# Forum for Evidence-Based Medicine

September/October | 2019

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| **Activity description** | Practicing evidence-based medicine (EBM) is important in today's health care environment because this model of care offers clinicians a way to enrich quality, provide patient satisfaction, reduce costs and improve outcomes. A common implementation of EBM involves the use of clinical practice algorithms during medical decision-making to encourage optimal care. This widely recognized practice is designed to address the persistent problem of clinical practice variation with the help of actionable information at the point of care. These E-newsletters will enable health care professionals (HCPs) to put new EBM into practice. |
| **Target audience** | This activity is designed to meet the educational needs of physicians, PAs, nurses, nurse practitioners and other HCPs who have an interest in EBM. |
| **Learning objectives** | At the end of this educational activity, participants should be able to:<br>• Explore the educational content surrounding chronic kidney disease as a means to advance optimal care outcomes.<br>• Review pharmaceutical recommendations for the management of precision medicine for COPD patients and the CDC Advisory Committee on Immunization Practices (ACIP) recommendations for the PREVNAR 13 pneumococcal vaccine.<br>• Apply medical management principles grounded in evidence-based medicine that could help modify and expand shared decision making in regards to adrenal incidentalomas and home glucose monitoring in type 2 diabetes. |

## Accreditation statement

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INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, this activity has been planned and implemented by OptumHealth Education. OptumHealth Education is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE) and the American Nurses Credentialing Center (ANCC) to provide continuing education for the health care team.

## Credit designation statements

### Nurses

The participant will be awarded up to 1.00 contact hour(s) of credit for attendance and completion of supplemental materials.

### Nurse practitioners

The American Academy of Nurse Practitioners Certification Program (AANPCP) accepts credit from organizations accredited by the ACCME and ANCC.

### Physicians

OptumHealth Education designates this enduring activity for a maximum of 1.00 AMA *PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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### Attendance

A certificate of attendance will be provided to learners upon completion of activity requirements, enabling participants to register with licensing boards or associations that have not been pre-approved for credits. To apply for credit types not listed above, participants should use the procedure established by the specific organization with which they wish to obtain credit.

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# Primary Care Management of Chronic Kidney Disease

There is an enlarging database to support early primary care intervention in CKD. This is related to three key issues:

1. Worsening of CKD can be prevented with early primary care interventions.
2. Cardiovascular risk is markedly increased in this population and can be reduced with the proper interventions.
3. Metabolic bone disease can be prevented or attenuated by early intervention.

Most of our CKD patients are at Stage 3 and primary care providers may be somewhat passive in their management.[1] Improving this trend is the focus of this article and the three above issues will be individually discussed. An attempt should be made to identify the cause of CKD. Examination of the urinalysis is important. If there is heavy proteinuria, glomerular disease is likely, and in a non- diabetic, this is an indication for early nephrology referral. If there are persistent WBC's in the absence of infection, this may represent chronic interstitial nephritis and nephrology referral should also be considered. Although infrequent, reversible causes should be addressed. There are two main categories to consider. The first is obstruction, typically from benign prostatic hyperplasia and less likely from stones and other causes. Ultrasound should be obtained when appropriate. The second is drug related causes. NSAID's and diuretics are the most frequent offenders. There is emerging evidence that low dose NSAID therapy may be safe in mild CKD 3.

1. **Slowing the Progression of CKD –** There are multiple factors to consider in limiting progression of CKD.
   - **HTN Control –** Although the BP targets have recently changed and are controversial, there is evidence to support decreased CKD progression with a systolic BP <130 mm Hg, particularly in patients with proteinuria. This is a good target if it can be safely achieved, otherwise target a systolic BP <140 mm Hg.
   - **Proteinuria Control –** Proteinuria is a risk for both CKD progression as well as an independent risk for vascular events. ACE or ARB's are the primary medications to reduce progression. They should not be used in combination. Diuretics can increase the benefit of an ACE/ARB and should be used when indicated. Diltiazem and verapamil also reduce protein excretion for patients unable to take an ACE/ARB or who need additional BP control. Amlodipine is neutral with respect to proteinuria, although more potent for HTN control.
   - **Role of newer hypoglycemic agents on progressive renal disease**
     - → **SGLT-2 Inhibitors –** There are strong and consistent data that when this drug class is used in diabetic patients with significant proteinuria (>300 mg/gm albumin), a decrease in CKD progression and decrease in the need for dialysis are both seen. [2] This drug class is expensive at >$6,000 yearly. Cost effective analyses have not yet been done in the above population but will likely show cost effectiveness. This degree of proteinuria is seen in less than 10% of patients with DM2. The large majority of patients with DM2 and CKD 2 or 3 do not have proteinuria to this degree and studies have not yet been done in this larger population. Given the cost, there might not be cost effectiveness in this larger population of patients. The mechanism of renal protection is not fully understood. It does not appear to be related to improved glucose control and is not likely due to the observed small (average 2-3 mm Hg) reduction in systolic BP, although these may be contributory. In animal models of diabetic nephrosclerosis, nephron hyperperfusion from elevated intraglomerular pressures is felt to be the most important etiology. One important mechanism is therefore likely related to the fact that the SGLT2 inhibitors increase sodium delivery to the distal nephron triggering reduction in intraglomerular pressure through afferent arteriole vasoconstriction at the glomerulus.

