

This quarterly research newsletter features articles written by the faculty and students of Ohio University's Division of Physician Assistant Practice.

## In this issue...

**Dangers of Vaping** Page 1  
**Infant Intussusception** Page 3

**Concerns About Generic Drugs** Page 4  
**Program Highlights & Photos** Page 6

### Unexpected Dangers of Vaping

by James Cacchillo, DO

Electronic cigarettes were developed in 2003 and became much more popular in the United States in 2007 after entering the market. Although some form of unregulated aerosolized products for inhalation have been around since the 1960s, the modern electronic cigarette has been credited to Chinese pharmacist Hon Lik in 2003. Data published in 2018 documents that 95% of electronic cigarettes are manufactured in China. Popularity in the US has exploded among youth, with e-cigarettes passing standard cigarettes among high school students since 2014. Since 2017, the use of e-cigarettes in US high school students has increased in prevalence from 11.7% to 20.8%<sup>1</sup>. A survey of younger e-cigarette users cited appealing flavors as the primary reason for use in 81% of cases<sup>2</sup>. Although e-cigarettes have been the most commonly utilized delivery system, there are many other devices utilized that include e-pens, e-cigs and pipes, hookah inhalation systems and even some products resembling a USB device<sup>1</sup>.

The term vaping refers to inhaling and exhaling the aerosolized vapor produced by electronic cigarettes and other devices through heating a liquid solution. Initially thought to be a safer alternative to cigarette smoking due to avoiding potential carcinogens and toxic chemicals created by burning tobacco, recent outbreaks associated with severe lung injury (termed EVALI, or e-cigarette/ vaping associated lung injury) have created a significant doubt as to the safety of using these products and caused the Centers for Disease Control to issue a warning against vaping.

Nicotine is the most commonly desired substance in e-cigarettes and other battery-powered vaping devices. However, there appears to be an increasing trend in the



use of other substances, such as tetrahydrocannabinol (THC), cannabidiol (CBD) and butane hash oils, commonly referred to as dabs<sup>3</sup>. In addition to the main aerosolized substance, the liquid also contains various other products, such as flavorings, propylene glycol additive, ultrafine particles and some heavy metals<sup>3</sup>. Possibly due to the explosion of substances and devices being utilized, it has been difficult to understand the entire composition of the e-liquid and combustible chemicals involved from a lung delivery standpoint. There are more than 460 different e-cigarette brands currently on the market<sup>1</sup>. In the United States, tobacco is regulated by the Center for Tobacco Products (CTP), which oversees the Family Smoking Prevention and Tobacco Control Act. However, e-cigarettes were not regulated under this act by FDA rule until 2016<sup>2</sup>. This regulatory oversight includes manufacturing (including vape shops), labeling, importing, advertising, promoting, sale and distribution of vaping products<sup>2</sup>.

On August 4, 2019, the first cases of e-cigarette/ vaping associated lung injury (EVALI) were reported to the CDC<sup>1</sup>. These initial cases were a prelude to a major outbreak that grew to 2506 cases by December 17, 2019 that involved hospitalization. Most of these patients were male

(67%), younger than 35 years of age (78%) and had reported vaping that involved THC (80%)<sup>4</sup>. There were cases in all 50 states and a total of 52 deaths in 25 states and the District of Columbia. Most patients developed a gradual onset of symptoms over days to weeks that included respiratory, constitutional and gastrointestinal complaints. Almost 50% of the patients required treatment in an intensive care unit for respiratory failure<sup>5</sup>.

Reports to the CDC on this outbreak revealed in general an atypical radiographic presentation by chest x-ray plain imaging and eventual predominant basilar consolidation and ground-glass opacity on thoracic CT scan imaging. Histopathologic pattern of injury was consistent with diffuse alveolar damage, acute fibrinous pneumonitis and organizing pneumonia. The CDC developed case definitions and criteria for diagnosis as either a confirmed or probable case<sup>5</sup>.



