NEW HORIZONS IN CANCER TREATMENT
Dear Colleagues,

Children Win - First Amendment Triumphs! It is indeed a great pleasure to write this note. We heard this month that the State of Florida will not appeal the Federal court decision that protected physicians' first amendment right and allow us to continue to protect our children. The Florida Gun Gag law is DEAD, and not a minute too soon. It feels so good to say this instead of the more routine news about "a child dead due to accidental shooting" or "several children are dead because of a mass shooting". We can continue to ask parents about firearms in the home and continue to provide anticipatory guidance in attempts to make homes with firearms safer.

This was a victory for advocacy and common sense.

This has been a long road. Our crack legal team showed grit and intelligence and those of us who had the privilege to work with them never doubted that they will ultimately lead us to success through this legal battle. In addition to our legal team, there are so many people and organizations inside and outside of the Florida Chapter who deserve credit and our gratitude. Most of all the credit goes to our members who were so patient, oh so patient, through this long six year journey.

This is actually a great victory for all children in the United States. As they say "as goes Florida so goes the whole country", and this is true outside an election year. Since several other States have similar laws in their legislatures, this victory will hopefully discourage these states from enacting nonsensical laws that not only chill our first amendment rights but also put our children at increased risk.

Hopefully this is also the end of legislators interfering in our examination rooms and preserving the sacred, time-honored patient-physician relationship.

Now is the time for celebration not just for our victory but in our system of checks and balances. In recent months, courts have made it abundantly clear that the government cannot take away our constitutional rights and cannot discriminate on religious grounds. This is just one battle won. The war to protect our children must continue either by ensuring common sense laws protect our children from firearm injuries or making sure that children continue to have easy access to healthcare so that parents can receive anticipatory guidance. This is all a continuum.

We have many other battles on behalf of our children. We cannot rest on our laurels, until there are no accidental firearm death tragedies in children, and no Sandy Hooks and Columbines. There is a lot more that needs to be done. Advocacy is critical and getting engaged in organized medicine will enhance our ability to practice medicine better, keep our children healthier and safer, and in the final analysis, advance medicine.

Regards,

Mobeen H. Rathore, MD, FAAP
with its genetics, not its histology or the organ from which it is derived. Based on these genetic and molecular classifications, and molecular characteristics (1-3). These classifications acknowledge that cancer is a disease that behaves in accordance with the immune system. The introduction of monoclonal antibodies capable of activating the patient’s own immune system to attack specific targets on the tumor cell or targets in the microenvironment of the tumor. Immunotherapy uses antibodies and small molecule inhibitors approved by the FDA and their indications are provided in Table 1. As the same mutations are found in different cancers, the drug’s indications broaden. The success of drugs such as imatinib that target the cancer genome has led to the rapid development of new inhibitors targeting various cancer mutations and their associated oncoproteins; an abbreviated list of small molecule inhibitors approved by the FDA and their indications are provided in Table 1. Aside from TKIs, other targeted small molecule therapies have been developed. All-trans-retinoic acid (ATRA) has substantially improved survival for patients with acute promyelocytic leukemia (APL) which is caused by the PML-RARA balanced translocation t(15;17). ATRA leads to the terminal differentiation of APL blasts. For adult patients with low risk APL, the combination of ATRA with arsenic trioxide (ATO), another differentiating agent, is quickly becoming the preferred treatment strategy, allowing patients to forego traditional chemotherapy and to benefit from improved survival. High risk patients continue to require ATRA plus chemotherapy. Various other targets are currently exploited as well. Cancer cells tend to have various mechanisms to evade apoptosis. Proteasome inhibition with agents such as bortezemib is currently used in adults with multiple myeloma and is in trials for various other cancers. Inhibition of B-cell lymphoma 2 (BCL-2), an anti-apoptotic protein that cancer cells rely on to evade cell death, is currently approved for chronic lymphocytic leukemia (CLL). Blockade of PD-1/PD-L1, an important signaling pathway used to drive growth and that is used by various cancers, has exhibited effectiveness against subependymal giant cell astrocytomas.
cell astrocytomas in tuberous sclerosis and is used in conjunction with other therapies in other cancers. In addition to genetic mutations driving tumor growth, cancer cells exhibit many epigenetic changes altering the rate of transcription of various genes. Histone deacetylase (HDAC) inhibitors and hypomethylating agents which target these epigenetic changes are currently used to treat myelodysplastic syndromes, lymphoma and other cancers. Also, combinations of targeted inhibitors are currently used to shut down multiple pathways, thereby improving efficacy. The combination of vemurafenib, a BRAFV600E inhibitor, with cobimetinib, a MEK inhibitor, for the treatment of BRAF V600E positive metastatic melanoma was found to be superior with cobimetinib with placebo, leading to FDA approval of this combination to treat metastatic melanoma in 2015(8).

Table 1. Abbreviated list of FDA approved small molecule inhibitors for cancer

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<th>TARGET</th>
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<td>2013 Metastatic NSCLC</td>
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<td>ALK, ROS1</td>
<td>2011 NSCLC</td>
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<td>DABRAFENIB MESYLA TE</td>
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Table 2: Abbreviated list of FDA approved monoclonal antibodies for cancer

