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ISMP
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Community/Ambulatory Care
ISMP Medication Safety Alert!®
Educating the Healthcare Community About Safe Medication Practices

Clear communication is critical when a ketogenic diet is used for seizure control

Problem: A treatment option for both pediatric and adult patients with intractable epilepsy is the ketogenic diet, which has been used since the 1920s. Although additional antiepileptic drugs are now available, 35% of patients remain refractory and there is a continued interest in the diet as a treatment option. The ketogenic diet has a high fat and low carbohydrate content. Similar to a state of fasting, it promotes the use of fats as a primary fuel source, and through catabolism of fatty acids in the liver, it produces ketone bodies resulting in a state of ketosis. There have been different theories on the exact mechanism of the diet to reduce seizures, some suggest it modifies neuronal metabolism and excitability to reduce the seizure frequency, or that the ketone bodies themselves have an anticonvulsant effect. The decision for a patient to start such a stringent diet should be in collaboration with a dietitian and neurologist.[1-3]

The success of the ketogenic diet relies on the restricted consumption of carbohydrates to promote a state of ketosis. Despite the benefits of reduced seizures that patients may experience, they may discontinue this high-fat diet because it can be unpalatable (e.g., butter, heavy whipping cream, mayonnaise, canola oil, olive oil). Adult patients particularly have difficulty maintaining the ketogenic diet because of the severe restrictions.[4] Another challenge is that patients willing to try the ketogenic diet are often already on several medications for seizure control. Practitioners must carefully evaluate each medication's dosage formulation to minimize the amount of carbohydrates as much as possible, avoiding the need to further restrict the limited amount of carbohydrates in the patient's diet.

Most medications contain carbohydrates, but information about the exact amount is not readily available to practitioners on the package label, in prescribing information, or in the electronic health record (EHR). Oral liquid medications (especially suspensions) and chewable tablets, typically preferred for children, often have higher amounts of carbohydrates than tablets and capsules. For example, according to the *Carbohydrate Content of Medications* table in UpToDate Lexidrug,[5] **CHILDREN'S TYLENOL** (acetaminophen) 160 mg/5 mL suspension contains less than 5 grams of carbohydrates per 5 mL, compared to **TYLENOL** (acetaminophen) 500 mg extra strength caplet which contains less than 0.125 grams of carbohydrates per caplet. However, there may be significant variations in the carbohydrate content of medications, dependent upon the varying inactive ingredients used by brand and generic manufacturers. So, practitioners often need to call each manufacturer directly, which can be time-consuming. While the exact quantity of carbohydrates that may precipitate seizures is unknown, some suggest limiting carbohydrates from medications to 1 gram per day.[6] If practitioners fail to account for the carbohydrate content of medications provided to patients on the ketogenic diet, the diet may fail (i.e., taking the patient out of ketosis) putting the patients at risk for seizures. Below is one example of a medication safety issue reported to ISMP that involves a patient on a ketogenic diet.

An infant with non-ketotic hyperglycemia and epilepsy had recently been placed on a ketogenic diet. When the infant was admitted to the hospital, a prescriber ordered 40 mg of ***CARNITOR*** *(lev****OCARN****itine) 1 g/10 mL by mouth four times a day. When completing the patient's medication history, the pharmacist noted that the patient should receive* ***CARNITOR SF*** *(sugar-free lev****OCARN****itine) which is not only sugar-free but also carbohydrate-free. The nurses administered the correct formulation while an inpatient. However, at discharge, the physician prescribed Carnitor rather than Carnitor SF and did not communicate with the outpatient pharmacy that the patient*

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Child received an entire multiple-dose vial of a COVID-19 vaccine. There is a risk of accidentally giving the entire undiluted vial of Pfizer-BioNTech coronavirus disease 2019 (COVID-19) vaccine for children aged 6 months to less than 5 years. The vaccine is available in cartons of 10 multiple-dose vials that have yellow caps and labels with yellow borders (**Figure 1**). The vials must first be diluted with 1.1 mL of 0.9% sodium chloride injection. This provides 3 doses of 3 mcg (0.3 mL) each. However, there is also a single-dose vial for children who are 5 years old to under 12 that does not require dilution. Both products may arrive frozen and must be thawed prior to use. Refer to the prescribing information for additional instructions.

Figure 1. Each multiple-dose vial of the Pfizer-BioNTech COVID-19 vaccine for ages 6 months to less than 5 years must be diluted prior to use and contains 3 doses of 0.3 mL each.

There is a risk that some users may confuse the two formulations and think that neither needs to be diluted. In a recent vaccine error report sent to ISMP, a prescriber ordered COVID-19 vaccine 0.3 mL (3 mcg) intramuscularly for an 18-month-old child. In this case, a medical assistant entered the proper vaccine in the child's electronic health record (EHR) but prepared and administered the entire undiluted contents of the vial. The carton and vial state, "DILUTE PRIOR TO USE," and the vial states, "after dilution—3 doses of 0.3 mL," but this may be overlooked by practitioners.