*(continued on page 2)*

# Primary Care Management of Chronic Kidney Disease

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- → **GLP-1 receptor agonists (GLP-1 RA) –** Unfortunately, primary renal outcomes studies have not yet been done for this drug class. There are however data available from three large scale CV outcomes trials of GLP-1 RA's in patients with DM2. In all of these trials, improvements in renal outcomes were seen. They variably reduced the components of the composite renal outcome of new macroalbuminuria, doubling of the serum creatinine, the development of ESRD, or death from renal disease. These reductions were in the range of 13% to 36%. [3]

- **Metabolic Acidosis Correction –** Typically this occurs late in stage 3 CKD and is an area that primary care often does not address, despite the fact that management is straightforward. Bicarbonate levels <22 mg/dl are associated with CKD progression. When treated to a level of 23 mg/dl with oral bicarbonate, there is an 80% lower risk of CKD progression without an increase in edema, BP or CHF exacerbations. Oral sodium bicarbonate tablets should be started in these patients and titrated up as needed to achieve a level over 23 mg/dl.

2. **CV Risk Reduction -** Patients with stage 3 CKD are 20 times more likely to die of CVD than progress to ESRD. The increased risk is related to the diseases causing their CKD such as HTN and diabetes, as well as a direct increased risk conferred by their CKD. Management is straightforward with BP control and statin therapy, which is well tolerated in patients with renal disease. Low dose aspirin should be added when appropriate based on the calculated 10 year CVD risk. The SGLT-2 class reduces CV events in patients with established CV disease or multiple CV risk factors, although the cost to prevent one CVD event is close to $500,000 and therefore not cost effective. However, in patients with type 2 diabetes who have both high CV risk and CKD 3, the SGLT-2 class may be cost effective, when considering the combined renal and CVD benefits, as well as the observed reduction in hospitalizations for CHF with this drug class. These cost effectiveness analyses have not yet been done, but of all the areas where the SGLT-2 class could be cost effective, it will likely be in this subset of patients.

3. **Metabolic Bone Disease -** This is somewhat more complex but the early management is not daunting. There are four labs to monitor and these should be done yearly in Stage 3 CKD, and twice yearly in Stage 4 CKD. These are calcium, phosphorous, 25 OH vitamin D3 and serum PTH. Remember that patients with an elevated PTH level and CKD, by definition, have secondary hyperparathyroidism which should be coded to remind providers about appropriate management. Vitamin D should be replaced when levels are low. Serum phosphorous should be measured and if greater than 3.5 mg/dl, corrected with a nutrition consult and, if needed, phosphate binders. Unless the patient is hypercalcemic, which is very unusual, the easiest phosphate binder to use is calcium carbonate 500 mg three times daily with food. When the above is done and PTH levels remain significantly elevated, or calcium levels significantly reduced, calcitriol is indicated. Nephrology consultation is indicated for management challenges.