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Trial design, including proper drug selection and interpretation of results, remains exceedingly important with the rapid influx of new small molecule inhibitors, especially in pediatric cancer patients where the small number of patients makes accrual into trials difficult. For example, the fms-related tyrosine kinase 3 internal tandem duplication (FLT3-ITD) mutation in acute myelogenous leukemia (AML) confers an especially poor prognosis in pediatric and adult AML patients. A pediatric trial with an early FLT3-3 inhibitor, lestaurtinib, was initiated by the Children’s Oncology Group (COG) but was closed early after it failed to demonstrate benefit in adults with recurrent FLT3 positive AML(9). Instead, the COG is currently conducting a phase III randomized trial, with the multi-kinase inhibitor sorafenib plus standard of care chemotherapy and HSCT for FLT3-ITD positive AML. Since the start of the COG trial, a separate randomized trial using sorafenib in young adults with AML revealed improved progression-free survival, but not overall survival(10). Recently, a phase III trial in adults with FLT3 positive AML using another multi-kinase inhibitor, midostaurin, plus chemotherapy and HSCT, showed improved median overall survival vs. the standard of care (74.7 months vs. 25.6 months) in this poor prognosis group(11). Midostaurin is the first drug shown to improve survival in AML patients in decades, and these results led to a Breakthrough Therapy designation by the FDA. Second generation FLT3 inhibitors are currently in trials and investigators are optimistic that they will be even more efficacious. It will likely be many years before we identify the optimal treatment for pediatric high risk designation by the FDA. Second generation FLT3 inhibitors are currently in trials and investigators are optimistic that they might achieve new effective therapies for many pediatric cancer patients with improved side effect profiles.

IMMUNOLOGIC THERAPY FOR CANCER:

Immunotherapy uses antibodies or the cells of the immune system to attack specific targets on the tumor cell or targets in the microenvironment of the tumor. Most immunotherapies to date come in the form of monoclonal antibodies (mAb). MABs
are monospecific antibodies created to target a specific antigen. These mAbs can induce cell death in various ways including: flagging the cell for attack by macrophages or for antibody-dependent cell-mediated cytotoxicity by natural killer cells and monocytes; induction of cell-cycle-dependent cytotoxicity; and through direct signaling of pathways leading to apoptosis. mAbs can be attached to radioisotopes or conjugated directly to the immune system. mAbs end in “-mab”. Table 2 is an abbreviated list of FDA-approved mAbs directed against cancer cells.

mAbs are currently used alone or in combination with chemotherapy to treat various cancers. Rituximab targets CD20, which is expressed on mature B cells and on the surface of various non-Hodgkin (NHL) and Hodgkin lymphomas (HL). In children with high risk neuroblastoma, the addition of dinutuximab, an anti-CD123 mAb, to front line chemotherapy, surgery, and radiation (along with isoretinoin, aka cis-retinoic acid, a differentiating agent), improved both event free survival and overall survival(2). Dinutuximab is the first FDA approved drug for patients with high risk neuroblastoma. Other examples of mAbs currently in use for cancer are herceptin for HER-2 Neu positive breast cancers and cetuximab, the anti-EGFR mAB, for colon cancer, non-small cell lung cancer and head and neck cancers.

Antibody-drug conjugates (ADC) consist of a toxic agent or drug attached to a mAb. When the mAb attaches to the surface of the cell, it undergoes receptor-mediated endocytosis, passing the antibody and drug into the cytosol where the drug can exhibit its effect. Because ADCs are targeted to the cell of interest, they can incorporate drugs that have far greater toxicity than would be possible to administer with systemic therapies. Brentuximab vedotin is an ADC that targets CD30 conjugated with monomethyl aurostatin E, an anticancer agent. CD30 is expressed on malignant cells of patients with HL and some NHLs, and brentuximab vedotin has been used successfully to treat patients with relapsed HL; the FDA has approved the drug for this indication (13). Trials are currently underway in adult and pediatric patients for the upfront use of brentuximab vedotin combined with chemotherapy in patients with HL. Other conjugates that can be attached to mAbs include radioisotopes that can deliver targeted radiation to tumor cells.

Monoclonal antibodies can also be conjugated with a second antibody in order to bring the tumor cell into contact with the immune system. Blinatumomab is a bispecific mAb conjugated with anti-CD19, a receptor found on pre-B-cell leukemias and immature B-cells, and anti-CD3 which is expressed on T-cells and functions as part of the T-cell receptor. This structure binds and activates the T-cell against the leukemia cell leading to targeted killing of the malignant cell by the immune system. In a single arm phase 2 trial of adult patients with relapsed or refractory pre-B ALL — a group with very poor prognosis — 32% achieved a complete remission (14). Based on these results blinatumomab was granted accelerated FDA approval. A confirmatory phase 3 trial in adults was recently stopped early after meeting predefined futility results of the study are pending(15). In addition, a phase 3 trial in relapsed and refractory pediatric ALL patients is underway. Improved understanding of the mechanisms that normal cells use to suppress an autoimmune response has also led to the development of mAbs capable of activating the patient’s own immune system against cancer cells. This process is called checkpoint inhibition. Normal cells express antigens on their surface such as programmed death ligand 1 (PD-L1) and PD-L2 which interact with receptors on the T-cell such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) to signal the T-cell not to attack. These antigens on normal cells and the immune system are called the immune checkpoint. Cancer cells evade the immune system by expressing these checkpoint antigens on their cell surfaces, thereby preventing the T-cell from responding to the abnormal tumor antigens on the tumor surface that would normally activate the T-cell. By targeting CTLA-4, PD-1 or PD-L1 with mAbs, the T-cell can identify the tumor as non-self and kill the tumor cell. Side effects are those that would be expected from an autoimmune response. Checkpoint inhibition, is currently in clinical trials for various cancers such as metastatic melanoma, relapsed or refractory HL, and metastatic non-small cell lung cancer. Trials are currently underway in several pediatric cancers. While not all patients respond to these therapies, many who do respond have impressive long term results. It is unclear why some patients respond to checkpoint inhibition while others do not respond. Further study is necessary to determine who will be the best candidates for checkpoint inhibition, and how to incorporate it into the upfront treatment of cancer.

