\geq$3 neurotoxicity; 70% had a CAR toxicity score of 0 requiring close monitoring, 27.8% of patients had seizures, one patient had nonconvulsive status epilepticus, and one patient developed cerebral edema (Table 1). CRS was present in 65% of patients, with shock developing in 23% and arrhythmias in 15%. Grade 1 toxicities such as fever and tachycardia were present in 61.5% of patients during their ICU stay. Respiratory (15%), renal (15%), hepatic (15%), and hematologic (5%) grade $\geq$2 toxicities were also observed.

After ICU admission, there were no significant differences between CART and comparator patients in the use of inotropes or performing echocardiogram, bronchoscopy, tracheostomy, thoracentesis, paracentesis, or other procedures performed by specialties such as interventional pulmonary, gastroenterology, or interventional radiology ($P > 0.5$). Use of renal replacement therapy was similar between CART and comparator groups (5% vs. 22%; $P = 0.12$) despite a lower incidence of acute kidney injury in patients treated with CART (10% vs. 43%; $P = 0.005$). Patients treated with CART were less likely to require mechanical ventilation (10% vs. 48%; $P = 0.002$), high-flow nasal cannula (5% vs. 48%; $P = 0.0003$), bilevel positive airway pressure ventilation (0% vs. 33%; $P = 0.001$), vasopressors (20% vs. 58%; $P = 0.002$), and sedation (15% vs. 50%; $P = 0.0057$) (Table 2). Patients treated with CART were more likely to undergo EEG (75% vs. 13%; $P < 0.0001$), which could be explained by the high incidence of nonconvulsive seizures in this patient population (11), and lumbar punctures (30% vs. 4%; $P = 0.001$) (Table 2). There was no difference in the use of computed tomography (45% vs. 27%; $P = 0.11$) or magnetic resonance imaging (20% vs. 12%; $P = 0.47$) of the brain in CART versus the comparator group. Patients treated with CART were less likely to undergo other imaging modalities such as X-rays, ultrasounds, and nonbrain computed tomography scans and magnetic resonance images (15% vs. 56%; $P = 0.001$) (Table 2).

Median ICU length of stay was similar between patients treated with CART and comparator patients (4 [2–10] vs. 4 [1–63] d; $P = 0.97$).

Supported in part by the Cancer Center Support Grant (National Cancer Institute grant P30 CA016672).

Author Contributions: A.R.T.B. and C.G. contributed equally to and had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. A.R.T.B., I.J., J.M., R.E., and C.G. contributed to data acquisition. L.F. conducted statistical analysis and all authors have interpreted the data. A.R.T.B. and C.G. drafted the manuscript and all authors have provided critical revision for content. All authors have read and approved the final manuscript.

Originally Published in Press as DOI: 10.1164/rccm.202002-0286LE on June 12, 2020

Table 1. Baseline Characteristics of Patients with Lymphoma Treated with CART and Comparator Patients with Lymphoma

Characteristics	CART (*n* = *20*)	Lymphoma (*n* = *100*)	*P* Value
Age, yr	54.5 (25–84)	63 (18–85)	0.17
Sex, M	13 (65)	67 (67)	0.86
Lymphoma type			0.0001
LBCL	20 (100)	45 (45)	
Hodgkin	—	9 (9)	
Follicular	—	8 (8)	
Other	—	38 (38)	
Lines of chemotherapy	5.5 (3–11)	3 (0–14)	<0.0001
Hospital to ICU admission, d	11 (3–37)	3 (1–54)	<0.0001
Charleston comorbidity index	3 (2–6)	5 (0–15)	0.0007
SOFA on ICU admission	4.5 (1–12)	6.5 (0–16)	0.08
Maximum SOFA score during ICU stay	6 (3–14)	7.5 (0–20)	0.08
ICU admission diagnosis			<0.0001
AMS	15 (75)	7 (7)	
Respiratory failure	1 (5)	37 (37)	
Seizures	1 (5)	3 (3)	
Shock	3 (15)	20 (20)	
Cardiac arrest	0 (0)	4 (4)	
Cardiac complications	0 (0)	8 (8)	
Renal failure	0 (0)	2 (2)	
Other	0 (0)	19 (19)	

Definition of abbreviations: AMS = altered mental status; CART = chimeric antigen receptor T-cell therapy; LBCL = large B-cell lymphoma; SOFA = sequential organ failure assessment.
Data are presented as *n* (%) or median (range).