The Pfizer-BioNTech COVID-19 vaccine intramuscular injection 2024-2025 formula for ages 5 years to less than 12 years has

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was on a ketogenic diet. The outpatient pharmacy dispensed Carnitor, which the patient's mom administered to her child. Unfortunately, the infant began to have increased seizure activity and was readmitted to the hospital, where the error was identified.

Safe Practice Recommendations: The complexity of medication regimens for patients on the ketogenic diet calls for a coordinated approach. Consider the following recommendations to prevent patient harm.

Avoid these inactive ingredients. Medications can be a source of hidden carbohydrates due to the fillers or sweeteners that are part of the drug formulation, especially liquid and suspension formulations created for children. Refer to resources such as ketodietcalculator.org and UpToDate Lexidrug *Carbohydrate Content of Medications* when evaluating drugs or formulations to order and dispense to patients.[5] Below are some common carbohydrates used in prescription and over-the-counter (OTC) medications that practitioners should avoid for patients on a ketogenic diet:[7,8]

- Glycerin
- Maltodextrin
- Organic acids (e.g., ascorbic acid, citric acid, lactic acid)
- Propylene glycol
- Sugars (e.g., dextrose, fructose, glucose, lactose, sucrose, sugar, palm sugar, cane syrup, cane juice, corn syrup, honey)
- Sugar alcohols (e.g., erythritol, isomalt, glycerol, mannitol, maltitol, sorbitol, xylitol)
- Starches (e.g., cornstarch, hydrogenated starch hydrolysates [HSH], pregelatinized starch, sodium starch glycolate)

Communicate with outpatient pharmacies. When a patient is on a ketogenic diet, prescribers must coordinate outpatient medication management with outpatient pharmacies. Ask patients where they typically fill their prescriptions and collaborate with the outpatient pharmacy to ensure they understand the patient's unique needs. Check if the pharmacy has a method to "flag" patients on the ketogenic diet, or how this information will be documented/communicated. Ensure the prescription designates that the patient is on a ketogenic diet, and requires a specific medication (e.g., dosage formulation, national drug code [NDC], and/or manufacturer). For patients that require a partial tablet dose, standardize prescription instructions for the patient using a template (i.e., "Crush and mix 1 tablet in # mL of water. Give # mL").

Evaluate computer functionality. Work with vendors and internal system analysts/developers to ensure your EHR or pharmacy dispensing system identifies that a patient is on the ketogenic diet (e.g., diagnosis, banner bar, alert). Build customizable clinical decision support (CDS). If a new medication is ordered, the system must clearly identify that the patient is on the ketogenic diet so the prescriber and pharmacist are aware and selects the most appropriate formulation. Vendors should also enhance the ability for practitioners to select a formulation that is ketogenic diet friendly (i.e., no or low carbohydrates) or alert users if a medication formulation is inappropriate for a patient on the ketogenic diet (e.g., drug-disease interaction checking). Without such safeguards, some organizations have implemented workarounds such as documenting dextrose as an allergy to communicate that the patient is on the ketogenic diet and cannot receive medications with dextrose. Consider building a ketogenic diet order set with the most common medications prescribed for this patient population. For example, since the diet typically provides only small amounts of fruits, vegetables, grains, and dairy, patients should take a low-carbohydrate multivitamin and mineral supplement daily.[1] Specific details of the medication that the prescriber ordered, and that pharmacy should dispense (e.g., dosage formulation, NDC, and/or manufacturer) must be clearly visible on electronic prescriptions and all applicable screens. Pharmacies should test their dispensing systems to ensure that a prescription for a carbohydrate-free NDC will not match to or substitute a regular carbohydrate-containing formulation.

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blue vial caps and labels (**Figure 2**). These are available as single-dose vials that should NOT be diluted. They each contain 1 dose of 0.3 mL (10 mcg).

If your practice purchases Pfizer-BioNTech COVID-19 vaccines, build order sentences with guidelines in the EHR that will help practitioners select the correct product and dose based on age; include preparation instructions that specify if the product is a single-dose vial that should not be diluted or a multiple-dose vial that must be diluted. Store vaccines in separate bins or containers based on name and formulation. Consider the use of signage in storage locations and/or auxiliary labels on the cartons and vials that specify if dilution is or is not required.

Figure 2. Pfizer-BioNTech COVID-19 vaccine for ages 5 years to less than 12 years is supplied as a 0.3 mL single-dose vial that should not be diluted.