Targeted killing of cancer cells is also possible with adoptive cell transfer (ACT), the transfer of cells into a patient. Examples of ACT are cytotoxic T-cells (CTL) and chimeric antigen receptor T-cells (CAR-T). These T-cells are isolated from either the patient or a donor, manipulated and grown in the laboratory, and then infused into the patient to multiply and attack the malignant cells. Anti-EBV CTLs, T-cells that are exposed ex vivo to EBV antigens, have been used successfully against EBV positive post-transplant lymphoproliferative disease. CAR-T cells are that genetically modified ex vivo to express a chimeric receptor called antigen receptors (CAR) towards a specific tumor antigen. Anti-CD19 CAR is currently in trials for the treatment of pre-B-cell ALL, chronic lymphocytic leukemia (CLL) and NHLs. In a trial of CAR-T at the Children’s Hospital of Philadelphia for patients with relapsing or refractory pre-B-ALL, 27 of the 30 patients achieved a complete remission with sustained remissions in 19 of 27 patients (16). Similarly, in a dose-escalation trial performed by the Pediatric Oncology Branch of the National Cancer Institute for relapsed or refractory ALL or NHL, 14 of 20 patients had a complete response (17). The most common side effect of CART was systemic inflammatory reaction which is also seen with blinatumomab, secondary to cytokine release during T-cell killing of tumor cells. Currently, adoptive cell transfer is only available for patients in clinical trials.

CONCLUSION:

The introduction of various small molecule inhibitors and immunotherapies has led to a new sense of optimism in our fight against cancer. With the many new drugs now available against cancer, future trials will be increasingly important in identifying the optimal mix of small molecule inhibitors, mAbs and traditional therapies for individual patients. Furthermore, other targeted therapies such as anti-cancer vaccines, one which is already approved for prostate cancer, are in the process of pre-clinical and early phase trials for pediatric patients. President Barack Obama, during his 2016 State of the Union address, announced the creation of a new national body to be led by Vice President Joe Biden. The monograph’s goal of increasing participation in clinical trials, especially in pediatric cancers, promise to speed the process of bringing these new medications to our pediatric patients.
INTRODUCTION

Given the increasing incidence and prevalence of type 1 diabetes (T1D) and type 2 diabetes (T2D), it is important for primary caregivers to appreciate the timely diagnosis of diabetes and to be proficient in basic new onset diabetes management strategies. According to the SEARCH for Diabetes in Youth Study, nearly 200,000 children in United States (US) live with diabetes, with more than 85% having T1D and at least 12% having T2D (1). Due to the recent obesity epidemic and the different ethnicities seen in typical US clinics, it can often be challenging to distinguish between T1D and T2D. Patients with either T1D or T2D can have considerable overlap at presentation including body habitus, signs of insulin resistance, and presence of ketones. In this article, we utilize case presentations to discuss important aspects of diabetes diagnosis, differentiate T1D versus T2D, and review management of new onset diabetes in the primary care setting.

CASE 1

A 12 year old Caucasian male presents to your clinic complaining of a two week history of progressive fatigue and vomiting. He also has been drinking more water than usual and waking up several times a night to void. He has lost 10 pounds since his last visit two months ago. His family history is positive for hypothyroidism in his maternal grandmother. On physical examination, he appears thin and tired with sunken eyes and tacky mucus membranes. He is tachycardic with regular heart rhythm. His breathing is rapid and deep. His point of care (POC) blood glucose (BG) is 540 mg/dL. Urinalysis is performed and has a specific gravity of 1.029 with 3+ glucose and 3+ ketones. You diagnose your patient with T1D on the basis of his ethnicity, history, presentation, and laboratory results. Diagnostic criteria for diabetes include any one of the following:

1. Fasting blood glucose of at least 126 mg/dL.
2. Random blood glucose of at least 200 mg/dL and symptomatic.
3. Blood glucose of at least 200 mg/dL 2 hours post standard oral glucose load (75g).
4. Hemoglobin A1c greater than 6.5%.

Table 1. Criteria for Diagnosing Diabetes* *(Adapted from American Diabetes Association, 2016 (2))

Once the diagnosis of diabetes is established, it is critical to determine the severity of your patient’s illness. Severity of dehydration and acid-base status (either measured or assumed based on the patient’s presentation) should be utilized to determine next steps in new onset diabetes management. Given this patient’s clinical presentation, hospital or emergency department (ED) transport should be coordinated as therapy is being initiated. As this patient is at least 10% dehydrated, and is demonstrating Kussmaul breathing (deep heavy respirations to provide respiratory compensation for a metabolic acidosis), ED transport should be coordinated as therapy is being initiated. If possible, an IV should be placed in your office and one 20 mL/kg normal saline bolus should be given to ensure hemodynamic stability. Once hemodynamic stability is re-established, IV fluids containing normal saline and 40mEq potassium (as long as the patient is not anuric) should be started at twice the calculated maintenance rate (3). Notably, insulin does not need to be initiated in the clinic and should never be given as a bolus in a patient with diabetic ketoacidosis (DKA). Similarly, bicarbonate should not be given to children with DKA. Both insulin boluses and bicarbonate therapy in children with DKA are associated with increased risk of cerebral edema.

As you are preparing to send the patient to an ED, clinic based labs, if available, will provide additional assistance in evaluating the patient. If a POC blood gas is drawn, a pH less than 7.30 and a bicarbonate less than 15 further supports the diagnosis of DKA. Patients with moderate to severe DKA will always require hospital or ED management while mild DKA may be managed in the outpatient setting (Table 2). Electrolytes should also be obtained. An HbA1c of 6.5% or higher is diagnostic of diabetes. Finally, autoantibodies including islet cell antibodies (ICA), insulin autoantibodies (IAA), glutamic acid decarboxylase (GAD), insulinoma associated-2 antibodies (IA-2), and zinc transporter 8 (ZnT8) can be sent to a lab to confirm the presence of autoimmunity. At least one autoantibody will be positive in 98% of patients with T1D (6). If your clinic is unable to obtain autoantibodies, they can be drawn shortly after the initial diagnosis for confirmation.

