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Forum in review

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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.

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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: • Explore the educational content defining the role of inhaled corticosteroid therapy in asthma and COPD as a means to advance optimal care outcomes. • Recall pharmaceutical recommendations for the management of antibiotic utilization and acute diverticulitis using evidence-based literature. • Apply medical management principles grounded in evidence-based medicine that could help modify and improve treatment for carotid endarterectomy, and prostate cancer screenings.

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Defining the Role of Inhaled Corticosteroid Therapy in Asthma and COPD

Four important trials were recently published addressing the role of inhaled corticosteroids (ICS) in the management of asthma and COPD. An update in management is thus warranted. This update does not conflict with the recommendations of the earlier March/April edition of the OptumCare Forum article. The goals of the trials were different. In COPD, the question asked was "is there a reduction in exacerbation rate when using triple inhaler therapy which includes an ICS in COPD?" On the other hand, in asthma, where the role of ICS therapy has been more clearly defined, the question raised was "what is the optimal ICS dosing regimen for the largest subpopulation of asthma patients: those with mild persistent asthma?"

COPD – The two trials looking at triple inhaler therapy were the IMPACT Trial[1] and the TRIBUTE Trial[2]. The IMPACT Trial was a one year trial which looked at over 10,000 patients with either:

- Moderate COPD and two exacerbations within the prior year, or
- Severe COPD and one exacerbation within the prior year

Patients were randomized to a three arm study which included triple inhaler therapy compared to dual therapy which was either a LABA/ICS or a LABA/LAMA combination. NewWest Physicians Medical Group, a part of OptumCare, was one of the research sites for this trial. The study design called for abrupt discontinuation of the ICS in the 70% of patients taking them at study entry and then re-randomization to one of the three treatment arms, only two of which included an ICS. Therefore, over 23% of patients on maintenance ICS therapy enrolling in the trial had the ICS abruptly discontinued. Importantly, patients with asthmatic COPD were not excluded. This study design would be expected to result in an early increase in exacerbations in those patients with asthmatic COPD who were previously well controlled on ICS therapy and then randomized to LABA/LAMA therapy. Overall, the study showed a small decrease in exacerbation rate in the triple inhaler group at 0.91 per year compared to 1.21 per year in the LABA/LAMA group. As might be expected, this was related to a significant increase in the exacerbation rate in the first month on LABA/LAMA therapy, after which the rate was similar to the triple inhaler group. This suggests that the subset of COPD patients with an asthmatic component in whom the ICS was withdrawn accounted for the increased exacerbation rate. This point was supported by the observation that the patients with elevated eosinophil levels (the "asthmatic "COPD phenotype) had higher rates of exacerbation when only on LABA/LAMA therapy. Also supporting this was the observation of only a small difference in exacerbation rates when the triple inhaler group was compared to the LABA/ICS group (exacerbation rate 0.91 versus 1.07 per year). In both of the ICS groups compared to the LABA/LAMA group there was also a small reduction in mortality (4 fewer deaths per 1000 patient years), as well as an increase in the bacterial pneumonia rate (34 excess pneumonias per 1000 patient years). This increase in bacterial pneumonia had been a consistent finding in COPD Trial using ICS therapy.

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See a summary of the data highlighted in the table below.

IMPACT Study	Triple Inhaler Therapy	LABA/ICS Therapy	LABA/LAMA Therapy
Exacerbation rate/year	0.91	1.07	1.21
Exacerbation rate/year if eosinophils > 150 cells per microliter (asthmatic)	0.95	1.08	1.39
Exacerbation rate/year if eosinophils < 150 cells per microliter (non-asthmatic)	0.85	1.06	0.97
Severe exacerbations/year	0.13	0.15	0.19
Bacterial pneumonias per 100 patient years	9.6	9.7	6.1

The TRIBUTE Trial looked at over 1,500 patients with either severe or very severe COPD who had at least one exacerbation in the prior year. Patients with asthma were excluded and patients needed to be stable following two weeks of withdrawal of their ICS to enroll in the trial. This avoided the increased exacerbation rate potentially due to abrupt ICS discontinuation seen in the IMPACT Trial. The study compared triple inhaler therapy with LABA/LAMA therapy. With the asthmatic phenotype largely excluded, there was only a marginal decrease in exacerbation rates, which was less than in IMPACT (0.50 per patient year versus 0.59 per patient year). The reduction was again seen mostly in the subset of patients with elevated eosinophil counts suggesting a component of underlying asthma that had not been previously recognized.