Provide practitioners with preprinted labels to affix to the prepared syringe specifying the vaccine name, indicated age range, and dose. Use barcode scanning before vaccine administration. Educate staff that the vaccine for patients 6 months to less than 5 years, must be diluted and once diluted, the vial will contain 3 doses. They should administer a 0.3 mL (3 mcg) dose. The vaccine for patients 5 years to less than 12 years, should not be diluted and they should administer a 0.3 mL (10 mcg) dose. Consider sharing immunization resources such as the tables provided by the Centers for Disease Control and Prevention (CDC).

Patient education critical to ensure correct preparation of Nemluvio. In August 2024, the US Food and Drug Administration (FDA) approved **NEMLUVIO** (nemolizumab-ilto) to treat adult patients with prurigo

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Reconcile medications. Evaluate the medication reconciliation process as it relates to orders for patients on the ketogenic diet. Add scripting to your medication reconciliation procedures that specifically asks patients about prescription medications and OTC medications (including herbals and dietary supplements). When documenting which medication the patient is taking, make sure to include the specific dosage formulation. Enhance the process to capture the product's NDC and/or manufacturer as this information is critical when determining the product's carbohydrate content.

Differentiate ketogenic formulations. Review medication storage locations and ensure the products are clearly labeled (e.g., "ketogenic diet preferred").

Connect patients with ketogenic diet services. Connect patients with ketogenic diet support services to help them manage their carbohydrate intake at home.

Educate practitioners. Provide practitioners who will be involved with ordering, dispensing, administering, and monitoring patients on a ketogenic diet with education and a competency assessment to complete. Below are some side effects patients on a ketogenic diet may experience:[1,2,8]

- Constipation (consider **MIRALAX** [polyethylene glycol] since it is carbohydrate-free)
- Kidney stones (side effect of both the diet and certain antiseizure medications [e.g., topiramate, zonisamide])
- Decreased bone density if on the diet long term (consider vitamin D/calcium supplementation, bone density monitoring)
- Depleted vitamin stores (consider multivitamin and mineral supplementation) and particularly carnitine stores (consider lev**OCARN**itine)
- Acidosis (may need to supplement with sodium bicarbonate)
- Hypoglycemia (consider an appropriate volume of juice or amount of dextrose)

Educate patients. Provide patients on the ketogenic diet with documentation of their medication list including the specific dosage formulation, NDC, and/or manufacturer, and encourage them to share this information with practitioners at all applicable care settings (e.g., primary care provider, hospital admission, pharmacy) as part of their medication history. Encourage patients to obtain medications from a single outpatient pharmacy that is familiar with their unique needs and that can consistently stock the formulation they require. Since a partial dose of a tablet may be needed for pediatric patients, educate patients and families about how to crush and mix the tablet, and how much volume to prepare and administer using the teach-back method. Educate patients about the need for minimal carbohydrate content and how this will impact their medication regimen. Teach them how to read medication labels and instill the importance of reading the labels for all products, including OTC products. Patients should examine medication labels and look for inactive ingredients to avoid, knowing that sugar-free does not always equate to carbohydrate-free. Teach them that they should avoid liquid medications unless they discuss this with their prescriber, pharmacist, or dietitian. Provide educational resources such as the *Charlie Foundation for Ketogenic Therapies* website.

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nodularis. It is available as a single-dose, prefilled, dual chamber pen. One chamber contains 30 mg of lyophilized powder while the other contains sterile water for injection (the diluent). The lyophilized powder must be reconstituted with the sterile water for injection prior to administration. While we have not received any error reports, we wanted to bring your attention to the uniqueness of the pen design and some of the preparation warnings and steps that must be relayed to patients.

If the pen has been dropped or damage can be seen, patients should not use the pen. Like many other refrigerated medications, Nemluvio should be removed from the refrigerator and allowed to reach room temperature over 30 to 45 minutes prior to use. To initiate the reconstitution process, hold the pen upright (gray cap pointing upwards) and turn the activation knob to the "unlock" position. This begins the transfer of sterile water into the powder chamber. Watch the inspection window until the gray rod has stopped moving. **According to the instructions for use, it is critical that patients do not shake the pen before the gray rod has completely stopped moving.** Shaking the pen before the gray rod has completely stopped can impact the medication dose. When the gray rod has completely stopped, the pen should then be shaken up and down for 30 seconds to dissolve the medication powder. Then, wait for 5 minutes for any bubbles to decrease and the powder to dissolve completely. If the medication has not dissolved completely, the patient is to shake the pen up and down again for 30 seconds and then wait 5 more minutes. It is normal for a small foam layer or a few small air bubbles to remain in the dissolved medicine. When ready to inject, hold the pen upright and remove the gray cap by first twisting until the orange needle guard

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Celebrating the 2024 Cheers Award winners

This month, ISMP celebrated the 27th annual **CHEERS AWARDS**, which recognize individuals, organizations, and groups that have demonstrated extraordinary commitment to advancing the science and study of patient safety. This year's winners were honored at an awards ceremony held on December 10, 2024, at the Civic Theater in New Orleans, Louisiana. Please join us in celebrating the amazing accomplishments of this impressive group.