Table 2. Criteria for Diabetic Ketoacidosis* *(Adapted from Umpierrez et al. 2002 (4))

Pediatricians should be aware that DKA is associated with an increased risk of cerebral edema in children. While cerebral edema occurs in less than 1% of episodes of DKA, cerebral edema is associated with a 40-90% mortality rate. The most prominent sign of cerebral edema is altered mental status, so any patient with new onset T1D and DKA who presents with abnormal sensorium requires emergency treatment with IV mannitol (3). Cerebral edema should be diagnosed clinically such that treatment should not be based upon or delayed in order to obtain imaging studies. Improved knowledge of the epidemiology of T1D can help to prevent patients from presenting in DKA. The incidence of T1D peaks in children 5 to 7 years of age and again in adolescence. Unlike most autoimmune diseases, T1D affects males and females equally and family history of diabetes is lacking in more than 85% of newly diagnosed patients (5). Despite ongoing efforts to educate the community and general pediatricians, nearly 30% of patients with new onset T1D will present with DKA (6). Hospitalization is indicated when children present in DKA, if the child is under 2 years of age, or if the family does not have access to appropriate outpatient resources (6). If the patient is clinically stable, without vomiting, dehydration,
mental status changes or acidosis, hospitalization is not required and a same day appointment should be scheduled with a pediatric endocrinologist who will provide appropriate education and initiate an insulin regimen. Initial education focuses on skills and concepts immediately necessary for management including blood glucose checks, insulin administration, and recognizing and treating hypoglycemia or ketonuria. More extensive teaching is typically provided in subsequent visits with the endocrinology team over the following days and weeks.

**CASE 2**

An 18 year old African American female presents to the emergency department. She complains of progressively worsening headache, dizziness, and weight loss over the past 5 months. On further questioning, she notes that she had increased urination and thirst for the past several weeks, but over the past two days, her urine output has decreased significantly. She has intractable vomiting, abdominal pain, and decreased appetite. On review of systems, you learn that she has intermittent blurry vision and frequent skin infections that are slow to heal. On your examination, she has obesity with a body mass index (BMI) of 40, acanthosis nigricans over the back of her neck and in her axillae, and her vital signs include a pulse of 120, blood pressure of 140/80, and dry mucus membranes. You decide to obtain a POC BG which reads “high” (greater than 600 mg/dl on the glucose meter). Next, you obtain a urinalysis which shows a specific gravity of 1.030, 3+ glucose, and trace ketones. Laboratory studies include a blood urea nitrogen (BUN) of 35 mg/dl, creatinine of 1.2 mg/dl, sodium of 149 mEq/L, potassium of 3.9 mEq/L, serum osmolality (Osm) of 340 mOsm/kg, and a bicarbonate level of 18 mEq/L, all of which are consistent with T2D and hyperosmotic hyperglycemic syndrome (HHS) (Table 3).

T2D is due to a progressive insulin secretory defect with underlying chronic insulin resistance resulting in hyperglycemia, hyperlipidemia, hypertension, and many other complications. Both insulin resistance and insulin deficiency arise through a combination of genetic and environmental influences, making it difficult to determine the exact etiology for each patient. Over the past 30 years, the prevalence of childhood obesity has increased dramatically, making T2D a rising concern in the pediatric population. Results from the 2007-2008 NHANES show that an estimated 16% of children and adolescents ages 2 to 19 had a BMI greater than the 95th percentile for age, which is doubled from 20 years ago (7). T2D is more prevalent in Hispanics, African Americans, Native Americans, and Asian Americans and is usually diagnosed in patients who are largely asymptomatic.

HHS is a rare but serious presentation of T2D, where BG is above 600, serum Osm is above 320, and there is limited, if any, ketosis. These patients have marked dehydration and will often require high volume fluid resuscitation. As HHS has approximately 25% mortality, patients should have isotonic fluid replacement followed by insulin to restore electrolyte balance. Patients with new onset diabetes with a BG over 250 mg/dl or an Hba1c over 9% require insulin therapy to restore glycemic control (8).

In patients with less critical presentations of T2D (i.e. those with BG is less than 250 mg/dl, Hba1c less than 9%, and no ketonuria), metformin should be started as first line therapy. Metformin remains a first line therapy for T2D as it is extremely economical, provides for a small amount of weight loss, has no associated risk for hypoglycemia, and supports improved insulin sensitivity. Also, in cases of females with polycystic ovarian syndrome (PCOS), metformin improves ovarian function and often allows for normalization of menstrual cycles. Although metformin and lifestyle changes are first line therapy for T2D, many children eventually require insulin for glycemic control. Metformin therapy may also be considered in patients with impaired fasting glucose (100-125), impaired glucose tolerance (two-hour oral glucose tolerance test results of 140-199), or those with Hba1c 5.7-6.4%, especially if their BMI greater than 35%.

Lifestyle changes should be recommended for all patients both at risk for or diagnosed with any type of diabetes. Initial interventions include moderate to vigorous exercise for at least 60 minutes per day and strict dietary monitoring by a nutritionist. Despite these interventions, two prospective studies revealed that treatment with lifestyle modification alone is associated with higher rate of loss to follow up. Other common reasons why lifestyle changes fail include the high rate of depression in teens with chronic disease and the peer pressure teens face to participate in unhealthy activities (8).

Given the lack of efficacy for metformin and lifestyle intervention and the challenges associated with insulin therapy, additional oral therapies may be considered. Recently, the TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) trial showed that metformin alone is inadequate for maintaining glycemic control in the majority of youth with diabetes. The study found that the addition of a thiazolidinedione such as rosiglitazone is superior to metformin alone (7). However, this finding is controversial because although rosiglitazone may have been found effective, it is currently not FDA approved for use in children.

In addition to aggressively treating children who present with T2D, general pediatricians are faced with the challenges of appropriately screening for those children who are at the highest risk for developing T2D. Children who should be screened for T2D include those with a BMI greater than the 85th percentile, in addition to any of the two following risk factors: family history of T2D (1st or 2nd degree relatives), at risk ethnicity as mentioned previously, signs of insulin resistance (acanthosis, PCOS, obesity, or PCOS), or a diabetes in a first or second degree relative. By and large, one of the most important facets of T2D that should be understood by every pediatrician is that complications are far more likely to be present at the time of T2D diagnosis than T1D diagnosis. Careful attention to risk factors and subsequent screening for complications in children with T2D is critical.