A recent study in the *New England Journal of Medicine* dated December 20, 2019 discovered a significant association of EVALI with vitamin E acetate<sup>5</sup>. Bronchoalveolar lavage (BAL) fluids were obtained from 51 patients in 16 states with EVALI (25 confirmed and 26 probable) and from 99 healthy subjects who were part of an ongoing smoking study since 2015 consisting of non-smokers, cigarette smokers and those using only e-cigarettes. In addition to vitamin E acetate, BAL fluid was analyzed for plant oils, medium-chain triglycerides, coconut oil, petroleum distillates and terpenes<sup>5</sup>. Vitamin E acetate was found in 48 of 51 patients with EVALI and none of the 99 healthy subjects. Additionally, 47 of the patients with EVALI had either detectable THC or its metabolites in the BAL fluid or had reported vaping THC products in the 90 days before the onset of the illness. Data from law enforcement seizure of illicit vaping products that contained THC revealed vitamin E acetate in 20 of 20 samples (Minnesota, non-marijuana state) and adding vitamin

E acetate to THC products as a product of improving viscosity was known to be occurring in the illicit market in late 2018 and gained steam in 2019, which correlates to the EVALI outbreak<sup>5</sup>.

Vitamin E acetate is the ester of vitamin E (alpha-tocopherol) and acetic acid and is commonly used in skin creams and in multivitamins. During absorption it is cleaved to vitamin E and has not been associated with any known significant adverse effects<sup>5</sup>. The possible respiratory effect of inhaling vitamin E acetate is poorly understood, however. The study in the *New England Journal* postulated 2 possible mechanisms that inhaled vitamin E acetate could result in pulmonary dysfunction<sup>5</sup>. First, tocopherols can trigger dysfunction in the phospholipid interface of surfactant, causing a transition from a gelatinous to a liquid crystalline phase and thereby result in decreased pulmonary surface tension at the alveolar level. Secondly, heating vitamin E acetate as with vaping can split off the molecule ketene, which is suspected of being a pulmonary irritant. Studies are currently ongoing into researching both of these postulates<sup>5</sup>.

As with any previously unregulated and fairly new form of substance use, the full extent of the dangers in vaping are unknown. However, the recent cluster of severe lung injuries attributed to vaping use suggests that the risk of added compounds can significantly alter the safety profile of these products. Until further regulation by the FDA occurs, practitioners need to be aware of the unexpected dangers associated with vaping.

#### References:

1. Vaping Devices- Electronic Cigarettes. (January 2020) Retrieved from <https://www.drugabuse.gov/publications/drugfacts/vaping-devices-electronic-cigarettes>
2. Vaporizer, E-Cigarettes, and other Electronic Nicotine Delivery Systems (ENDS). (January 2020) Retrieved from <https://www.fda.gov/tobacco-products/products-ingredients-components/vaporizers-e-cigarettes-and-other-electronic-nicotine-delivery-systems-ends>
3. Giroud C, et.al. (2015). E-Cigarettes: A Review of New Trends in Cannabis Use, *International Journal of Environmental Research and Public Health*, DOI: 10/3390/IJERPH120809988
4. Hartnett, KP, et.al. (2019). Syndromic Surveillance for E-Cigarette, or Vaping, Product Use-Associated Lung Injury, *New England Journal of Medicine*, DOI: 10.1056/NEJMs1915313
5. Blount, BC, et.al. (2019). Vitamin E Acetate in Bronchoalveolar-Lavage Fluid Associated with EVALI, *New England Journal of Medicine*, DOI: 10.1056/NEJMoa1916433

## Infant Intussusception

by Ann Crickard, DO

KH is a 7 week old female with no significant PMHx born at term with no complications or post-delivery issues. She was first encountered in a pediatric Urgent Care with the chief complaint of vomiting. The infant was seen earlier that same day at a local adult emergency department, where the parents were told that the infant was being overfed. They took the infant back home, but remained concerned that she seemed to be vomiting everything that she was fed. They noted that her emesis was liquid yellow, and presented for re-evaluation. In the UC the infant was found to be intolerant of feeding, and in addition had discomfort with abdominal palpation, and had mild abdominal distention. She was then transferred to the local pediatric emergency department for medical management.