Median hospital length of stay, however, was longer in patients treated with CART (24.5 [17–66] vs. 18 [2–79] d; $P = 0.01$), and they were admitted to the ICU later during their hospital stay (Tables 1 and 2). ICU (5% vs. 31%; odds ratio [OR], 8.4; 95% confidence interval [95% CI], 0.9–71.9; $P = 0.05$), hospital (15% vs. 47%; OR, 5.9; 95% CI, 1.5–23.4; $P = 0.01$), 30-day mortality (20% vs. 56.3%; OR, 7.1; 95% CI, 1.9–26.4; $P = 0.003$), and 60-day mortality (21.1% vs. 58.9%; OR, 7.4; 95% CI, 1.9–27.6; $P = 0.003$) were significantly higher in the comparator patients even after adjusting for SOFA, age, and refractory disease in a multivariate model (Table 2). Lastly, patients treated with CART were more likely to be discharged home when compared with other patients with lymphoma (75% vs. 32%; $P = 0.009$) (Table 2). Readmission to the hospital and ICU within 60 days of ICU admission was similar between patients treated with CART and comparator patients. Complete remission rates at 30 and 60 days were higher in patients treated with CART.

This is the first study to explore resource use in patients treated with CART admitted to the ICU for CART-related complications. Despite the significant cost of CART and a higher rate of ICU admissions for this patient population, overall resource use once admitted to the ICU in this population is not disproportionate when compared with other patients with lymphoma. Additionally, even when accounting for severity of illness, in-hospital and out-of-hospital mortality of critically ill patients treated with CART is significantly lower. This could suggest that organ failure scores should not guide decisions about limiting treatment and determining prognosis in patients treated with CART, and that reversibility of the underlying pathology is the most important factor for survival. Our study evaluates objectively the perceived impact patients treated with CART may have on ICU resource use and costs for a hospital. Although the introduction of CART has increased training requirements, need for clinical expertise, and multidisciplinary collaboration, it has not had a negative impact on overall ICU resources with regard to medication use, hemodynamic and respiratory support, procedures, or ICU length of stay. On the contrary, we did observe a higher rate of ICU admission in patients treated with CART when compared with the general lymphoma population, which should be considered when initiating a CART program; however, two things need to be considered regarding these findings. First, the initial increase observed in ICU admission rates within patients treated with CART decreases with time as providers become more comfortable managing mild to moderate toxicities on the floor (data not published). Second, in comparison with other patients with lymphoma, their acute illness is reversible, leading to higher rates of home discharge and short- and long-term survival. Further future collaborative investigations are needed to assess management strategies to improve the care of critically ill patients following CART. In the meantime, sharing these findings with the critical care community, while acknowledging that there are limitations due to the small sample size and nature of a single oncological center study, is of extreme importance because they suggest that aggressive support of these patients is warranted and may not incur higher costs. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Anne Rain T. Brown, Pharm.D., B.C.C.C.P., F.C.C.M.*
Irfan Jindani, P.A.-C.
Judd Melancon, A.G.A.C.N.P.
Rose Erfe, B.S.
Jason Westin, M.D.
Lei Feng, M.S.
Cristina Gutierrez, M.D.
The University of Texas MD Anderson Cancer Center
Houston, Texas

