Take 3 – Practical Practice Pointers© June 17, 2019 Edition

Diabetic Nephropathy, Gabapentin, Tonsillectomy in Children

From the Guidelines and the Updated ADA Standards of Care

1) Preventing Renal Complications in Diabetes

On June 3rd, the American Diabetes Association (ADA) updated their "living" Standards of Medical Care in Diabetes regarding renal management/care for persons with diabetes. This change reflects the results from the CREDENCE trail (Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy) trial. The CREDENCE trial found that for patients with T2D and chronic kidney disease (CKD), canagliflozin (Invokana), a sodium-glucose cotransporter type 2 (SGLT2) inhibitor, lowered the risk for progression to end-stage renal disease (ESRD) by 30%, and was also associated with significantly lower rates of major cardiovascular events, including death and hospitalization for heart failure. Additionally, the risk of the renal-specific composite outcome of ESRD, doubling of serum creatinine, and death from renal causes was lowered by 34% in the canagliflozin group compared with placebo.

Based on these results, the ADA now recommends the following as part of section 11 (Microvascular Complications and Foot Care):

- At least once a year, assess urinary albumin (eg, spot urinary albumin-to-creatine ratio) and estimated glomerular filtration (eGFR) rate in patients with type 1 diabetes with duration of ≥ 5 years; in all patients with T2D, **regardless of treatment**; and in all patients with comorbid HTN. *Grade of evidence: B*
- For patients with T2D and diabetic kidney disease, consider use of an SGLT2 inhibitor in patients with an eGFR ≥ 30 mL/min/1.73m^2 and particularly in those with > 300 mg/g albuminuria to reduce risk of CKD progression, cardiovascular events, or both. *Grade of evidence: A*
- In patients with CKD who are at increased risk for cardiovascular events, use of a glucagon-like peptide 1 (GLP-1) receptor agonist may reduce risk of progression of albuminuria, cardiovascular events, or both. *Grade of evidence: C*

Based on the above, the ADA also modified their January 2019 recommendation by **removing** the following: "... continued monitoring of urinary albumin-to-creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of CKD."

My Comment:
These are "practice-changing" recommendations, so please take note. Screening all patients with T2D yearly for albuminuria with a microalbumin/creatinine ratio now INCLUDES those who are taking an ACE-I or ARB medication. Additionally, there is more and more research being published regarding potential benefits of both SGLT2 inhibitors ("flozins") and the glucagon-like peptide 1 receptor agonists (GLP-1 or "incretins") for patients with DM and other complications. The use of the SGLT2 inhibitors is a strong recommendation in this guideline. Unfortunately, this does not account for cost, which can be prohibitive for many patients.

References:

- Perkovic V, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. NEJM April 14, 2019. DOI: 10.1056/NEJMoa1811744. Article
- *Living* Standards of Medical Care in Diabetes. Diabetes Care June 3, 2109. Link

From the Virginia Board of Pharmacy and General Assembly

2) Scheduling of Gabapentin as a Controlled Substance

Gabapentin is approved by the FDA for the treatment of epilepsy and postherpetic neuralgia. It is often prescribed off-label for other pain syndromes, anxiety and mood disorders, restless legs syndrome, alcohol withdrawal, and other conditions.

Though gabapentin is an analog of gamma-aminobutyric acid (GABA), it does not bind to GABA receptors or affect the production or uptake of GABA. How gabapentin works and how it relieves pain and suppresses seizures is unknown. The action of both benzodiazepines and alcohol are due to their binding to GABA receptors in the brain.

In fact, gabapentin does not exhibit affinity for benzodiazepine, opioid (mu, delta, or kappa), or cannabinoid 1 receptor sites, which are often activated in drugs of abuse. Gabapentin is not yet scheduled as a controlled substance in most states. However, there are case reports and postmarketing reports indicating there appears to be potential for abuse, dependency, and withdrawal symptoms associated with gabapentin use, particularly when used at doses above the recommended dose. Additionally, when used concomitantly with other medications such as opioids, muscle relaxants, and benzodiazepines, it appears to potentiate the patient's "high."

In 2019, the Virginia General Assembly passed HB2557 which classifies gabapentin as a Schedule V controlled substance as of July 1, 2019 (presently classified as a Schedule VI, drug of concern). Pharmacies will then also begin reporting gabapentin to the Virginia Prescription Monitoring Program as a Schedule V controlled substance.

As of July 1, the dispensing and refilling of gabapentin must also comply with the requirements of Board of Pharmacy Regulation 18VAC110-20-320 that a Schedule V controlled substance shall not be dispensed or refilled more than six months after the date on which such prescription was issued, nor may it be refilled more than five times. Dispensers with active prescriptions on file with a date of issuance greater than 6 months or that have been refilled five times or more will be considered expired. While a prescriber should authorize no more than 5 refills of gabapentin beginning July 1, 2019, should a pharmacist receive a prescription authorizing more than 5 refills, the prescription will still expire six months after the date of issuance or after 5 refills, whichever occurs first.

