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Forum for Evidence-Based Medicine

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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	• Evaluate post-acute sequelae of SARS-CoV-2 infection • Review medication harm that results in ER visits and review polypharmacy in dementia patients. • Discuss the following: optimal management of intermittent claudication; cardiovascular risks associated with fatty liver disease; ineffectiveness of preoperative stress testing in asymptomatic patients.

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Post-acute sequelae of SARS-CoV-2 infection

Post-acute sequelae of SARS-CoV-2 (PASC) infection is defined by the NIH consensus group[1] as symptoms persisting greater than 30 days following the onset of COVID-19. SARS-CoV-2 has now infected over 254 million persons globally and 48 million persons in the United States.[2,3,4] This is an underestimate of total cases with a significant percent of cases either asymptomatic or mildly symptomatic and often undetected.[5] Survivors of infection with SARS-CoV-2 are experiencing a spectrum of post-infection outcomes. We are just beginning to understand the nature and extent of these outcomes.

SARS-CoV-2 is primarily a respiratory pathogen and this is reflected in the high percentage of patients presenting with primarily respiratory symptoms. The only symptom that predicts hospitalization is dyspnea or shortness of breath. Cough, fever and shortness of breath were present in 45% of all patients and 68% of those hospitalized.[6] However, SARS-CoV-2 also manifests unusual symptoms with greater frequency compared to other pathogens, notably anosmia and dysgeusia present in over 50% of patients and more commonly in ambulatory patients.[7] The large variety of presenting symptoms is one of the diagnostic challenges of COVID-19.

PASC will generally present as one of two syndromes. The first is serious persistent organ dysfunction in those who had critical illness. This can include pulmonary fibrosis, cardiomyopathy, sequelae of thrombosis, and neurocognitive symptoms. The second syndrome is seen in outpatients with milder disease and the most common symptoms are fatigue, myalgias, dyspnea, anxiety, sleep disturbances, and residual taste/smell dysfunction.[6] While duration of symptoms is often more prolonged in patients with more severe disease even younger patients and those with milder disease can have prolonged symptoms.[8]

A recent meta-analysis was conducted to characterize PASC.[9] The 57 included studies comprised a group of 250,351 survivors of COVID-19; 140,196 (56%) were male; 197,777 were hospitalized (79%). Symptoms were frequent both acutely (up to one month) after infection and distantly (> 5months) after infection (Table 1).

Table 1. Patients with at least one PASC (median and interquartile range, (IQR))

Symptom duration (Months)	Median (%)	IQR	Number of studies
1 (short term)	54	45–69	13
2-5 (intermediate term)	55	35–65	38
6 or longer (long term)	54	31–67	9

Like symptoms were clustered into categories and the most common symptoms fell into the categories of pulmonary, neurologic, mental health, functional mobility impairments and general/constitutional. The most common abnormalities in each category were chest imaging abnormality (62%), difficulty concentrating (24%), general anxiety disorder (30%), general functional impairments (44%) and fatigue or muscle weakness (37%). These high sequelae rates were likely skewed by the high rate of hospitalization in this cohort of patients.

Several additional meta-analyses have looked at PASC. Many of the analyses have been limited by the lack of an agreed upon definition of post-acute sequelae as they were published before the consensus definition of PASC. There has also been great variability in how symptoms are reported or assessed post-infection.

Nasserie et al. reviewed 92 studies reporting on 9751 patients (Table 2, Row 1).[10] Researchers considered persistent symptoms to be those lasting longer than 60 days after diagnosis, symptom onset, or hospitalization or at least 30 days after hospital discharge. Neurocognitive symptoms were common (25%) but only recorded in four studies.

Lopez-Leon et al reported on almost 50,000 patients and included patients as soon as two weeks after disease onset as having persistent symptoms (Table 2, Row 2).[11] There were limited data on disease severity. With the early definition of persistence, 80% of patients had at least one symptom. Inclusion of patients as early as 14 days after symptom onset likely overestimating prevalence of persistent symptoms.