Table 2. Resource Use and Clinical Outcomes

Variables	CART (*n* = *20*)	Lymphoma (*n* = *100*)	*P* Value
Resource use			
Mechanical ventilation	2 (10)	48 (48)	0.002
Duration of MV, d	5 (3–7)	5 (1–62)	0.78
HFNC	1 (5)	48 (48)	0.0003
BPAP	0 (0)	33 (33)	0.002
AKI in ICU	2 (10)	43 (43)	0.005
RRT	1 (5)	22 (22)	0.12
Medications			
Vasopressors	4 (20)	58 (58)	0.003
Inotropes	0 (0)	2 (2)	1.0
Sedation	3 (15)	50 (50)	0.006
Procedures			
Bronchoscopy	2 (10)	25 (25)	0.24
EEG	15 (75)	13 (13)	<0.0001
LP	6 (30)	4 (4)	0.001
Tracheostomy	0 (0)	7 (7)	0.59
Thoracentesis	1 (5)	7 (7)	1.0
Paracentesis	0 (0)	3 (3)	1.0
Imaging			
Brain CT	9 (45)	27 (27)	0.11
Brain MRI	4 (20)	12 (12)	0.47
Echocardiogram	12 (60)	48 (48)	0.33
Other imaging	3 (15)	56 (56)	0.001
Outcomes			
ICU LOS, d	4 (2–10)	4 (1–63)	0.97
Hospital LOS, d	24.5 (17–66)	18 (2–79)	0.01
ICU readmission	3 (15)	15 (15)	1.0
ICU mortality	1 (5)	31 (31)	0.01
Hospital mortality	3 (15)	47 (47)	0.01
30-d mortality	4 (20)	54 (56.3)	0.005
60-d mortality	4 (21.1)	56 (58.9)	0.004
Discharge disposition			0.009
Deceased	3 (15)	47 (47)	—
Home	15 (75)	36 (36)	—
LTAC	2 (10)	16 (16)	—
Other	0 (0)	1 (1)	—

Definition of abbreviations: AKI = acute kidney injury; BPAP = bilevel positive airway pressure; CART = chimeric antigen receptor T-cell therapy; CT = computed tomography; HFNC = high-flow nasal cannula; LOS = length of stay; LP = lumbar puncture; LTAC = long-term care facility; MRI = magnetic resonance imaging; MV = mechanical ventilation; RRT = renal replacement therapy.
Data are presented as *n* (%) or median (range).

ORCID IDs: 0000-0002-6633-1596 (A.R.T.B.); 0000-0001-6381-6216 (C.G.).

*Corresponding author (e-mail: artanner@mdanderson.org).

References

1. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, *et al*. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol* 2019;20: 31–42.
2. Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, *et al*. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med* 2014;371:1507–1517.
3. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, *et al*.; JULIET Investigators. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med* 2019;380: 45–56.
4. Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, *et al*. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* 2020;382:1331–1342.
5. Nastoupil LJ, Jain MD, Spiegel JY, *et al*. Axicabtagene ciloleucel (Axi-cel) CD19 chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory large B-cell lymphoma: real world experience. *Blood* 2018;132:91.
6. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, *et al*. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med* 2017;377:2531–2544.
7. Bach PB. National coverage analysis of CAR-T therapies - policy, evidence, and payment. *N Engl J Med* 2018;379:1396–1398.
8. Azoulay E, Shimabukuro-Vornhagen A, Darmon M, von Bergwelt-Baildon M. Critical care management of chimeric antigen receptor T cell-related toxicity: be aware and prepared. *Am J Respir Crit Care Med* 2019;200:20–23.
9. Brown AR, Jindani I, Melancon J, *et al*. Resource utilization in the ICU in critically ill patients following CAR T cell therapy. *Crit Care Med* 2020; 48:42.
10. Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, *et al*. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol* 2018;15:47–62.
11. Santomasso BD, Park JH, Salloum D, Riviere I, Flynn J, Mead E, *et al*. Clinical and biological correlates of neurotoxicity associated with

CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. *Cancer Discov* 2018;8:958–971.

Potential of Ethenone (Ketene) to Contribute to Electronic Cigarette, or Vaping, Product Use–associated Lung Injury

To the Editor:

In 2019, the United States experienced an unprecedented outbreak of electronic cigarette (e-cigarette), or vaping, product use–associated lung injury (EVALI) (1–4). Although reports of lipid-laden macrophages in BAL fluid raised the possibility that EVALI represented exogenous lipoid pneumonia (5, 6), case series that focused on histopathology found patterns of acute lung injury, including diffuse alveolar damage and organizing pneumonia, often with bronchiolitis (7, 8). Thus, the available evidence to date suggests the outbreak is characterized by an airway-centered chemical pneumonitis rather than acute exogenous lipoid pneumonia.

Vitamin E acetate (VEA) has been strongly linked to the outbreak, as demonstrated by *1*) the presence and high concentrations of VEA in vaping product samples recovered from patients with EVALI; *2*) the detection of VEA in tetrahydrocannabinoid-containing vaping products seized by law enforcement in 2019 but not 2018, indicating temporality; and *3*) the identification of VEA in 94% of BAL fluid samples from patients with EVALI but not in samples from healthy controls (9).