### Physical Exam

Temp 37.3 C (99.2F), Pulse 152, Resp: 60, BP 82/55

Weight 4.7 kg (10 lb 5.8 oz), Length: 57.5 cm (22.64 in), BMI 15.09 kg/m<sup>2</sup>

General: irritable infant resting on dad's lap

Hydration: well hydrated with good skin turgor

Head: normocephalic, atraumatic

Eyes: no eyelid swelling, no conjunctival injection or exudate, pupils equal round and reactive to light

Ears: no external swelling or tenderness, canals clear, tympanic membranes normal in appearance and position

Mouth/throat: mucous membranes moist, no focal lesions, no tonsillar enlargement or exudate

Neck: nontender, full range of motion, no mass, no focal lymphadenopathy

Chest: mildly tachypneic, breath sounds clear and equal bilaterally, no respiratory distress, respirations easy and regular

Cardiovascular: tachycardic, regular rate and rhythm, no murmur, brisk capillary refill

Abd: high pitched BS, mild distention, diffusely tender to palpation. No masses.

GU: term female genitalia

Skin: pale, no rashes noted

Neuro: alert, normal tone, no focal deficit

### ED Course

Labs in the ED were normal. A head CT was obtained due to vomiting and lethargy and was normal. An acute abdominal series showed multiple gas dilated bowel loops with a filling defect noted in the right hemiabdomen, concerning for intussusception. An abdominal ultrasound showed fluid containing septations as well as a 1.6 cm cyst like structure in the free fluid in the RLQ of uncertain etiology.

An air enema was performed to reduce the intussusception, but was unsuccessful. She was then admitted to the surgery service with the plan to reattempt an air enema treatment in a few hours. A bolus of normal saline was given to address her low urine output.

The second air enema was also unsuccessful. At this point she was taken to the OR for surgical reduction of the intussusception. She required a laparotomy with partial small bowel resection to remove the portion of bowel affected by the intussusception. The 1.6 cm cyst like structure turned out to be a blood clot which most likely prevented a successful reduction with the air enema attempts.

Her postoperative course was uneventful. Her pain was controlled with Tylenol and Toradol, and she passed a normal bowel movement on the first postoperative day. She was introduced to her normal diet on the first postoperative day, advancing to full feedings over the next 24 hours, and was discharged home on the second postoperative day.



### Discussion

Intussusception typically presents between 1-2 years of age. This case was very unusual in that intussusception presented in a 7 week old infant. In the differential diagnosis for acute vomiting in a 7 week old infant, pyloric stenosis is at the top of the list, followed by an infectious

process, metabolic or hepatobiliary disease, CNS infection or other disorder, other anatomic obstruction such as volvulus. At the bottom of the list gastroesophageal reflux disorder and overfeeding would be considerations. These are less likely in the setting of an acute onset of vomiting.

Intussusception is the “telescoping” of a segment of proximal bowel into the downstream bowel. In the most commonly affected patient population of 1-2 year olds, the cause is unknown. When a “lead point” of bowel is observed, it is commonly virally induced lymphoid hyperplasia. In other settings, particularly older children, a lead point is often found to be pathological, such as a tumor or anatomical malformation<sup>1</sup>.

In this case a 1.6 cm blood clot was found in the wall of the affected portion of bowel. It is suspected that this clot formed after the intussusception, as opposed to being a lead point for the process. None the less, the clot most likely prevented successful air reduction.



Air reduction has replaced fluid enemas as treatment for intussusception. It has a high success rate with very low complication rate. The procedure is done under fluoroscopy, allowing visualization of the moment of reduction. Following successful air reduction, a child should be observed for several hours, to watch for recurrence. The risk of short term recurrence is 5-10%<sup>1</sup>.

When air reduction is unsuccessful, most of the time a laparotomy will be necessary, without delay, as the affected portion of bowel is at risk of becoming gangrenous. In the patient described, there was a length of necrotic bowel, necessitating a partial small bowel resection, including the area of the blood clot, with anastomosis of healthy segments of bowel.

#### Reference:

1. Marcdante, Karen, and Kliegman, Robert, Section 17, Digestive System, Nelson, Essentials of Pediatrics, 8th Ed., Elsevier, 2019. Pages 492-493

## Addressing Patient (and Provider) Concerns About Generic Drugs Part 1: How a Drug Becomes Generic

by Kristin Lugo, Pharm.D

Since 2010, generic drug prescriptions have increased over 26%.<sup>1,2</sup> In 2019, 90% of filled prescriptions were for a generic medication.<sup>2</sup> Even with more generic drugs being used by patients, many people have little idea what it means for a drug to be generic. In this two-part article, we will explore the generic drug process, how generic drugs compare to their brand name counterparts, and what to do when there are concerns about generic products.