**CASE 3**

A 15 year old Hispanic female presents to your office with one month of polyuria and polydipsia. She has an older sister with T1D and came in because she was concerned that she had also developed diabetes. She denies weight loss, headache, fatigue, nausea, or vomiting. On exam, you find she has acanthosis present over the back of her neck and that she is obese with a BMI of 31. Her vital signs are stable and her exam is otherwise benign. You check her BG in the office and find it is 250 mg/dl. A urinalysis demonstrates moderate ketones. At a later date, she is found to have positive ICA and GAD antibodies. Given her presentation, this patient has T1D with features of T2D. As such, it is important to keep in mind that it may sometimes be difficult to identify patients as having classic T1D or T2D without the assistance of diabetes specific autoantibodies. As mentioned in the previous cases, patients with advanced new onset T1D typically present with DKA and patients with T2D more commonly present with hyperglycemia without ketoacidosis. However, ketoacidosis with T2D can occur. In illness or infection, stress can increase secretion of many counter regulatory hormones such as cortisol and further increase insulin resistance. The already impaired insulin secretion is unable to respond to the increased demand, which leads to hyperglycemia and glucose toxicity. Without the presence of diabetes autoantibodies, this case would be somewhat ambiguous. Your patient has insulin resistance secondary to obesity, and as such, it is increased risk for T2D. However, she also has a family history of T2D. As such, the higher risk of developing T1D (1 in 20) when compared to the rest of the US population (1 in 300). This patient can be classified as having T1D with a T2D phenotype. In these cases, treatment requires insulin to prevent development of DKA but may also benefit from the use of metformin to assist with insulin resistance. In addition to screening for T1D comorbidities, these patients should be screened for complications associated with metabolic syndrome and T2D.

**CONCLUSION**

General pediatricians must be vigilant to make appropriate diabetes diagnoses, initiate emergency therapy when needed, and refer children to emergency departments or subspecialists for acute or long term care. As the first point of contact for children, awareness of the laboratory and physical examination features associated with T1D, T2D, and cases with overlapping phenotypes will greatly improve our capacity to provide optimal care for children with diabetes.

<table>
<thead>
<tr>
<th>DKA</th>
<th>HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose 100-1000 mg/dL</td>
<td>&gt;600 mg/dL</td>
</tr>
<tr>
<td>pH &lt;7.3</td>
<td>&gt;7.3</td>
</tr>
<tr>
<td>Bicarbonate &lt;15 mEq/L</td>
<td>&gt;15 mEq/L</td>
</tr>
<tr>
<td>Urine ketone Large</td>
<td>None/trace</td>
</tr>
<tr>
<td>Serum Osm 290 to &gt;320 mOsm/kg</td>
<td>&gt;320 mOsm/kg</td>
</tr>
<tr>
<td>Mental status Variable</td>
<td>Stupor/Coma</td>
</tr>
<tr>
<td>Mortality &lt;5%</td>
<td>25%</td>
</tr>
</tbody>
</table>

*Adapted from Umplemy et al. 2002 (4)*
REFERENCES

ABSTRACT
Cystic Fibrosis is an autosomal recessive disorder caused by mutations at both alleles on chromosome 7 at the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) site. This defect results in abnormal chloride transport across the epithelial cells on mucosal surfaces resulting in decreased hydration of mucus. The symptoms include thick mucus that builds up in the lung, pancreas and GI tract resulting in chronic cough, frequent lung infections, poor growth and weight gain and for some patient’s frequent greasy and bulky stools. Previously a clinical diagnosis, now through newborn screening for cystic fibrosis and research identifying over 1800 mutations at the CFTR location, we can diagnose most patients soon after birth. Once diagnosed patients with cystic fibrosis are identified as to what class/type of CF they have to provide more personalized care.

We currently have two novel targeted drugs that treat the abnormal function at the CFTR location and not just the symptoms. The future focus of CF is looking at genotype and phenotype to improve treatment options and revisiting gene therapy.

INTRODUCTION
Cystic Fibrosis (CF) is an autosomal recessive disorder, caused by mutations at the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) site. This defect results in abnormal chloride transport across the epithelial cells on mucosal surfaces resulting in decreased hydration of mucus. The symptoms commonly include chronic cough, frequent lung infections, poor growth and weight gain and for some patients’ frequent greasy and bulky stools. Previously a clinical diagnosis, now through newborn screening for cystic fibrosis and research identifying over 1800 mutations at the CFTR location, we can diagnose most patients soon after birth. Once diagnosed patients with cystic fibrosis are identified as to what class/type of CF they have to provide more personalized care.

We currently have two novel targeted drugs that treat the abnormal function at the CFTR location and not just the symptoms. The future focus of CF is looking at genotype and phenotype to improve treatment options and revisiting gene therapy.

Although a rare disease, 30,000 people in the US and 70,000 people worldwide have cystic fibrosis and most of them have been classified into one of six classes of cystic fibrosis. Each class of cystic fibrosis has an identified pathogenesis which helps explain some of the variabiliy in disease. Knowing the mutations associated with specific pathology at the CFTR
location has allowed researchers to focus on the abnormal CFTR function. Although we have multiple chronic therapies that we recommend for patients to improve their morbidity and mortality, they focus more on symptom relief and target distal sequelae of cystic fibrosis. Today and tomorrow’s research in cystic fibrosis has advanced and is now focusing on the proximal dysfunction at the CFTR location. Two recent novel targeted drugs, ivacaftor and lumacaftor, have been approved by the FDA to treat CF patients with a specific genetic makeup. It is a great example of personalized medicine and the future of CF care.