A Swiss group used self-reported symptom assessment to characterize symptoms seven to nine months post COVID-19 infection.[12] Patients requiring hospitalization were excluded. In this patient group of 410 patients, 39% continued to have symptoms seven to nine months post-infection. Persistent symptoms increased with age and were more common in females (Table 2, Row 3).

Table 2. Representative studies looking at PASC

Reference	# Studies	# Patients (% male)	Median age (yrs)	Persistent definition range (days)	At least 1 symptom persistent (%)	Hospitalized (%)	Most common symptoms (%)
Nasserie	92	9751 (54)	NR	30 after d/c 60 after recovery	72.5	23–80	D (36); F (40) Sl (29)
Lopez-Leon	15	47910 (NR)	NR	14-110	80	NR	F (58); H (44); AD (27); HL (25); D (24)
Nehme	1	410 (33)	43	210-270	39	none	F (21); A (8); H (10)

D = Dyspnea; F= Fatigue; Sl= Sleep disturbance; AD= Attention disorder; HL= Hair loss; H= Headache; A=Anosmia NR=not reported

Complicating the understanding of symptom persistence after COVID-19 is the well described post-intensive care syndrome.[13] Post-intensive care syndrome includes the cognitive, psychological, physical and other consequences that plague ICU survivors. This syndrome occurs after ICU stays from any number of causes. Most common sequelae in some cases lasting for years after an ICU stay include cognitive impairment (30-80%), psychiatric illness (8-57%), frequent exercise intolerance and pulmonary function abnormalities.

A significant portion of the United States population will be affected by COVID-19 with some portion of these going on to have PASC. This is not persistent infection; it is the aftermath of an acute infection. We are early in our understanding of how these patients should be best managed. Patients who experience persistent dyspnea three months post COVID-19 may benefit from pulmonary evaluation and echocardiography due to the known sequelae of pulmonary fibrosis and myocarditis.[8] Currently, there are no pharmacologic interventions recommended for PASC, other than early observational trials of steroids in patients with ongoing interstitial lung inflammation.[6] Optimal diagnostic evaluation and treatment of PASC is critical to avoid excessive low value diagnostic testing and non-evidenced based treatments. A coordinated rehabilitation program may be needed for some persons recovering from COVID-19 to meet specific patient needs. Multidisciplinary management may be needed in many cases.

In summary, most patients with SARS-CoV-2 infection will recover with symptom resolution in a week or less. An unknown number of patients will have minimal symptoms or asymptomatic infection. A small but significant number of patients will have persistent symptoms lasting more than 30 days and meet diagnostic criteria for PASC. The NIH is coordinating a multidisciplinary task force in an attempt to quickly define optimal diagnostic and management strategies for PASC.

Medication harm resulting in ER visits

The recent article by Budnitz et al. highlights the dangers and relative frequency of inappropriate prescribing.[14] In this cross-sectional study, authors examined records from U.S. emergency department (ED) visits from a nationally representative sample during the period between 2017-2019 to determine how many visits were primarily related to harm from medication management. Interestingly and disappointingly, the data from the 2017-2019 time-period shows higher rates of harm from medications compared with four years earlier as reported for the 2013-2014 timeframe.[15] Harms attributable to medications that were used as directed were higher in those age ≥ 65 years compared to younger patients, estimated at 11.6 per 1000 people seen in the ED. Of cases identified in all age groups, roughly 38.6% needed to be hospitalized, with even higher proportions in the ≥ 65 years age groups. In those ≥ 65 years of age, the most common medication categories associated with harm were anticoagulants and agents used to treat diabetes mellitus. These two categories were also the top causes of medication-related harms seen in the ED in the 45–65-year age group, although at lower rates. Over half of harms relating to anticoagulants involved the use of warfarin, although direct oral anticoagulants (DOACs) were also implicated. Almost all harms from anti-diabetic medications involved the use of insulin. There are additional and important findings pertaining to the appropriate use of psychoactive medications and of antibiotics in younger age groups.

