



Forum in review

Jun., 2019 | vol. one



FEATURED ARTICLES FROM THE 2018 FORUM FOR EVIDENCE-BASED MEDICINE



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Forum in review, revisits previously published articles from our 2018 OptumCare Evidence-Based Medicine Forum newsletters. If you missed it the first time, here is another opportunity to read and discuss information relevant to optimal care. The articles have not changed, but offer you the chance to claim CME credit and recall content from last year. We will create three volumes of the Forum in Review in 2019.

Claiming credit	CME/CNE credit is available. For more information, visit optumhealtheducation.com/ebm-forum
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: <ul style="list-style-type: none"> • Explore the educational content surrounding long-term safety of PPI inhibitors as a means to advance optimal care outcomes. • Recall pharmaceutical recommendations for the management of resistant hypertension (HTN) and short course antibiotic therapy using evidence-based literature. • Apply medical management principles grounded in evidence-based medicine that could help modify and improve treatment and clinic guidelines for colon cancer screening and adrenal incidentaloma management.

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Long-term safety of PPI inhibitors

Since we now have reliable estimates of the NNT to benefit elderly patients with prophylactic use of PPI's, it is timely to review the current literature on the potential harms of therapy. Unfortunately this data is more difficult to come by and often is available only from retrospective or observational studies, which are weak sources of evidence.

The information below has been gleaned only from prospective or case control studies and therefore represents the best available evidence.

Chronic kidney disease - There is no putative mechanism whereby renal damage would be caused by PPI use. However, a prospective study¹ of over 10,000 patients followed for 14 years found a slight increased risk of CKD with a hazard ratio of 1.45. Hypomagnesemia with QT prolongation is a rare event captured only in case reports.

Dementia - The only study² found to suggest this was a claims data base analysis of prescriptions in Germany. There were multiple flaws in study design and this is widely regarded as an unreliable report. A much more precise case control study was conducted in Finland looking only at patients with an established diagnosis of Alzheimer's and did not show any relation to PPI use.

Osteoporosis and fracture - Calcium absorption is less efficient in the absence of gastric acid. Prolonged PPI use, in observational studies, has been associated with increased fracture risk.

A prospective study³ followed over 9,400 patients for 10 years and found a shorter time to first fracture with PPI use. However, a much larger prospective study⁴ looked at 80,000 postmenopausal women and controlled for all confounding variables. There was no association found between PPI use and fracture risk. It is believed no data associating PPI use with increased risk of osteoporosis has been found.

Vitamin B12 deficiency - Gastric acid is required to split salivary binding proteins from Vitamin B12 so it can bind to intrinsic factor and then be absorbed. There is thus a plausible mechanism for B12 deficiency with long-term PPI use. A case control study⁵ of 26,000 patients suggested an increased relative risk of PPI induced B12 deficiency of 1.65. Thus, 67 patients would need to be treated with PPI therapy for two years to induce one case of B12 deficiency.

Community acquired pneumonia - A case control study⁶ of 160,000 patients, after adjusting for confounding factors, found no association between CAP and PPI use.

In summary - Vitamin B12, Vitamin D, and calcium supplementation would appear to be reasonable additions to those patients on prolonged PPI therapy, particularly in the elderly. However, specific conclusions regarding the other risks as noted above will need to await better studies. With respect to the elderly cohort in whom the risk of GI bleeding with antiplatelet therapy is high, the very long-term risks of PPI use may be less important considering the life expectancy of this cohort and the short-term morbidity and mortality of upper GI bleeding.

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Amiloride in the treatment of resistant hypertension

Resistant HTN occurs in about 10% of patients and has a high CV morbidity and mortality.