TRIBUTE Study	Moderate to Severe Exacerbations per year	Moderate Exacerbations per year	Severe Exacerbations per year
Triple Inhaler Therapy	0.50	0.41	0.07
LABA/LAMA Therapy	0.59	0.47	0.09

Taken together, how should this new data inform our prescribing? Neither study result suggests the need for a change in our COPD algorithm. Choice of therapy should continue to be predicated on the GOLD Guideline and informed by the phenotypic management recommended in the April/May 2018 Forum. In summary:

- The use of ICS in COPD is best reserved for the subset of COPD patients with an asthmatic component to their disease. To identify this patient subset, look either for a prior asthma history, or a peripheral blood eosinophil count of >4%. These patients will often do well on a LABA/ICS dual regimen and only require triple therapy if there are uncontrolled symptoms on the dual regimen.
- The use of triple inhaler therapy is best reserved for the subset of patients with severe disease and frequent exacerbations; however this will be a small population of patients.

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The cost of triple inhaler therapy looks to be about $1,000 more per year than dual inhaler therapy, at $6,600 yearly. This would calculate to a high cost to prevent each severe exacerbation of approximately $50,000. Only the IMPACT Trial showed a mortality benefit to triple inhaler therapy. This may have been related to the trial required elimination of ICS therapy in the subset of asthmatic COPD patients, thus increasing the mortality in this subset. Nonetheless, even using the IMPACT data, 250 patients would need to be treated with triple therapy for five years to prevent one COPD related death at a cost of $1,250,000. This does not meet the QALY test of cost effectiveness. Despite the fact that only small benefits were noted in these two trials, it is expected that triple inhaler therapy will be heavily marketed by the two pharmaceutical companies which are selling these products.

Asthma – Mild persistent asthma accounts for about 50-75% of all asthma. Although symptoms may not be severe, up to 40% of all severe exacerbations do occur in this group of patients, resulting in significant morbidity and health care costs. SYGMA 1 and 2 were two trials conducted in concert, with slightly different study designs[3] . Each trial enrolled about 4,000 patients with mild persistent asthma and followed them for one year. Both studies compared the "as needed" use of ICS/LABA (using formoterol as the LABA due to its rapid onset) to maintenance ICS with a prn SABA, which is the current standard of care for mild persistent asthma. The study results were similar in that both of the "as needed" regimens compared favorably to maintenance ICS in terms of reduction of exacerbation frequency. There were two significant findings in the results which were consistent in both studies.

1. In the "as needed" ICS/LABA regimens, total ICS use was 75-83% lower than the maintenance ICS arm.
2. Asthma symptom control and pulmonary function were both slightly better in the maintenance ICS arm.

In SYGMA 1 this was somewhat more pronounced with 10% higher (44% versus 34%) weeks during the study with well controlled asthma measured by a daily electronic diary of asthma symptoms. In SYGMA 2, which was designed as a "real world" trial, patients were asked to retrospectively score their asthma control at their study visits and here the differences favoring maintenance ICS were small and not felt to be clinically meaningful. So how do we best reconcile these data? The editorial accompanying the studies pointed out that using the "as needed" LABA/ICS regimen would dramatically reduce the overall ICS use in the asthma population. This is important as, at least in the COPD population, there is now good evidence of reduced bone density and increased fracture risk with inhaled corticosteroids that is dependent on both the strength and duration of the treatment[4]. Using the "as needed" regimen would also reduce the national expenditure on asthma related ICS use by close to $1 billion annually, with no increase in exacerbation rates. Since the difference in asthma related symptoms with the two regimens was small, it would therefore make sense to begin treatment for mild persistent asthma with the ''as needed" LABA/ICS regimen and change therapy to maintenance ICS with an as needed SABA only in the subset of patients with uncontrolled symptoms on the "as needed regimen". This represents a paradigm shift in our asthma management, but is well supported by the results of these two trials.