- **Stage 4 CKD -** Nephrology consultation is generally indicated at Stage 4 CKD unless it is a frail elderly patient whose life expectancy is limited and the decision has been made not to pursue renal replacement therapy. Keep in mind that it is critically important to discuss dialysis and advanced directives in this group so that reasonable decisions can be made in advance of the need for dialysis. Most frail elderly patients with ESRD, or those over age 80, irrespective of their health status, have a decreased quality of life and limited survival benefit when dialysis is initiated. There are unfortunate data that nephrologists may inappropriately push patients onto hemodialysis against their wishes. When this was recently studied it was observed that when patients declined dialysis, some nephrologists "tended to repeatedly question this decision over time, deliberated about patients' competency to make this decision, used a variety of strategies to encourage patients to initiate dialysis, and prepared for patients to change their minds and start dialysis." [4]

- **Management of Renal Anemia –** Iron deficiency should be excluded via measurement of serum ferritin. When ferritin levels are normal or elevated, evaluation for blood loss anemia is not indicated. Use of erythropoietin to increase hemoglobin levels to the normal range has not improved outcomes in three consecutive studies. The only indication is to avoid the need for transfusions in severe anemia.


1. Abboud, H., & Henrich, W. L. (2010). Stage IV chronic kidney dosease. NEJM, 362, 56-65.
2. Ingelfinger, J. R., & Rosen, C. J. (2019). Clinical credence- SGLT2 Inhibitors, diabetes, and chronic kidney disease. NEJM, 380, 2371-2373.
3. Boer, I. H. (2017). A new chapter for diabetic kidney disease. NEJM, 337(9), 885-887.
4. Wong, S., McFarland, L. V., & Liu, C. (2019). Care practices for patients with advanced kidney disease who forgo maintenance dialysis. JAMA Internal Medicine, 179(3), 305-313.

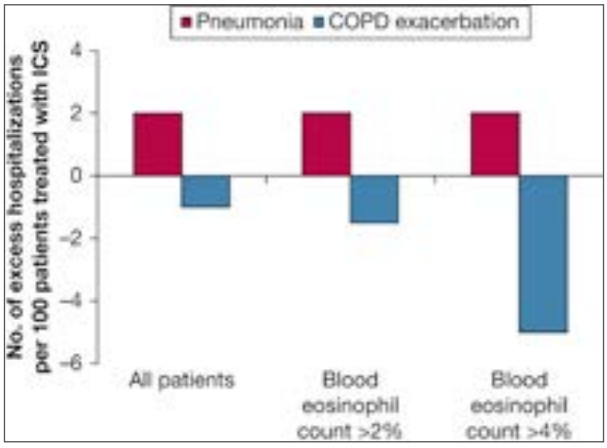
## Precision medicine to guide step therapy for COPD patients

Through a series of studies published over the past several years, and reviewed in the Forum, the pharmacologic management of COPD is becoming more evidence-based. A new study [5] adds further data to the conversation. For COPD patients whose symptoms are inadequately controlled on a prn short acting beta agonist (SABA), current guidelines recommended a long acting muscarinic antagonist. If step therapy is needed for additional symptom control, options are an inhaled corticosteroid/long acting beta agonist combination (ICS/LABA) versus a LAMA/LABA combination. In a real world setting, 2,000 patients initiating each of these two regimens were followed for one year with the following observations:

- Evidence of severe pneumonia was higher in the ICS/LABA group at 8 vs 5 cases per 100 patients per year.
- Patients with higher eosinophil counts (>6% on peripheral smear), had a slight reduction in exacerbations when treated with the ICS/LABA regimen, although this barely reached statistical significance.

This data is consistent with the recent trials of triple vs. dual inhaler therapy for COPD. It is estimated that 70% of the COPD population is currently receiving an ICS and the data favor treatment in only a quarter of these patients. An editorial in [6] Chest compiled much of the recent data and offered several evidence-based observations.

- In patients who do not have the asthma/COPD overlap syndrome or a blood eosinophil percentage of over 4%, ICS treated patients have twice as many episodes of severe pneumonia as there are saved severe COPD exacerbations. When this population needs step therapy from single inhaler treatment, a LAMA/LABA combination should be used.
- In patients with the asthma/COPD overlap syndrome or blood eosinophil percentages >4%, there are 5 severe COPD exacerbations prevented and 2 episodes of severe pneumonia caused as a result of ICS therapy, favoring use of an ICS in this population. When this population needs step therapy from a single inhaler, an ICS/LABA should be used.




Applying this algorithm to the entire US population compared to current treatment patterns would prevent 60,000 hospitalizations for severe COPD exacerbations and prevent 120,000 admissions for severe pneumonia. Triple inhaler therapy should be reserved for patients with severe COPD and repeated exacerbations on the above regimens.