GENETICS

The care of patients with cystic fibrosis has changed significantly since the basic genetic defect was discovered in 1989. Cystic fibrosis is a defect of the CFTR gene resulting in defective anion secretion and sodium hyperabsorption across the airway surfaces and submucosal glands.1 This results in mucous obstruction of the lung and commonly affects the GI tract, pancreatic and biliary ducts. Although almost 2000 mutations at the CFTR location have been identified, a much smaller number of mutations account for the majority of cases.2 To understand the current and future therapies for patients with cystic fibrosis, a basic knowledge of CFTR defects is imperative.

The current CFTR mutations are classified into six broad classes which vary based on the mechanism by which they affect CFTR synthesis, trafficking and or function. Please see Figure 1 below which helps document the different classes of CFTR.

CFTR TREATMENTS: MODULATORS AND GENE THERAPY

To understand the current and future therapies for patients with cystic fibrosis, delta F508, was not as successful. About 80% of patients with cystic fibrosis have at least one copy of delta F508. Researchers focused on another type of CFTR modulator called correctors which would be more likely to help patients with the most common class of cystic fibrosis, class II. These agents are thought to improve trafficking of the CFTR protein to the cell membrane. The first corrector, lumacaftor, was identified and used in combination with ivacaftor and after a few phase II and III trials in patients homozygous for delta F508 mutations, it was found to minimally improve lung function but decrease pulmonary exacerbations.16,17 Lumacaftor/ivacaftor was considered a safe agent with few side effects of shortness of breath, upper respiratory tract infections, nausea, diarrhea, and rash and two rare but serious side effects of elevated liver function and cataracts.16-18 In 2015 oral lumacaftor/ivacaftor was FDA approved for patients 12 years of age and older who are homozygous for delta F508 and as of September 2016, it is now approved down to 6 years old. This patient group represents approximately 34% of the CF population in the US and Europe.18,19

Another modulator called production correctors are important treatment options for patients with class I mutations that do not produce any CFTR protein due to stop codons. Please see Figure 2 for more detail. Production correctors are thought to allow ribosomes to read through the stop codons so they can still create CFTR protein. There are no current FDA approved production correctors but a few agents are being evaluated at this time.

GENE THERAPY

Gene therapy for cystic fibrosis has had its ups and downs over the past 25 years of research. The simple concept of replacing a disease causing gene with a normal version has not been that easy. One major hurdle was to find an animal model that develops lung disease similar to humans to test possible treatments options. The CF mouse model does not acquire airway infections or develop CF lung disease, but recently a pig model and possible ferret model has been identified and may be future options for therapeutic development.20 Second involves the vectors that transfer the gene which can be viral and non-viral. The viral vectors have limited success because of our immune response to viruses which effect the efficacy and duration of expression of the gene and do not work well for life-long diseases like cystic fibrosis.20 The non-viral vectors had showed mixed results and still being tested. Today there is one group leading the way and conducting CF gene therapy trials, The UK CF Gene Therapy Consortium (GTC).21 They recently completed a double-blinded, placebo-controlled multi-dose trial using a non-viral gene transfer agent GL67A in 116 patients with CF.22 The agent was well tolerated and resulted in a small improvement in lung function. This is an exciting step forward in gene therapy.
Cystic fibrosis is the most common autosomal recessive life-limited disorder. Ever since the basic defect was identified in 1989 research has been advancing which translates into people with CF living longer and healthier lives. Today mutation analysis is required testing to provide the best treatment options for the patient. We can now provide some patients with novel gene transfer agents in clinical trials with the hope to restore CFTR function. Gene transfer agents are already in clinical trials with the hope to restore CFTR function. The next generation of gene transfer agents is expected to be more effective and have fewer side effects.

REFERENCES
ever tried marijuana and 23.4% use it at least monthly. While the use of other substances of abuse are much less common than the big three above, this paper will concentrate on new psychoactive substances (NPS) as well as emerging drugs of abuse. NPS are unregulated psychoactive (mind-altering) substances that have become available on the market and are intended to copy the effects of more typical illegal drugs. From bath salts to kratom, newer drugs are ever changing and are sometimes easier to access than the more typical drugs of abuse. NPS substances are not detected on routine drug screens.

**ELECTRONIC CIGARETTES**

Electronic cigarettes, or E-cigarettes (EC’s), were first used in the United States in 2007. Instead of tobacco, electronic cigarettes contain a liquid cartridge that typically contains nicotine derived from tobacco. The device has an atomizer and a rechargeable battery. When the user draws on the device it atomizes the liquid and delivers a vapor (vape) that is inhaled. Part of the popularity of EC’s is that they have been sold in flavors, ranging from bubble gum to peach schnapps. These devices have diethylene glycol (in antifreeze) and nitrosamines in them (both known human carcinogens) as well as nicotine, and before the Food and Drug Administration began oversight in May of 2016 there was little consistency between the labeling of EC cartridges and what was actually in them.

Several children have drunk liquid from the cartridges and overdosed, with some deaths. Many experts think that, in children, use of EC’s will increase the use of tobacco cigarettes in the future. This is because of the fact that most adolescents are not at a stage of change in which they are considering stopping their use of the substance. In adults these products may help current smokers cut back or even quit.