These findings underscore the importance of appropriate use of all medications, highlighting the risks of drifting outside of the therapeutic window when using anticoagulants or anti-diabetic medications particularly in older populations. Previous issues of the Forum outline appropriate use of newer anticoagulants and, if put into widespread practice, should result in fewer harms. Based on safety and cost-effectiveness, **apixaban is the preferred DOAC.**[16,17]

Recall that over 50% of seniors on insulin or sulfonylureas have an A1c<7% and are therefore overtreated, significantly increasing the risk of ER and hospital admission. Regarding treatment drugs and targets for patients with Type 2 diabetes mellitus as described in this Forum previously, therapeutic targets in patients should be adjusted according to age and comorbidities to minimize risk of harms. **HgbA1c in the range of 7.5-8.5% should be the target in older adults. Use of generic NPH insulin over new basal insulin analogs is more cost effective and possibly safer.**[18,19,20]

Although associated costs have not been clearly quantified for all conditions, the cascade of treatment and patient harms stemming from inappropriate prescribing are evident, and can be mitigated with appropriate medical management.

Polypharmacy more likely among patients with dementia

Polypharmacy, defined as the use of multiple medications or more medications than are medically necessary, is common among older adults, with the highest number of medications taken by those residing in nursing homes.[21] Polypharmacy increases risks of drug reactions, falls, cognitive decline, and mortality. Among patients with dementia, polypharmacy may not align with overall treatment goals and may cause harm. A recent study evaluated rates of polypharmacy among adults with dementia compared to adults without dementia.[22]

Researchers conducted an observational study of survey data from the National Ambulatory Medical Care Survey (NAMCS) from 2014-2016.[22] The NAMCS is a probability sample survey of patient visits to office-based physicians. The study definition of polypharmacy was ≥5 continued or newly prescribed medications (including all prescriptions and over-the-counter medications and vitamins). A secondary analysis compared the use of ≥10 medications between cohorts.

There were 918 sampled visits for patients with dementia and 26,543 sampled visits for patients without dementia, corresponding nationally to 29 million and 780 million visits, respectively. Patients with dementia were older than the patients without dementia, were more likely to be female, and had more comorbidities. Patients with dementia had a median number of eight medications compared to a median of three medications among patients without dementia ($p<0.001$). The adjusted odds that patients with dementia had ≥5 medications were three-fold higher compared to patients without dementia (adjusted OR 3.0; 95% CI: 2.1-4.3). The adjusted odds of having ≥10 medications were similarly higher (adjusted OR 2.8; 95% CI: 2.0-4.2). Additionally, patients with dementia were more likely to receive at least one sedating or anticholinergic medication.

Use of the NAMCS has some limitations, including:

- Potential under coding of patients with milder forms of dementia and cognitive impairment
- A lack of granular data about disease severity and chronicity
- Possible inconsistencies in medication reporting and listing

However, none of these are likely to have caused extensive inflation of the numbers of medications used. Thus, polypharmacy appears to be more among older patients with dementia than patients without dementia, which may be discordant with overall treatment goals and can cause harm. This once again underscores the important role of the primary care provider in deprescribing unnecessary and harmful drugs in the elderly.

Optimal management of intermittent claudication is maximal medical therapy

Many of our Optum Care CDO's have recognized the value of vascular plaque assessment to identify individuals who may benefit from maximizing CVD guideline directed medical therapy (GDMT). There are three predominant options for plaque assessment: carotid intima media thickness (CIMT), coronary artery calcium (CAC) scoring, and peripheral artery disease (PAD) assessment. Because it can be done quickly in the primary care office, PAD screening is now frequently used.