5. Suissa, S., Dell'Aniello, S., & Ernst, P. (2019). Comparative effectiveness and safety of LABA-LAMA vs LABA-ICS treatment of COPD in real-world clinical practice. Chest, 155(6), 1158-1165.
6. Suissa, S., & Ernst, P. (2017). Precision medicine urgency: The case of inhaled corticosteroids in COPD. Chest, 152(2), 227-231.
7. Suissa, S., & Ernst, P. (2017). Precision medicine urgency: The case of inhaled corticosteroids in COPD (figure 1). Chest, 152(2), 227-231. Retrieved from https://marlin-prod.literatumonline.com/cms/attachment/0bcb3e8d-4c0e-47bf-b3ff-3aa118c36d78/gr1_lrg.jpg



## SGLT-2 Inhibitors and the risk of Fournier's Gangrene (FG)

FG is a rare infection characterized by necrotizing fasciitis of the external genitalia, perineum, and perianal region. It is seen with increased frequency in patients with diabetes. It has both a high morbidity and mortality rate and often requires extensive surgery and prolonged rehabilitation. Examining the FDA adverse event reporting system revealed only 19 cases in patients with diabetes taking various regimens over the 35 years prior to the approval of the SGLT-2 class of drugs. Over the first 6 years since approval, 55 cases have been seen in patients taking SGLT-2 inhibitors. [8] This is consistent with the known increased rate of genital and bladder/renal infections seen with this drug class. Although FG remains a rare diagnosis, it should be added to the increased risk of DKA (often normoglycemic), as potential lethal complications of SGLT-2 use. Knowledge of this potential complication can allow for prompt evaluation and aggressive treatment of suspected cases.

## Prevnar 13 vaccination and major change in the recommendations for use

Prevnar 13 was approved based on a single large phase III trial which showed a small clinical benefit in the frequency of pneumonia, which was only borderline, cost effective. The pneumonia rate decreased with vaccination from 2 per 1,000 patients down to 1.2 per 1,000 patients. There was no effect on the mortality of pneumonia and the cost to prevent one episode of pneumonia was $134,000. Since release of the vaccine, there is increasing herd immunity from our immunization of children and the vaccine currently has minimal efficacy. It has had no discernable direct effect on risks for either invasive disease (i.e., bacteremic pneumonia or meningitis) or nonbacteremic pneumonia in adults. In fact, most pneumococcal disease in the U.S. is now caused by serotypes not covered by the conjugate vaccine. The CDC estimates its price tag at between US $200,000 and >$500,000 per quality-adjusted life-year. The "number needed to vaccinate" to prevent one case of invasive pneumococcal disease is estimated to be 26,000 annually; the estimated number to prevent one case of pneumonia ranges from 2600 to 14000. The CDC [9] June 2019 meeting of the CDC's Advisory Committee on Immunization Practices has therefore issued the recommendation in adults to be routinely used only in immunocompromised patients.

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8. Bersoff-Matcha, S. J., Chamberlain, C., Cao, C., Kortepeter, C., & Chong, W. H. (2019). Fournier Gangrene associated with sodium-glucose contransporter-2 inhibitors: A review of spontaneous postmarking cases. Annals of Internal Medicine, 170(11), 764-69.

9. Centers for Disease Control and Prevention. (2019, March). Advisory Committee on Immunization Practices (ACIP). Retrieved from CDC Web site: https://www.cdc.gov/vaccines/acip/index.html

## Adrenal Incidentalomas (AI)

The natural history and clinical management of AI's was reviewed in the July/August 2018 Forum. These are seen in 5% of the population. The benign nature and rare progression to adrenal carcinoma was stressed, in an attempt to limit the excess imaging and attendant risks and costs associated with this. A new study adds important data to this dialog and will therefore be reviewed. Elhassan et al [10] performed a meta-analysis of 32 studies including over 4100 patients, followed for a mean of over four years. The three primary questions of concern related to AI's are:

1. What is the rate of malignant transformation?
2. What is the rate of new autonomous hormone secretion?
3. What is the natural history in the subset of AI's with mild autonomous cortisol excess (MACE)?

This study provided strong data to answer all three of these questions and should inform our future management of AI's.

Nodule growth and rate of malignant transformation during follow-up was negligible and only 2.5% of nodules increased in size by 10 mm. Recall that the average size of an adrenal carcinoma at diagnosis is 6 cm, a size not attained by AI's. When MACE nodules were excluded, only 1.2% increased in size by 10 mm. Interestingly, the larger the nodule at baseline, the less likely to grow, suggesting the natural history of AI's is stability once maximal growth has occurred. On average, the maximal size attained by AI's is in the range of 2.5 cm. More importantly, in the 26 studies which evaluated over 2800 patients, the rate of malignant transformation was zero.