The FDA approves a brand name medication (also known as the pioneer, innovator, or reference listed drug) for marketing only after the submission and approval of an Investigational New Drug (IND) application, followed by a New Drug Application (NDA).<sup>3,4</sup> The IND application is a request to test the potential drug in humans. For several years prior to the IND submission, clinical testing is done in animal models, assessing toxicity and lethality, tweaking the original molecule, and sometimes scrapping the discovery and starting over. Once the IND is approved, the applicant will begin several years of human clinical trials to evaluate the potential new drug's safety, tolerability, efficacy, and appropriate dosages. The applicant may also compare the new entity to similar therapies already marketed. When an applicant has completed human trials, they can apply for an NDA, requesting to take the drug to market. The process from IND application to NDA may take 10 years or more.<sup>4</sup> The patent for brand name drugs tends to begin around the time of IND approval and lasts 20 years.<sup>5</sup> The patent protects the initial manufacturer of the drug for a period of time, allowing them the opportunity to not only develop an innovative product but also to recover a portion of the development cost. By the time a drug is approved for market, there may be less than 10 years left on the patent.<sup>5</sup> This is, in large part, why brand name drugs are relatively expensive.

Once the patent on a drug expires, other manufacturers can apply for an Abbreviated New Drug Application (ANDA), asking to bring a generic version to market. Animal and human trials do not need to be repeated in this case because safety and efficacy of the pioneer drug was shown in the NDA.<sup>6</sup> The ANDA demonstrates that

the proposed generic version of the drug is bioequivalent, meaning it will perform the same as the pioneer. The ANDA begins with a reiteration of the reference listed drug properties.<sup>7</sup> It then goes on to explain the generic product's attributes including pharmacokinetic data from healthy human subjects, composition of the product, and descriptions of the manufacturing process.<sup>7</sup> As the FDA states, "the generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug."<sup>6</sup>

In order for a drug to qualify as a generic, not only must it perform the same as the brand, but also it must be the same dosage form and route of administration. A generic drug will look different from the brand and may contain different inactive ingredients. These differences must not affect the bioequivalence of the drug if it is to be approved for marketing. The first manufacturer to receive ANDA approval for a specific drug will have 180 days of market exclusivity before other generics can enter the market.<sup>8</sup>

There is a common misconception that a generic drug can be 20% different from its reference listed drug. This stems from the FDA requirement that the area under the curve (AUC) and maximum concentration ( $C_{max}$ ) of a generic drug must fall within 80% to 125% of the reference level.<sup>9</sup> In other words, the total systemic exposure to the generic must not differ more than 20% from the brand. This is actually the same difference allowed between different batches of the same drug produced by any manufacturer, including those that produce brand name products.<sup>10</sup> Although a 20% total systemic exposure is acceptable when comparing generics and their innovators, the actual observed variation is closer to 3.5%.<sup>10</sup>

While the process to bring a generic drug to market is abbreviated, it still requires a significant amount of scientific evidence and explanation before the FDA will offer its stamp of approval. The FDA's robust methods of vetting products ensures that consumers receive generic drugs equivalent to their brand name counterparts. But that is not the end of the story. What happens once mass production of generic drugs occurs? Who oversees the quality control? How should we respond when we think there is a problem with a generic medication? In part 2 of this series, we will attempt to answer these questions with the ultimate goal of providing our patients with high quality care.