As part of the evaluation for resistant HTN several issues should be addressed:

- Noncompliance with the treatment regimen is perhaps the most common cause
- Pseudo-resistance may be present which can be caused by excess alcohol and/or salt intake
- Concomitant drugs such as NSAID's, decongestants, SNRI antidepressants, glucocorticoids and contraceptives may cause resistance to medications
- Atherosclerotic RAS has not been found to be a significant contributor nor has angioplasty/stenting of atherosclerotic RAS been shown to improve BP or CV outcomes

Assuming the above have been addressed, most patients should be treated with a three drug regimen including a thiazide diuretic (chlorthalidone is the most potent), an ACE/ARB and a dihydropyridine CCB. The "Pathway Studies" have defined the optimal fourth drug. These trials have shown that the chief mechanism of resistant hypertension is aldosterone mediated intravascular volume overload which requires a diuretic with activity in the distal nephron. The best studied of these is spironolactone with a systolic BP reduction in the range of 20 mm Hg in this setting. Unfortunately, in males there is a high incidence of gynecomastia and decreased libido limiting its use. Eplerenone is the alternative but this is expensive at \$1400/year and is less potent than spironolactone. In the Pathway 2 substudy⁸ amiloride was also studied and at the 10 mg daily dose was found to be as effective as spironolactone, with identical potassium retaining properties. The dose can be increased as high as 20 mg daily if needed. This is available as an inexpensive generic. The marked response to the addition of these drugs is often of sufficient magnitude that the CCB can be eliminated or reduced. Remember that patients with resistant HTN who respond to aldosterone inhibition or amiloride can be diagnosed with hyperaldosteronism.

Short course antibiotic therapy

With the recognition of neurotoxicity from quinolones and the increasing incidence of C diff with most antibiotic classes, there is an increased emphasis on short duration antibiotic therapy. A recent study in JAMA Internal Medicine⁷ looked at patients hospitalized with community acquired pneumonia. Despite the requirement for hospitalization and the fact that 40% of patients were characterized as severe, five days of antibiotics were more effective than ten. The criteria for stopping antibiotic at five days were afebrile for 48 hours, and no more than one sign of clinical instability (hypotension, tachycardia, hypoxia). Seventy percent of patients met criteria for the five day course. In the short course group, not only were the pneumonia outcomes the same, the readmission rate was 1.4% in the five day arm compared to 6.6% in the ten day arm. Similar studies have looked at antibiotic treatment for acute sinusitis and found equal outcomes with five day versus ten day antibiotic courses. A recent study showed that despite the available data on the benefits of short course therapy for sinusitis, nationally over two thirds of patients still receive a treatment course of 10-14 days⁹. Studies of UTI have shown cure rates in excess of 90% with single dose and 48 hour courses of therapy. It is time to educate our patients and change the duration of antibiotic therapy for these common infections.

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How does the colon polyp pathology predict the future risk of colon cancer?¹⁰

Up to one third of patients have adenomatous polyps at colonoscopy, although the lifetime risk of colon cancer in the population is only in the 3-4% range. Current algorithms suggest surveillance frequency based on the size and histology of the polyps, although the evidence supporting this approach is weak. Particularly in the most common group, those with one to two small adenomas, there are not good data to inform whether follow up should be at five, seven or ten years. Using the data from the PCLO Trial which enrolled patients from 1993 through 2001, over 16,000 patients were followed for a median of 13 years. These patients were referred for colonoscopy due to abnormal findings on screening sigmoidoscopy, however 50% of these patients had subsequent normal colonoscopies and served as the control group. In the subset of patients with advanced adenomas, defined as over 10 mm in size or having high risk histology, the cumulative incidence of colon cancer over the next 13 years was 2.9%. For comparison, the incidence in the non-advanced (i.e. small tubular) adenoma group was 1.4%, and in the no adenoma group was 1.2%. These latter two incidence rates are not significantly different. There is an ongoing large, prospective trial looking at 5 year versus 10 year surveillance for one to two small adenomas. Until these data become available, our current guideline is supported by the above findings, which suggest that patients with one to two small tubular adenomas can safely have surveillance colonoscopy at intervals of 7-10 years, and stop screening at age 75.