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2. Papi, A., Vestbo, J., Fabbri, L., Corradi, M., Prunier, H., Cohuet, G., . . . Singh, D. (2018). Extrfine inhaled triple therapry versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): A double-blind, parallel group, randomised controlled trial. Lancet, 391(10125), 1076-1084. Retrieved from https://www.ncbi.nlm.nih.gov/labs/articles/29429593/

3. O'Byrne, P. M., FitzGerald, J. M., Bateman, E. D., Barnes, P. J., Zhong, N., Keen, C., . . . Reddel, H. (2018). Inhaled conbined Budesonide-Formoterol as needed in mild asthma. NEJM, 378, 1865-1876. doi:10.1056/NEJMoa1715274

4. Gonzalez, A. V., Coulombe, J., Ernst, P., & Suissa, S. (2018). Long-term use of inhaled corticosteroilds in COPD and the risk of fracture. Chest, 153, 321-328.

Decreasing Antibiotic Utilization

There are few circumstances in daily practice where a single drug class may simultaneously be lifesaving, life threatening, and seriously misused. In an ideal world, antibiotics would be safe enough that intense prescribing scrutiny would not be needed. Unfortunately, this is clearly not the case. Antibiotic toxicity falls generally into four categories:

1. Antibiotic resistance which impacts both public health as well as the likelihood that any patient will suffer the consequences of an inadequately treated infection due to a resistant organism.
2. Alterations in the gut microbiome which can range from life threatening C. difficile infection down to transient or persistent diarrhea. C. diff infections are becoming increasingly severe, resistant, and more difficult to treat.
3. Direct toxicity such as the tendinopathy and neurotoxicity of quinolones and the vestibular and renal toxicity of the aminoglycosides.
4. Idiosyncratic and/or allergic drug reactions which may be dermatologic or systemic and may be severe and life threatening.

Given this conundrum, are there circumstances where antibiotic utilization may be more targeted to the clinical circumstances where the benefits exceed the risks? Existing as well as emerging data call for a closer look at antibiotic indications related to the following clinical scenarios.

Acute Diverticulitis

The standard of care for decades has been antibiotic treatment, but surprisingly there is a paucity of data to support this approach. There are now two randomized trials of CT confirmed uncomplicated acute diverticulitis and both trials showed no improvement at one year of follow-up when antibiotic therapy was compared to observation.[5,6] The larger and more recent trial, DIABOLO Trial [7] looked at over 500 patients with an uncomplicated first episode of left sided acute diverticulitis and randomized them to observation versus amoxicillin/clavulanic acid for 10 days, with the first two days as IV therapy. Recovery rates were similar, and the rates of hospitalization, complicated diverticulitis, and sigmoid resection did not statistically differ between the two groups. There was however, a non-significant trend towards more cases of complicated diverticulitis and sigmoid colon resection with observation in both of these trials and therefore the DIABOLO Trial followed these patients for an additional year and recently reported the results at two years of follow-up. At two years of follow-up, the findings included:

- Recurrence rates were virtually identical in both groups at 15%.
- No statistical differences in the occurrence of complicated diverticulitis or the need for emergency surgery.
- Slight increase in the number of elective sigmoid resections in the observation group. This last point is difficult to explain since the recurrent rate was identical in both groups. The treating physicians were not blinded to the study arm and it is therefore possible that the physicians had a lower threshold to operate in the placebo group.
- 8.3% of the antibiotic treated patients experienced morbidity related to antibiotic treatment.

Given these data, how should this inform our use of antibiotic therapy for acute uncomplicated diverticulitis? When faced with a patient presenting with an acute, painful, febrile episode of LLQ pain and associated CT confirmation of acute diverticulitis, we will likely feel compelled, albeit without supporting evidence, to treat with antibiotic therapy. However, the more common scenario we encounter is mild diverticulitis, or more importantly LLQ pain without fever or leukocytosis which is often presumed to be mild diverticulitis. We should use the above studies to feel comfortable in not treating with antibiotics in these patients, understanding that the literature supports a greater likelihood of harm than benefit. We should also feel comfortable that even if a case of mild LLQ pain is attributed to functional disease such as IBS, that no harm would be done in the case of a missed diagnosis of mild diverticulitis since antibiotics should not have a role in treating this. Lastly, given the absence of data supporting the need for antibiotics in acute diverticulitis, unless complicated diverticulitis is suspected, there should be fewer indications for CT scanning with a significant decrease in radiation exposure and cost to our patients.