The mechanism by which VEA might cause a chemical pneumonitis is still not understood. Vitamin E is a natural component of lung surfactant, and experimental models of phospholipid bilayers suggest that increasing concentrations of vitamin E or VEA could affect the physical structure and phase behavior of surfactant (9). Whether such effects alone sufficiently impact surfactant function *in vivo* to cause a cascade of increased surface tension, alveolar collapse, and acute lung injury is currently unclear.

Another potential mechanism involves a toxic agent, ethenone (C_2H_2O), the simplest of the ketene class of compounds. Ketenes, including ethenone, are highly reactive compounds used as intermediates in industrial chemical synthesis reactions. Wu and O'Shea recently demonstrated both the theoretical basis and experimental formation of ethenone from VEA under heated conditions through the pyrolytic cleavage of the acetate group (Figure 1) (10).

Early literature on ethenone creation reported its formation from acetone at 700°C in the presence of a tungsten catalyst (11). Several subsequent patents describe the use of other catalysts to assist the formation of ketenes of various sizes from acetate and other carboxylic acids, including fatty acids, at temperatures as low as 326°C, which are reachable with electronic vaping devices that

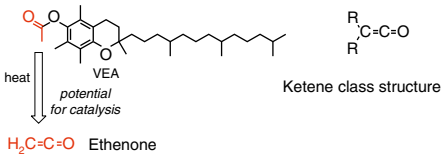

Figure 1. Formation of ethenone from vitamin E acetate and ketene class structure. VEA = vitamin E acetate.

allow variable user settings (12–15). These patents employed metal catalysts, including nickel, titanium, magnesium, iron, copper, and the metalloid silica. Though Wu and O'Shea formed ethenone from VEA without a catalyst (10), the presence of metals and silica in the vaping devices of patients with EVALI could theoretically amplify the creation of ethenone.

Though nicotine-based e-cigarette liquids and aerosols were already known to contain various metals, some of which overlap with the catalytic metals in ketene patents (16), whether EVALI-associated tetrahydrocannabinoid vape cartridges contain potential reaction catalysts was uncertain. Thus, we have been disassembling these devices under a reflected light microscope and analyzing the metal composition of the individual components using a portable X-ray fluorescence unit and scanning electron microscopy with energy dispersive X-ray spectroscopy. Our preliminary analyses suggest conditions favorable to ethenone formation, including evidence of high temperatures, thermal insulation, and nickel and chromium filaments encased in charred, oil-soaked, silica ceramic (Figure 2). Additional studies will build on the results of Wu and O'Shea (10) to evaluate the wide-ranging conditions that could influence ethenone formation, such as temperature, power, and vaping device type and components.

Ethenone toxicological literature is scant and historic but still alarming. Acute (10-minute) inhalation exposures were observed to lead to mortality in 0.8–16 hours in small studies of multiple species across a range of concentrations (50–1,000 ppm) (11). The only study to use high-purity ethenone (98–99%) observed acute pulmonary congestion and alveolar edema in monkeys exposed to concentrations of 12 ppm and higher (11). Mice in this same study exposed at 1 ppm for 14 days, 7 hours/day, had a 10% mortality rate (11).

Human data on ethenone toxicity are even sparser. One case report described a chemical industry worker who developed hypoxic

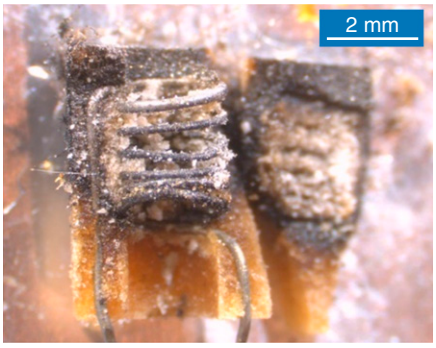

Figure 2. Stereozoom microscope image of dissected, cylindrical ceramic heating element from the vaping cartridge of a patient with electronic cigarette, or vaping, product use–associated lung injury, showing charring from high temperatures. Scale bar, 2 mm.

Originally Published in Press as DOI: 10.1164/rccm.202003-0654LE on June 18, 2020