**BATH SALTS**

Bath Salts are sympathomimetic stimulants with hallucinogenic and serotoninergic properties. These drugs are chemically related to cocaine, a stimulant found in the krat plant, which is a shrub that grows in East Africa and on the Arabian Peninsula. In that region the leaves are chewed or used to make a tea with psychoactive properties. Bath salts are manufactured in China, India, and Pakistan and sold under many names such as Flakka, Bloom, Lunar Wave and Vanilla Sky, to name a few. They are often marketed as a cheaper alternative to cocaine or methamphetamine, or methenledioxy-methamphetamine (MDMA) (ecstasy). Synthetic cathinones usually take the form of a white or brown crystal-like powder and are sold in small plastic or foil packages labeled as “aromatic potpourri” or “plant food” and “not for human consumption.” Also sometimes referred to as “jewelry cleaner,” “phone screen cleaner.” People can buy them online and in drug paraphernalia stores. These substances are usually ingested or snorted and cause an intense euphoria followed by withdrawal symptoms that mimic those of other stimulants. Side effects seen from Bath Salts range from hallucinations (both auditory and visual), tachycardia, hypertension, palpitations, and/or chest pain (classic symptoms of a sympathomimetic toadstrome) They are also associated with violent behaviors and rhabdomyolysis. Necrotizing fasciitis has been reported after intramuscular injection. Deaths are uncommon after use of bath salts but appears to occur following extreme hallucinations, agitation, psychosis, and delirium, with the end result being rhabdomyolysis and multi-organ failure or cardiopulmonary arrest. There have also been deaths reported due to cerebral edema and brainstem herniation related to hyponatremia. Their effects last for 3 to 4 hours before the user has a potentially harsh crash. The total experience occurs over 6 to 8 hours.

Management of bath salt ingestion should include a urine and serum drug screen to detect other frequent co-ingestions, serum electrolytes and creatine phosphokinase (CPK), and EKG and possible CXR if chest pain is present. Hydration is important to limit renal damage from muscle breakdown. Benzodiazepines can help with the hyperactivity and anti-psychotics with psychotic behaviors.

**SPICE**

Spice, or K2, is a synthetic marijuana that first appeared in the United States in 2008. These mind-altering chemicals can be either sprayed on dried, shredded plant material so they can be smoked (herbal incense) or sold as liquids to be vaporized and inhaled in e-cigarettes and other devices (liquid incense). They are commonly labeled as “incense” or “potpourri” in an effort to bypass legislation in the USA. Other names for these products include Black Mamba, Scooby Snax or Bliss. When smoked, this substance gives a high like marijuana, with altered perception, elevated mood, and relaxation. In fact, many of these synthetic cannabinoids have a higher binding affinity for cannabinoid receptors than THC. As a result the effect of the drug does not plateau as happens in the dose response curve of true marijuana, increasing the potential for overdose and toxic effects.

The adverse effects of spice include tachycardia, irritability, agitation, anxiety, nausea, vomiting, confusion, and psychosis. In severe cases synthetic cannabinoids can also be associated with severe hypertension that reduces blood supply to the coronary arteries, as well as causing kidney damage and seizures. Synthetic cannabinoids are addictive and may have associated withdrawal manifested by headaches, depression, and memory impairment. These symptoms can last for weeks. More concerning is the fact that studies with rats have shown long term loss of serotonin in neurons after use of MDMA.

**FENTANYL ANALOGS**

Fentanyl analogs, such as carfentanil, have been the subject of recent drug alerts from the CDC. Fentanyl is an extremely potent synthetic opioid—50 times stronger than heroin—and carfentanil is one of the strongest opioids on the market, with a potency approximately 10,000 times that of morphine and 100 times that of fentanyl. Side effects of carfentanil are similar to those of fentanyl which include, itching, nausea, and potentially serious respiratory depression, which can be life-threatening.

**KRAMAT**

Kratom is an old supplement which recently has surfaced as a new drug of abuse. Kratom leaves are ground into pills and powders, and sold as a dietary supplement. It can be found in head shops and online. It is even made into drinks in some bars. In low doses it acts as a stimulant, but in higher doses it has opioid properties. It has this effect because mitragynine and 7-hydroxymitragynine—the active ingredients in kratom—bind to endogenous opioid receptors. Until recently it has not been regulated, however the DEA has looked into the possibility of placing Kratom on the Schedule 1 drug list. This was going to be done on September 30, 2016 however it has since been placed on hold. Kratom does act as an opioid analog and therefore symptoms of overdose are similar to those seen in opioid overdose such as nausea, vomiting, agitation, sweating, itching, and hallucinations.
CONCLUSION

In 1992 in its Annual Report the Robert Wood Johnson Foundation stated the following:

“It is the worst of plagues. It knows no season and no boundaries. No mosquito will be identified, no microbe isolated, no vaccine invented to end its reign. It is a pestilence with all the classic trappings of social disruption, suffering, and death—and one terrible, defining difference: We invite it to kill and maim and diminish us. We know how it enters us, and we open the doors to it, lured by the short-term pleasure it offers, lulled by the years or decades it incubates before erupting into host-killing maturity….and because its vector is pleasure and its mask is time, we have not even recognized its horror fully enough to grant it a name worthy of its grisly power. How inadequate it is to call this peerless filler of graves and plunderer of nations by so pallid a name as ‘substance abuse.’ “

Despite our best efforts as medical professionals to prevent use of illicit substances and educate our patients we continue to struggle against the ever evolving world of street drugs.

REFERENCES


These facilities allow us to meet the needs of our patients, with more than 6,500 annual admissions, nearly 10,000 total surgeries and over 48,000 visits annually to our emergency center. This past year, the total number of ambulatory visits completed within our St. Petersburg campus as well as our 8 outreach sites included over 450,000, which reflects our growing catchment areas over the west coast and central Florida. Our patient volumes and acuity continue to reflect the breadth and depth of high acuity and specialty care provided to patients and families through our clinical programs.

Because improving patient outcomes through research is an integral part of our mission, on November 20, 2015, new ground was broken in preparation for the Johns Hopkins All Children’s Research and Education building, a new campus facility that represents the continued academic growth of our institution. This 225,000-square-foot building will accommodate 7 floors including a 250-seat auditorium, research offices, resident conference rooms, a full floor dedicated to simulation, basic science research facilities and a biorepository. Construction is scheduled to be completed in 2018. With the opening of this new campus facility, we anticipate not only an immediate benefit to our researchers and learners, but we also estimated adding more than 300 construction jobs to the community while also opening up to 30 new highly-skilled jobs for faculty, educators, researchers and support staff. Additionally, we anticipate providing learning space for more than 200 faculty, educators, researchers, physicians, nurses and support staff within the new building. Thus, the return on our immediate community with this building is expected to be significant.