5. van Dijk, S. T., Daniels, L., Unlu, C., de Korte, N., van Dieren, S., Stockmann, H. B., . . . Consten, E. C. (2018). Long-tern effects of omitting antibiotics in uncomplicated acute diverticulitis. The American Journal of Gastroenterology, 113, 1045-1052. Retrieved from https://www.nature.com/articles/s41395-018-0030-y

6. Chabok, A., Pahlman, L., Hjern, F., Haapaniemi, S., & Smedh, K. (2012). Randomized clinical trial of antibiotics in acute uncomplicated divertulitis. British Journal of Surgery, 99(4), 532-539. doi:10.1002/bjs.8688

7. Unlu, C., Korte, N. d., Daniels, L., Consten, E. C., Cuesta, M. A., Gerhards, M. F., . . . van der Zaag, E. S. (2010). A multicenter randomized clinical trial investigating the cost-effectiveness of treatment strategies with or without antibiotics for uncomplicated acute diverticulitis (DIABOLO trial). BMC Surgery, 10(23), 1-10. Retrieved from http://www.biomedcentral.com/1471-2482/10/23

Carotid endarterectomy real world data

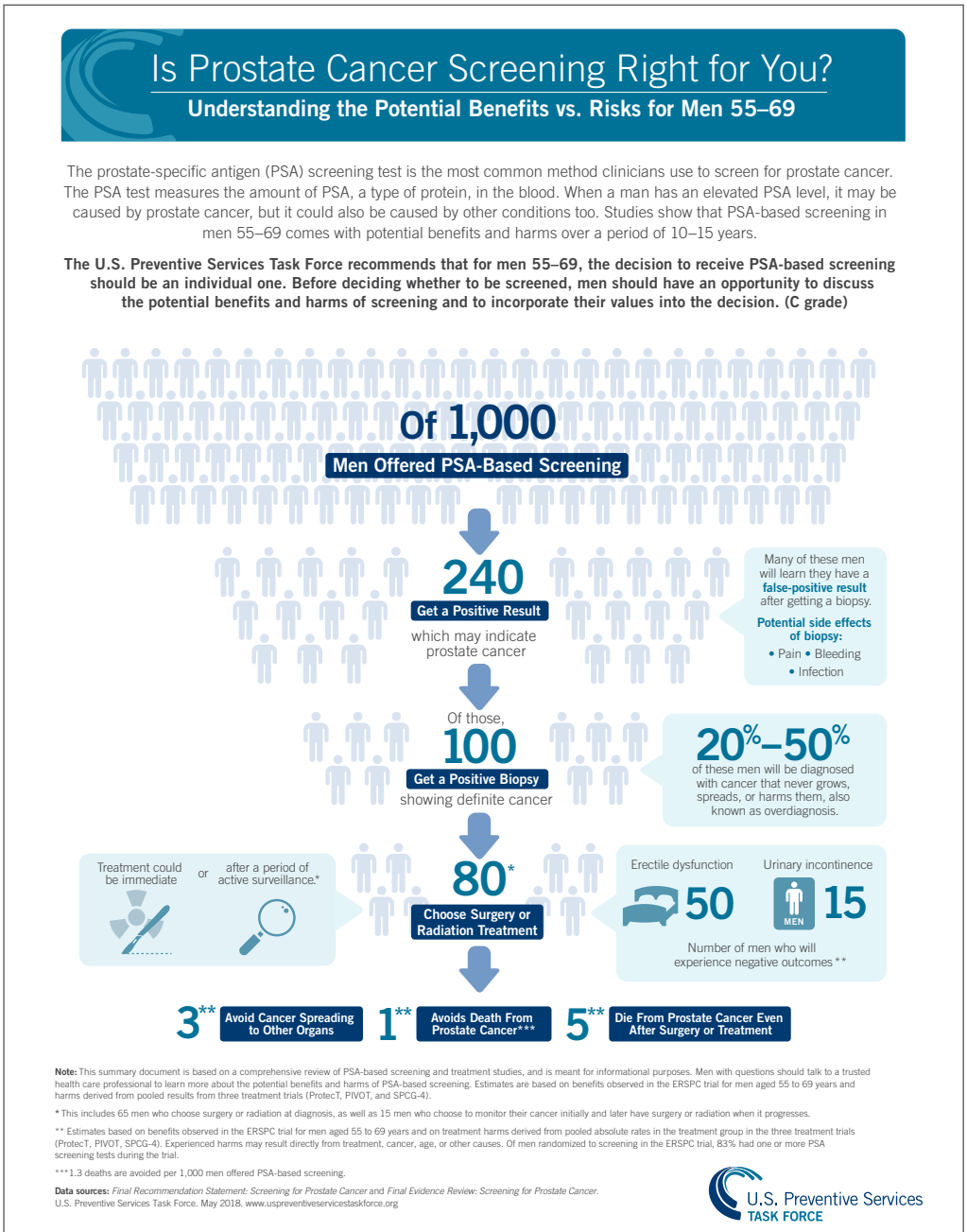
Only 8-15% of ischemic strokes are attributable to carotid atherosclerosis. The USPSTF recommends against screening for asymptomatic carotid stenosis. This is related to two key facts. The first is that the benefit of CEA in asymptomatic patients was established in the ACAS trial[8] in which the improvement in stroke rate in the operated group was 1% per year, providing for a marginal benefit compared to medical therapy (there was no established benefit in women who overall have lower stroke rates than men). With improvements in medical therapy, contemporary stroke rates in patients with asymptomatic carotid stenosis have fallen to 1% per year, eclipsing any benefit of surgery. The second reason is that the stroke and death rate in operated patients in this trial was felt to be lower than the community experience since these surgeons were performing in excess of 50 CEA's yearly, a number rarely achieved in practice today. A study in JAMA[9] sheds very important light on this latter point. It looked at the national trends in the use of CEA from 1999-2014. Unfortunately, even in 2014, 74% of these procedures were in asymptomatic patients, and overall 45% of the patients were women. The rate of ischemic stroke or death at 30 days was 7%. This study of real world outcomes suggests a surgical stroke rate that is 7 fold higher than medical therapy. It highlights the point that there should be strikingly few clinical circumstances where evaluation or subsequent surgery should be considered for asymptomatic carotid stenosis, in this author's opinion. There are several ongoing trials of contemporary medical therapy compared with endarterectomy in patients who are asymptomatic. Hopefully, these studies will define best evidenced based care for these patients.