The Adrenal Incidentaloma

Adrenal Incidentalomas (AI) are nodules within the adrenal gland, > 1 cm in size, that are incidentally discovered while performing abdominal CT scans for other diagnoses. They occur in 3-6% of the population and increase with age. The majority are nonsecreting benign adenomas. Only 15% are secreting tumors. The initial evaluation involves assessment for hormone hypersecretion as well as determination of the likelihood of malignancy. When the initial evaluation shows a nonsecreting adenoma, follow-up studies reveal that fewer than five percent will become hypersecreting adenomas. Likewise, less than one percent will eventually be diagnosed as adrenal carcinomas. These require only minimal evaluation and are often over investigated¹¹.

Assessment for Cushing's disease - In a study of ~2,000 patients with AI's, five percent of patients has autonomous secretion of cortisol without obvious clinical indicators of Cushing's. These patients can be identified when a fasting cortisol level is >5 mcg/dl the morning after a bedtime 1 mg. dose of dexamethasone. If the result is abnormal, endocrine referral is indicated. The likelihood of developing cortisol hypersecretion is in the range of one percent per year and usually in lesions over 3 cm, therefore lesions smaller than 3 cm do not require further hormonal testing.

Assessment for pheochromocytoma - Five percent of AI's are pheochromocytomas. They will often have characteristic imaging features, including increased vascularity and delayed contrast washout. Only 50% found incidentally are associated with hypertension. All patients should have measurement of fractionated metanephrines and catecholamines in a 24 hour urine specimen. This is highly sensitive and specific for the diagnosis. Endocrine referral is indicated for an abnormal 24 hour urine study or suggestive imaging features.

Assessment for hyperaldosteronism - Only one percent of AI's are associated with increased aldosterone secretion. Evaluation is not indicated if hypertension is not present. Hypokalemia is suggestive but not necessary for the diagnosis. An accurate screening test is the morning plasma ratio of plasma aldosterone to plasma rennin. A ratio of >20 is strongly suggestive of hyperaldosteronism and indicates the need for endocrine referral.

(continued on page 6)

Assessment of malignancy – In a series of 2,000 patients, only 5% were found to have adrenal carcinomas and 2.5% were found to have metastatic disease¹². These are large tumors with most cancers >4 cm at the time of diagnosis. One large series showed an average size of 12 cm for adrenal carcinomas at the time of diagnosis. Benign adenomas are lipid rich (<10 Hounsfield units) and washout contrast rapidly. If the adenoma is lipid rich or if >60% of the CT contrast is washed out in ten minutes, 100% of the lesions were benign adenomas. No follow up imaging is needed in these patients. Benign adenomas, however, may enlarge over time. In a series of patients with AI followed for four years, only 1 out of 20 enlarging lesions was malignant. Metastatic disease is often bilateral and the primary tumor is often known when the adrenal mets are found. Endocrine referral should be considered if a lesion is >4 cm in size (>3 cm in a patient under 50 years of age).

In summary, if the imaging characteristics suggest a benign etiology and the results of hormonal testing are normal, a reasonable recommendation for follow-up is noted below.

Initial evaluation:

1. Overnight dexamethasone suppression test
2. 24 urine for metanephrine and catecholamines
3. Morning plasma aldosterone/renin level if hypertensive or hypokalemic

Indications for endocrine referral:

1. Abnormal results on diagnostic hormonal evaluation
2. Imaging characteristics that are typical for pheochromocytoma even with normal 24 hour urine studies
3. >4 cm in size (> 3 cm in a patient under age 50), or >1 cm enlargement during follow-up imaging

Follow-up evaluation - Repeat CT scans at 6, 12, and 24 months for lesions where the initial imaging has indeterminate features. Due to the rare progression to adrenal carcinoma in patients with smaller lesions (<2 cm), it is reasonable to have the first follow-up CT scan at twelve rather than six months in these individuals.

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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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