CHEERS AWARDS Winners

The Quality Improvement Team at **Cook Children's Health Care System** in Fort Worth, Texas, received a **Cheers Award** for significantly reducing the number of vaccine errors within their pediatric network. The team was formed to address errors related to immunizations, especially those involving complex vaccine age eligibility and vaccine series interval timing. They collaborated with the information technology department to integrate a clinical decision support (CDS) tool into the electronic health record system that alerts healthcare providers to potential errors in real time. Since it was implemented, more than 9,000 inappropriate vaccine orders have been successfully averted by following the guidance provided by the clinical alerts. A substantial decrease in error rates was noted for most vaccines, with the most pronounced decline for the hepatitis A series, which achieved an impressive 91% reduction. The team also implemented a dashboard-based monitoring system for patient safety to ensure continuous improvement and oversight.

The Perioperative Opioid Stewardship Research Program at the **Hospital for Sick Children (SickKids)** in Toronto, Canada, was honored for improving the way opioids are managed during post-surgery hospital discharge. The program aims to address overprescribing of opioids in pediatrics, minimize the volume of unnecessary opioids entering the community, and decrease the volume of unused opioids. The program team identified risks, modified practice standards, re-evaluated processes, and expanded their reach to other diagnoses. Their achievements include using technology and quality improvement methodology to safely decrease the amount of unused opioids retained by patients in the home from 83% to 17% and creating a new pathway to facilitate the return and disposal of unused opioids. They also addressed language barriers and improved access by translating all educational documents into the ten most used languages in their surgical population, allowing more families to participate.

LIFETIME ACHIEVEMENT AWARD Winner

One of the highlights of the evening was the presentation of the 2024 **MICHAEL R. COHEN LIFETIME ACHIEVEMENT AWARD**. This award has recently been re-dedicated in honor of ISMP Founder and President Emeritus Michael R. Cohen and is given to individuals who have made ongoing contributions to patient safety throughout their careers. This year's honoree, ***David W. Bates, MD, MSc***, an internationally renowned safety expert, has conducted groundbreaking work evaluating the incidence and preventability of adverse drug events. He has demonstrated that information technology such as computerized prescriber order entry (CPOE) and CDS can decrease the risk of serious medication errors, and CPOE has now been implemented in health systems and facilities across the United States. Dr. Bates has published more than 1,200 peer-reviewed papers that have been cited over 155,000 times and is among the 400 most cited biomedical researchers. His research has been referred to in Health Care Financing Administration regulations, the Medicare Patient Advisory Commission's 1999 Report to Congress, and the Institute of Medicine's report *To Err is Human*.

Thanks and Looking Forward

We would like to express our gratitude to all of the organizations and individuals who attended and/or supported this year's **CHEERS AWARDS**. Visit the Cheers Event webpage for a list of contributors and winners; you can also make a Donation to help support ISMP's lifesaving efforts.

ISMP wishes you happy holidays, and we look forward to continuing to work together on preventing errors and keeping patients safe in 2025.

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pops up, then pull the gray cap off. The patient should not remove the cap by just trying to pull it off as this could damage the device. If the gray cap cannot be removed, ensure the activation knob is turned completely to the unlock position. Remind patients to not remove the gray cap until the medication has been dissolved and the injection site prepared to prevent accidental needlesticks.

Healthcare practitioners should use the teach-back method to educate patients and verify that the patients are able to prepare the pen and administer the medication correctly.

Special Announcements

ISMP survey on parenteral nutrition (PN)

We are conducting a short survey about PN including the usage and safety of multi-chamber bag parenteral nutrition (MCB-PN) and patient-specific compounded (i.e., custom) PN. Please take 10 minutes to complete this **survey** by **January 23, 2025**.

Expanding Our Impact | ECRI acquires The Just Culture Company

ECRI is excited to welcome The Just Culture Company to its portfolio of solutions. For a limited time, we are offering special pricing on Just Culture training. To learn more about The Just Culture Company and to register for one of the programs to take advantage of the discounted pricing, click here.

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Report medication and vaccine errors to ISMP: Please call 1-800-FAIL-SAF(E), or visit www.ismp.org/report-medication-error. ISMP guarantees the confidentiality of information received and respects the reporters' wishes regarding the level of detail included in publications.

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Happy Holidays from the staff, Board of Directors, and Advisory Board at the Institute for Safe Medication Practices (ISMP). We wish you joy, health, and happiness this holiday season!

Production of this peer-reviewed newsletter would not be possible without the assistance of a reliable and talented clinical advisory board. As 2024 nears an end, we want to thank each of the following members of the advisory board for their dedication to making this newsletter a valuable medication safety resource for clinicians.

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