THE JOHNS HOPKINS ALL CHILDREN’S HOSPITAL INSTITUTES:

Our new research and education building will provide the physical space for the growth of our Institutes. The Institutes aim to build on our past strengths and pave the way for innovation as it relates to these clinical, educational and research programs over the next 5 years. Our institutes are summarized below:

- Heart Institute
- Institute for Brain Protection Sciences
- Cancer and Blood Disorders Institute
- Maternal, Fetal and Neonatal Health Institute
- Translational Science Institute

The institutes are focused on areas of need to reassess our learning environments such that education and patient care are prioritized over service and duty hours.

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In considering the national conversation and challenges in graduate medical education, both groups of leaders at Johns Hopkins All Children’s as well as within the Johns Hopkins University School of Medicine identified a unique opportunity to build educationally-driven programs equipped to offer new skills and content relevant to the current health care environment. The inception of the new Johns Hopkins All Children’s pediatric residency program was built specifically to achieve these goals and was accredited in July, 2012 under this innovative philosophy.

Being educationally driven is facilitated by our leadership’s commitment to continue supporting full clinician staffing across the hospital such that patient care and needs are not driven solely by trainee efforts. Decisions related to resident experiences are structured such that residents may achieve ACGME training milestones while also considering the educational value of their work. In this model, we observe our residents are not only able to provide high-quality care but also gain a greater understanding of the individual needs of patients and families while engaging meaningfully with their faculty. As a new program, we have committed to describing early outcomes from this educationally-focused training approach in an effort to study and describe the advantages of this model as it relates to patient care and graduate medical education.

The residency experience is also centered on individualized learning plans that ensure each physician is following a career development path toward leadership in patient care and research. We have the opportunity to introduce non-traditional, yet critical curricular components, including the business of medicine, leadership, cultural competence and individualized medicine secondary to provide immersive learning experiences structured within each year of training. Secondary to the work of our institutes, we have built opportunities to centrally participate in translational research for trainees seeking this career path. Our Clinical Translational Research Track (CTRT) is offered to trainees within their second year as a longitudinal curriculum that offers mentorship, grant-funding opportunities and skill building in research design.

With a highly committed group of faculty that spans pediatric specialties, facilities that promote an ideal learning environment and leadership committed to innovation, we are thrilled about the early outcomes of our new program. This, on top of having St. Petersburg named as the #1 ranked city among millennials, has allowed us to attract and recruit medical students from the nation’s best medical schools. Having recently completed the recruitment of our third class of residents, our program now has 36 residents, the full complement, as of July of 2016. We were also fortunate to have participated in the Florida Chapter Annual Meeting Resident Brain Bowl where our trainees took first place in a friendly trivia competition with other residency programs in the state.

In addition to the pediatric residency program, we are developing pediatric clinical and research fellowship programs as well as pediatric training opportunities for fellows in adult specialties. The first such program put in place include fellowships in pediatric cancer research, pediatric surgery and pediatric surgery research. Additional fellowships will be introduced over the next few years as our academic infrastructure grows with the new residency program.

RESEARCH

The Clinical and Translational Research Organization (CTRO) at Johns Hopkins All Children’s Hospital provides a centralized infrastructure to enhance and support the design, execution and oversight of clinical and translational research in fulfillment of the research mission at Johns Hopkins All Children’s Hospital: to improve the health of children by providing patients and health care professionals with access to innovative research opportunities that will advance the diagnosis, treatment and prevention of pediatric-onset diseases and their adverse outcomes.

Core resources, services and programs include:

• Research Operations
• Research and Grants Administration
• Database Design & Data Management
• Study Design & Analysis
• Biorepository
• IND/IDE Core
• Investigational Drug Services
• Regulatory Affairs & Quality Assurance

As with our expanding educational programs, the focus is on the development of personalized medicine by identifying and understanding how individual factors can apply to children on a broad scale and contribute to the foundation of an essential “population” focus to medicine.

Effective Fall 2013, the Institutional Review Board at Johns Hopkins All Children’s Hospital is fully integrated with research administration on the Baltimore campus as the seventh IRB within Johns Hopkins Medicine. This will facilitate collaboration among individual faculty members as well as multidisciplinary programs in St. Petersburg and Baltimore.

NATIONAL RECOGNITION

Johns Hopkins All Children’s Hospital continues to rise in the US News & World Report rankings. U.S. News & World Report ranked JHACH as a best children’s hospital in six specialty areas in the new 2016-17 Best Children’s Hospitals rankings in cardiology and heart surgery, orthopedics, neonatology, pulmonology and cancer. Johns Hopkins All Children’s Hospital was the only children’s hospital ranking in Florida’s West Coast in orthopedics. In August 2015, our new residency program was fortunate to have received a national grant from the Hearst Foundations in support of our LEAD the PACC residency curriculum (Leadership Executive Academic Development/Professional Academic Colleagues and Community) residency curriculum. Two of our pediatric residents received recognition as young investigators at this year’s National AAP Meeting for their work in CPR education for high school students within the community. In January 2016, the New England Journal of Medicine featured our Surgical Extended Care Unit as a case study in hospital innovation.

2016 marked the 90th anniversary of Johns Hopkins All Children’s Hospital’s pioneering endeavor to provide the best health care for children. The rich history of this hospital in collaboration with the expertise of Johns Hopkins Medicine has set us on a journey toward a very bright future in pediatrics. We remain grateful for the privilege to care for the wonderful children and families that drive our mission. Our new vision for education has been driven by the wonderful faculty, staff and trainees within our institution who push us towards excellence in all that they do. Our achievements in research will provide the foundation for discovery. Finally, the connection and support from our community partners, practitioners and pediatricians is unparalleled and has allowed for us to continue to advocate for children at regional and national levels. We look forward to many future milestones on this journey to help improve the care of our patients and ultimately improve their futures.

This Department Report was published under the 2016 guidelines.

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