The rate of new autonomous hormone secretion was also extremely low. In the 23 studies which evaluated over 2700 patients, new development of overt hormone secretion almost never occurred. Over four years of follow up, the rate of development of Cushing's Syndrome or pheochromocytoma was 0.003%, and no patient developed primary hyperaldosteronism.

The natural history of MACE has been less well understood and there have been concerns that this is a progressively worsening entity. This analysis showed that these nodules rarely progress to Cushing's Disease with a rate of 0.002%, and the rate of conversion from a non-functioning adenoma to MACE was only 4.3%. There are concerns however, about the long term metabolic effects of mild autonomous cortisol excretion. The analysis did show that these nodules were unlikely to spontaneously stop producing cortisol. The general population in which AI's are found has higher rates of hypertension and metabolic syndrome compared to controls. Additionally however, patients with MACE had a 21% rate of weight gain over time and a 28% incidence of Type 2 diabetes. It would also be expected, but not documented, that there would be an increased incidence of osteoporosis in this population.

The above results were corroborated by a similar meta-analysis done by the European Society of Endocrinology, showing no malignant transformation of any AI and a risk of developing clinically overt hormone secretion of 0.3%. How should this new data inform our clinical management of AI's?

- Patients with AI's determined by initial imaging not to be suspicious for adrenal carcinomas will not benefit from repeated imaging and patients may experience harm and excess costs. This is supported by the new European Society of Endocrinology guideline which states that if an AI is less than 4 cm and has benign features, repeat imaging should not be done. The accompanying editorial to this study states "This meta-analysis should end the controversy about the need for routine follow up imaging".
- Patients with initial negative evaluations for Cushing's Syndrome and pheochromocytoma should not require repeated hormonal evaluations in the absence of new clinical findings suspicious for either of the above conditions.
- Patients with MACE require ongoing follow up for progressive weight gain, type 2 diabetes, and other features of the metabolic syndrome, although the natural history of MACE is for only rare progression to Cushing's Disease. Because of the above natural history, those patients with autonomous cortisol excretion, manifested by lack of cortisol suppression on the overnight dexamethasone test, might benefit from endocrine consultation and follow up.

10. Elhassan, Y. S., Alahdab, F., Prete, A., Delivanis, D. A., Khanna, A., Prokop, L., et al. (2019). Natural history of adrenal incidentalomas with and without mild autonomous cortisol excess: a systematic review and meta-analysis. Annals of Internal Medicine, 171(2), 107-116.

## Home glucose monitoring in DM2

Patients with type 2 diabetes who are not on insulin therapy do not require regular home glucose monitoring (HGM). Both patients and providers underestimate the cost of these supplies. WellMed for instance, spent over $30 million on HGM last year, and the average cost per patient is $1800. HGM use in non-insulin regimens has been examined in the literature many times. A large meta-analysis supported the lack of clinical benefit. [11] There was a non-significant 0.2% reduction in HbA1c at 3-6 months which was no longer present at one year. Scenarios where temporary HGM may be useful in patients on oral regimens include:

- Suspected hypoglycemia
- Changes in drug regimen
- Intercurrent illness or glucocorticoid use

Many of our patients appropriately learn HGM as part of their initial diabetes education, but are not counseled once they are on a stable regimen that ongoing monitoring is not routinely required. Additionally, patients on once daily basal insulin do not generally require multiple daily glucose measurements.

11. Malanda, U. L., Welschen, L. M., Riphagen, I. I., Dekker, J. M., Nijpels, G., & Bot, S. (2012). Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin. Cochrane Database of Systematic Reviews.



## Kenneth Roy Cohen, MD, FACP

*Chief Medical Officer*

Dr. Kenneth Cohen is an experienced physician leader, practicing internist, and researcher who has attained national recognition for health care quality improvement. He has successfully developed and reported numerous clinical quality studies in primary care, including tobacco cessation, osteoporosis, asthma, diabetes, hypertension, and ischemic vascular disease. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of OptumCare. He has served as Chief Medical Officer since 1995. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship New West Physicians was awarded the AMGA Acclaim award in 2015 and the Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

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