With increased PAD screening comes increased diagnosis of patients with both asymptomatic disease and intermittent claudication. One of the risks of increasing PAD diagnosis is overtreatment with revascularization. The Society for Vascular Surgery and the American Heart Association recommend supervised exercise therapy, smoking cessation, and optimal medical management as first-line treatment.[23,24] Revascularization procedures are controversial.

To this end, an important study was recently published in the Journal of Vascular Surgery.[25] It looked at over 1,000 patients who presented with intermittent claudication and studied the outcomes in the one third that were surgically treated compared to the two thirds that were medically treated. Propensity score methods were used to reduce confounding. The group that received revascularization was slightly younger, reported more tobacco use within the past 90 days, had higher rates of Type 2 diabetes (32.3% versus 16.3%), and higher rates of COPD (4.3% versus 1.7%), but otherwise matched similarly with the non-revascularized group in terms of sex and comorbidities.

The key outcome was progression to chronic limb threatening ischemia (CLTI). During the 15-year study period, patients who received revascularization were significantly more likely to progress to chronic limb-threatening ischemia (hazard ratio, 2.9) and a significantly greater number required ipsilateral limb amputation (hazard ratio, 4.5). Specific differences in chronic limb-threatening ischemia among patients with and without revascularization were 13% versus 6% at 3 years, 18% versus 8% at 5 years, and 27% versus 10% at 10 years (all $p<0.01$). Specific differences in limb amputations were 3% versus 1% at 3 years, 6% versus 1% at 5 years, and 11% versus 2% at 10 years (all $p<0.001$).

Although this was a single institution retrospective study, it underscores the importance of following our current algorithm for the management of PAD. Patients with intermittent claudication should not undergo surgical evaluation but rather be treated with maximal GDMT unless there is evidence of critical limb ischemia.

The cardiovascular risks associated with fatty liver disease

A recent and robust meta-analysis by Mantovani et al.[28] provides updates since previous articles in this Forum about non-alcoholic fatty liver disease (NAFLD) (Nov/Dec 2018; March 2021; July 2021). Recall the burden of disease is quite high, with some estimates as high as 46% in the United States.[29] Associations with other metabolic derangements including diabetes mellitus, hyperlipidemia,[30] and cancers such as hepatocellular carcinoma and some extrahepatic cancers are well described,[31] and NAFLD has at times been referred to as the liver manifestation of the metabolic syndrome. Findings of the Mantovani et al. meta-analysis clarify how the magnitude of cardiovascular disease risk increases with severity of NAFLD. This study aggregated data from over 5.8 million adults with median follow-up of 6.5 years and demonstrated that risk of fatal and non-fatal CVD events was higher in those with NAFLD (HR 1.45, 95% CI 1.31-1.62). This risk was even higher for those with more advanced forms of NAFLD, such as non-alcoholic steatohepatitis (NASH) (HR 2.5, 95% CI 1.68-3.72). NAFLD is not a static disease but rather a spectrum of fatty liver diseases with multisystem involvement that can progress from simple steatosis to NASH with fibrosis and, at its extreme, cirrhosis with liver failure. The findings from the meta-analysis were independent of co-morbidities such as diabetes mellitus, age, sex, smoking, hypertension, and other cardiovascular risk factors, indicating that NAFLD itself is a potential independent risk factor for poor cardiovascular outcomes.

This article adds to the scientific evidence of disease burden associated with this condition. This further highlights the importance of appropriate diagnosis and aggressive management of NAFLD to prevent progression and worsening CVD risk, as well as progression to DM2 and liver fibrosis. Evidence-based interventions previously described include weight loss through behavioral intervention, pharmacotherapy or bariatric surgery.[32]

- Behavior modification for weight loss must be intensive and sustained to be effective in slowing or stopping NAFLD progression.
- Bariatric surgery is highly effective and has proven cost effectiveness.
- The GLP1-RA's and the newer GLP1-RA/GIP drugs are also highly effective but very expensive, and cost-effectiveness data are not yet available for these drug classes.