Clinicians should assess patients for drug abuse history when prescribing gabapentin, and monitor patients for the development of tolerance as well as for any signs of misuse or abuse, including unauthorized escalation of dosing, and requests for early refills or other aberrant behavior. If abuse is suspected, clinicians should consider requesting testing for the presence of gabapentin in urine drug screens.

It should be noted that this scheduling action occurred under State law. The Drug Enforcement Administration has not yet scheduled gabapentin.

My Comment:
My thanks to Sarah Melton, PharmD and good friend, for her very helpful Medscape review of this topic. Many states have or are moving toward this same action. For most clinicians, this will not change practice, other than the limitation in terms of refills. How it may change practice for some is raising awareness that our "comfort" with gabapentin as a "safe substitute" for other controlled meds may turn out to be misguided. It will also be important to educate those who are on gabapentin about the potential harms from long-term use as with other controlled substances.

Reference:
Melton S. Has Gabapentin Become a Drug of Abuse? Medscape Jun 17, 2014. Link

From the Guidelines and the AAO-HNSF

3) Tonsillectomy in Children

Tonsillectomy is the second-most common ambulatory surgical procedure performed on children in the United States. The only procedure with greater frequency was myringotomy with insertion of tubes. The 2 most common indications for tonsillectomy are recurrent throat infections and obstructive sleep-disordered breathing (oSDB). Studies report that the overall incidence rates of tonsillectomy have significantly increased in the past 35 years, with oSDB being the primary indication for surgery in up to 67% of children. oSDB represents a spectrum of disorders, ranging in severity from primary snoring to hypoventilation and obstructive sleep apnea (OSA).

Children with oSDB versus controls have a significantly higher rate of antibiotic use, 40% more hospital visits, and an overall elevation of 215% in health care usage, mostly from increased respiratory tract infections. Children with tonsillar disease, including children with throat infections and oSDB, also show significantly lower scores on several QoL subscales, including general health, physical functioning, behavior, bodily pain, and caregiver impact, when compared with healthy children. Up to 40% of children with oSDB exhibit behavioral problems that include enuresis, hyperactivity, aggression, anxiety, depression, and somatization.

Controversy persists regarding the actual benefits of tonsillectomy as compared with observation and medical treatment of throat infections. Tonsillectomy can lead to short-term improvement in sleep outcomes when compared with no surgery in children with oSDB (moderate strength of evidence) and there is evidence that behavioral parameters, school performance, and QoL improve after resolution of oSDB.

The American Academy of Otolaryngology–Head and Neck Surgery Foundation (AAO-HNSF) recently updated their 2011 guideline regarding tonsillectomy in children. The guideline development process included representation from Family Medicine. It is presented as a series of Key Action Statements (KAS). These include:

Strong recommendations were made for the following key action statements (KASs):
- Recommend watchful waiting for recurrent throat infection if there have been <7 episodes in the past year, <5 episodes per year in the past 2 years, or <3 episodes per year in the past 3 years.
- Recommend ibuprofen, acetaminophen, or both for pain control after tonsillectomy.

Recommendations were made for the following KASs:

- Assess the child with recurrent throat infection who does not meet criteria outlined above for modifying factors that may nonetheless favor tonsillectomy, which may include but are not limited to multiple antibiotic allergies/intolerance, PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenitis), or history of >1 peritonsillar abscess.
- Ask caregivers of children with oSDB and tonsillar hypertrophy about comorbid conditions that may improve after tonsillectomy, including growth retardation, poor school performance, enuresis, asthma, and behavioral problems.
- Before performing tonsillectomy, refer children with oSDB for polysomnography if they are <2 years of age or if they exhibit any of the following: obesity, Down syndrome, craniofacial abnormalities, neuromuscular disorders, or sickle cell dz.
- Advocate for polysomnography prior to tonsillectomy for oSDB in children without any of the comorbidities listed in above for whom the need for tonsillectomy is uncertain or when there is discordance between the physical examination and the reported severity of oSDB.
- Recommend tonsillectomy for children with OSA documented by overnight polysomnography.
- Counsel patients/caregivers and explain that oSDB may persist or recur after tonsillectomy and may require further management.

Strong recommendation against the following actions were made:

- Clinicians must not administer or prescribe codeine, or any medication containing codeine, after tonsillectomy in children younger than 12 years.

The following was noted in the guideline as an ***option***:

- Clinicians may recommend tonsillectomy for recurrent throat infection with a frequency of at least 7 episodes in the past year, at least 5 episodes per year for 2 years, or at least 3 episodes per year for 3 years with documentation in the medical record for each episode of sore throat and ≥1 of the following: temperature >38.3°C (101°F), cervical adenopathy, tonsillar exudate, or positive test for group A strep.

My Comment:
The most enlightening part of this guideline for me was gaining a deeper appreciation of the extent of sleep disorders in children and adolescents. The threshold for surgery for recurrent throat infections was also notable. During my residency, tonsillectomy was considered quite "routine," with the potential complications downplayed. It's good to see that vigilance continues to insure that we are providing the best evidence-based care.

Reference:
Mitchell RB et al. Clinical Practice Guideline: Tonsillectomy in Children (Update). *Otolaryngol Head Neck Surg.* 2019 Feb;160(1_suppl):S1-S42. Article

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