8. Gray W, Connoly E. Carotid endarterectomy in patients with asymptomatic carotid artery stenosis. Asymptomatic Carotid Artery Stenosis. June 2007:165-174. doi:10.3109/9780203089859-16.

9. Lichtman JH, Jones MR, Leifheit EC. Carotid Endarterectomy and Carotid Artery Stenting in the US Medicare Population. JAMA. September 2017:1035-1046. doi:10.1001/jama.2017.12882 .

USPSTF recommendation for prostate cancer screening update

Screening for prostate cancer remains controversial with only one study demonstrating improved survival. This was the ERSPC trial[10] which looked at 182,000 men ages 50-74. 781 patients needed to be screened to prevent one prostate cancer after 13 years of follow up. Over diagnosis was estimated in 40% of the patients. 27 patients needed to be treated to save one prostate cancer death[11]. A British study looked at screening 420,000 men aged 50-59 years of age randomized to screening with a single PSA versus no screening[12]. In the screened group, biopsy with treatment as indicated was provided for those with a PSA level >3.0. After ten years of follow up the prostate cancer specific mortality was not statistically different averaging about 1% in both groups. When men are provided with a high quality shared decision making tool, they elect PSA screening only one third of the time. In 2017, the USPSTF (US Preventative Services Task Force), updated the previous "D" recommendation to a "C" recommendation (selectively offering to individuals based on professional judgment and patient preference) for patients ages 55-69. Note that this is still not an A or B recommendation. Best practice mandates that we have this discussion with our patients. Moreover and perhaps more importantly, there are no data supporting improved outcomes with treatment of Gleason 6 prostate cancer. Management of these patients should be active surveillance in most if not all patients.



Graphic used with permission from U.S.Preventive Services Task Force

10. Schroder, F. H., Hugosson, J., Roobol, M. J., Tammela, T. L., Ciatto, S., Nelen, V., . . . Lilja, H. (2009). Screening and prostate-cancer mortality in a randomized european study. NEJM, 360, 1320-1328. doi:10.1056/NEJMoa0810084

11. Thompson, I. M., & Tangen, C. M. (2014). Prostate cancer screening comes of age. The Lancet, 384(9959), 2004-2006. doi:10.1016/50140-6736(14)61008-4

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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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