Futility of preoperative stress testing in asymptomatic patients

In 2004, a landmark study was published in the NEJM.[26] It looked at over 500 patients with known high-grade CAD based on preoperative catheterization. Patients were undergoing two of the highest risk surgeries: abdominal aortic aneurysm resection and surgery for occlusive peripheral arterial disease. Half the patients were sent to the OR without revascularization and the other half had either stenting or bypass surgery. At three months, six months, and two years postoperatively, there was no reduction in CV events in the revascularized groups. This study moved the needle somewhat away from routine preoperative stress testing, but these continued to occur at a high enough rate that it ranks in the top ten "wasted care" interventions as defined by Medicare.

We now have new data from a recent study looking at surgeons participating in the Vascular Quality Initiative.[27] They looked at over 52,000 patients undergoing abdominal aortic aneurysm surgery via either the endovascular aneurysm repair (EVAR) or open (OAR) approach. The median proportion of stress test usage across centers before EVAR was 35.9% and before OAR was 58%. There was a striking 7-fold variation in the use of preoperative stress testing among the surgeons. There was no difference in perioperative CV risk between those who did and did not undergo preoperative stress testing. Importantly, there was also no difference in CV risk in high testing centers compared to low testing centers.

The rate of major adverse cardiac events (MACE) was 1.8% after EVAR and 11.6% after OAR. The 1-year mortality was 4.6% for EVAR and 6.6% for OAR. Interestingly, the centers in the highest quintile of stress testing had a higher adjusted likelihood of MACE after both EVAR (OR 1.78) and OAR (OR 1.99). This is the opposite of what would be expected if preoperative stress testing positively impacted perioperative CV events. The 1-year mortality was similar across all quintiles and therefore not impacted by the rate of preop stress testing.

These data once again suggest the futility of preoperative stress testing in patients who do not have symptoms of active coronary artery disease. An algorithm created by the Optum Care algorithm committee is available that could help triage patients who may benefit from preoperative cardiac evaluation.

Pre-operative cardiac risk assessment for non-cardiac surgery

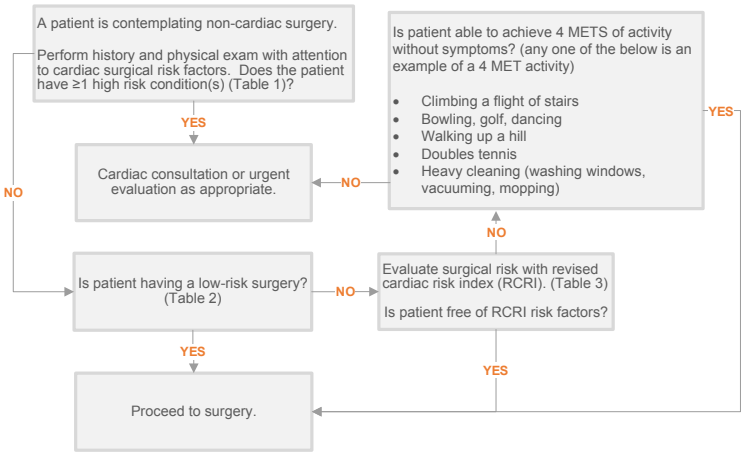

Table 1: Examples of High-Risk Surgical Conditions

- Moderate or greater valvular stenosis or regurgitation (particularly aortic)
- Cardiac implantable device
- Moderate or severe pulmonary hypertension
- Congenital heart disease
- Decompensated heart failure
- Unstable angina or MI within 60 Days
- High-grade arrhythmias

Table 2: Examples of Low-Risk Surgical Procedures

- Dermatology procedure
- Arthroscopic procedures
- Simple mastectomy (complete breast)
- Ophthalmologic surgery
- Endoscopic procedures