#### References:

1. Pal S. Shifts in the Generic-Drug Market: Trends and Causes. U.S. Pharmacist. <https://www.uspharmacist.com/article/shifts-in-the-generic-drug-market-trends-and-causes>. Published June 21, 2013. Accessed January 9, 2020.
2. Generic Drug Facts. FDA. <http://www.fda.gov/drugs/generic-drugs/generic-drug-facts>. Published April 26, 2019. Accessed January 6, 2020.
3. Katzung BG. Introduction: The Nature of Drugs & Drug Development & Regulation. In: Katzung BG, ed. *Basic & Clinical Pharmacology*. 14e. New York: McGraw-Hill; 2018. <http://accessmedicine.mhmedical.com.proxy.library.ohio.edu/content.aspx?bookid=2249&sectionid=175215401>. Accessed February 12, 2020.
4. Rivera SM, Gilman A. Drug Invention and the Pharmaceutical Industry. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*. 13ed. New York, NY: McGraw-Hill; 2018. <http://accessmedicine.mhmedical.com.proxy.library.ohio.edu/content.aspx?bookid=2189&sectionid=166182795>. Accessed February 12, 2020.
5. Berger J, Dunn JD, Johnson MM, Karst KR, Shear WC. How drug life-cycle management patent strategies may impact formulary management. *Am J Manag Care* (2017) 22 (16):S487-95.
6. Abbreviated New Drug Application (ANDA). U.S. Food and Drug Administration. <https://www.fda.gov/drugs/types-applications/abbreviated-new-drug-application-anda>. Accessed January 21, 2020.
7. ANDA Submissions – Content and Format Guidance for Industry. U.S. Food and Drug Administration. <https://www.fda.gov/media/128127/download>. Published June 2019. Accessed February 13, 2020.
8. Gershman J. Generic Drugs 101: What Pharmacists Need to Know. *Drug Topics*. <https://www.drugtopics.com/article/generic-drugs-101-what-pharmacists-need-know>. Published November 5, 2019. Accessed January 6, 2020.
9. O'Shea, T. Debunking a Common Pharmacy Myth: The 80-125% Bioequivalence Rule. *Pharmacy Times*. <https://www.pharmacytimes.com/contributor/timothy-o-shea/2016/06/debunking-a-common-pharmacy-myth-the-80-125-bioequivalence-rule>. Published June 8, 2016.
10. Dunne S, Shannon B, Dunne C, Cullen W. A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study. *BMC Pharmacol Toxicol*. 2013;14:1. Published January 5, 2013. doi:10.1186/2050-6511-14-1

## PA Program Highlights

by Eva Roberts, PA-S  
Class of 2021

As we began our third didactic semester in January, the Class of 2021 began to prepare for a somewhat right-of-passage experience here at The Ohio University Physician Assistant Program. The professors of our Patient Assessment II course, Molly Beakas, PA-C and Jeffrey Fisher, PA-C had again organized for students to visit two local retirement and skilled nursing homes to speak with patients, engage with our community, and practice our newly acquired history taking and physical exam skills.

Our randomly-selected residents for the day included individuals from all walks of life, with whom we each found to share many similarities - those who had defied odds, beaten cancer, previously worked in healthcare, served in the army, or simply shared our birthdays. Each resident had a truly unique and intricate health history with an equally interesting life story to match.

Spending time with these residents, some may say our first 'patients', was an invaluable opportunity for which we are humbled and grateful. We cannot thank the staff and residents of the facilities enough for allowing us their time and patience. These residents will be marked as having shaped our education and the care of our future patients, as well as having a lasting impact on our approach to medicine.



Over the summer, first year students were assigned group projects to present various groups of bacteria to the class and encouraged to incorporate some fun into their presentation! Pictured above are (L-R) Laura Packard, Reese Walaszek, and Lauren Kaufman .



Medical Director Dr. Ann Crickard recently taught our third semester students all about prenatal and neonatal physical examinations. Community volunteers and staff members brought in their little ones for members of the Class of 2021 to practice with.



After completing the musculoskeletal block, Program Director Melissa Bowlby, PA-C lead the students through a casting and splinting lab! Seen above with short and long arm splints are (L-R) Hannah Shortridge, Kat Armstrong, Maddy Allen, & Paige Henry.



Staff, students, and community members also came together to bring their slightly larger little ones in for pediatric exams, again led by Medical Director Dr. Ann Crickard. Seen here are Colin Echard and Amanda Quinn.

*Please contact Jeff Vasiloff, MD, MPH at [vasiloff@ohio.edu](mailto:vasiloff@ohio.edu) with any questions regarding this issue.*

*If you would like to subscribe to receive this newsletter in the future, please contact [nbell@ohio.edu](mailto:nbell@ohio.edu).*



**OHIO**  
UNIVERSITY

COLLEGE OF HEALTH SCIENCES AND PROFESSIONS  
**DIVISION OF PHYSICIAN ASSISTANT PRACTICE**