Table 3: Revised Cardiac Risk Index

- High-risk site (any vascular, intraperitoneal, or intrathoracic site)
- History of ischemic heart disease
  - Previous myocardial infarction or a positive exercise test
  - Current complaint of chest pain considered to be secondary to myocardial ischemia
  - Use of nitrate therapy
  - ECG with pathological Q waves
  - Coronary revascularization procedures (DO NOT COUNT unless at least one other criterion for ischemic heart disease is present)
- History of heart failure
- History of cerebrovascular disease
- Diabetes requiring insulin therapy
- Preoperative serum creatinine > 2 mg/dl

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Algorithms reviewed and approved by the Optimal Care clinical team, CDO nominated clinicians, and the Optimal Care Clinical Committee on behalf of the OptumCare Clinical Leadership Congress and Physician Executive Council. ©2021 Optum, Inc. All rights reserved. May 2021.

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Kenneth Roy Cohen, MD, FACP

Dr. Kenneth Cohen is an experienced physician leader, practicing internist, and researcher who has attained national recognition for health care quality improvement. 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 Optum Care. He served as Chief Medical Officer from 1995 - 2020. He now serves as the Executive Director of Clinical Research for UHG R&D and Senior National Medical Director for Optum Care. 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.

John Hitt, MD, MBA

Dr. Hitt is the Evidence-Based Medicine Implementation Sage and Senior National Medical Director for Optimal Care. He has been a physician executive for more than 25 years. Prior to joining Optum, he was Chief Medical Officer at Maricopa Integrated Health System (MIHS) in Phoenix Arizona. Dr. Hitt was a key member of the senior leadership team at MIHS having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and coordinated the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

He served as the Chief Medical Quality Officer for Hennepin Health System. He was a physician leader for VHA (now Vizient), Medical Director at Caremark International and the Vice President of Medical Affairs at the University of Minnesota Hospital.

Dr. Hitt graduated from the University of Virginia where he played division one soccer. He received his Medical Doctorate from the Medical College of Georgia (AOA honors), completed his Internal Medicine and Infectious Disease Fellowship at the University of Minnesota Hospital and Clinics and his MBA at the Carlson School of Management at the University of Minnesota. He is the proud father of seven children.

Geoffrey Heyer, MD

Dr. Heyer is board certified in neurology with special certification in child neurology and in headache medicine. Prior to joining our team, Dr. Heyer was an associate professor of neurology and pediatrics at The Ohio State University and Columbia University Medical Center, specializing in autonomic disorders, headache, and pain management. He has published over 50 peer-reviewed research papers and numerous editorials, clinical reviews, and textbook chapters. He also co-authored a textbook on childhood stroke and cerebrovascular disorders.

Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons. He completed his neurology and child neurology residencies at Columbia-Presbyterian Medical Center. He has additional research training from the Mailman School of Public Health, Columbia University.

Joshua Jacobs, MD, FAAFP

Dr. Jacobs is a Fellow of the American Academy of Family Physicians and an educator with over 20 years of clinical, academic, and leadership experience regionally, nationally, and internationally. He currently serves as National Medical Director for Provider Intelligence within Clinical Performance at Optum Care. In his various roles, he has established new organizational systems to empower clinicians, administrators, researchers, students and staff to thrive and succeed. Examples prior to joining Optum include establishing a new US LCME-accredited medical school; moving the national dialog at the Association of American Medical Colleges (AAMC) medical education services to be more student-centric and evidence-informed using principles of design thinking; helping the country of Singapore transition, accredit and modernize its medical educational model; consulting for the Japanese government on national patient safety initiatives; and creation and oversight of a successful medical device start-up company's research arm culminating in successful FDA clearance. He also has extensive experience in designing and presenting curricula and training sessions, editing, publishing, and grant writing in medical fields.

Dr. Jacobs is a Clinical Professor at the Washington State University College of Medicine. He graduated from Pomona College with honors and from the John A. Burns School of Medicine as a member of the Alpha Omega Alpha honor society.

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