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Geriatrics update 2015: Vaccination, frailty, chronic disease guidelines, and cognition

ABSTRACT

This paper discusses recent developments and recommendations for elderly patients concerning immunizations, heart failure, lipid therapy, blood pressure control, and dementia.

KEY POINTS

Vaccination costs will increase—with unclear added value—with new guidelines for influenza and pneumococcal vaccines.

Multiple simultaneous interventions for heart failure have additive value. These are education, a beta-blocker, an angiotensin-converting enzyme inhibitor, and, in some, an aldosterone antagonist, anticoagulation for atrial fibrillation, and an implantable cardioverter-defibrillator or cardiac resynchronization therapy.

Statin therapy should be intensified with an eye to goals of care and tolerability rather than a specific lipid goal.

Exercise improves physical and mental health in all, including the elderly.

Dementia still has no magic bullet. Selective serotonin reuptake inhibitors might help behavior issues, and vitamin E might bring modest cognitive improvement but with possible risk.

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Guidelines for the management of chronic disease are starting to recognize vulnerable elderly patients. The topics in this review, culled from recent studies and recommendations, were chosen because they may change geriatric care. They include the newest influenza and pneumococcal vaccines; recommendations for managing chronic heart failure, cholesterol, and blood pressure; preventing frailty; drug treatments for dementia; and the impact of cognitive impairment on health outcomes.

INFLUENZA VACCINATION: HIGH-DOSE SUPERIOR BUT COSTLIER

Three classes of influenza vaccines have been available for some time:

- The standard-dose, trivalent inactivated injectable vaccine (IIV3-SD) contains H1N1, H3N2, and influenza B strains and is approved for all ages over 6 months.
- The quadrivalent vaccine (available mostly for nasal administration) has the same strains as the trivalent vaccine plus a second, different influenza B strain. The inactivated vaccine is injectable for all persons over the age of 6 months; the live-attenuated vaccine is available as a nasal spray only for ages 2 through 49.
- The high-dose injectable vaccine (IIV3-HD) contains the same strains as the trivalent vaccine plus four times as much hemagglutinin—the influenza virus antigen that stimulates immunity.

Although IIV3-HD has been available since 2010, no clinical data existed until 2014 showing it to be superior to standard-dose vaccine.

DiazGranados et al[1] randomized nearly 32,000 adults age 65 and older to receive either the standard-dose or the high-dose vaccine. The primary end point was laboratory-confirmed influenza caused by any influenza viral type or subtype, in association with a protocol-defined influenzalike illness.

The primary end point was reached in 1.4% of those with the high-dose vaccine and 1.9% of those with the standard-dose vaccine (relative efficacy 24.2%, 95% confidence interval 9.7–36.5). There was also a 26% reduction in respiratory illness regardless of laboratory confirmation. Mortality rates were identical and low (0.5%) in both groups. In those without laboratory confirmation of respiratory illness, there was a 26% lower rate of pneumonia but no statistical difference in rates of hospitalization, medication use, routine office visits, and emergency department visits.

These results can be interpreted as meaning that the high-dose vaccine prevented about a quarter of the laboratory-confirmed influenza cases that would have occurred with the standard-dose vaccine. However, due to the low rate of disease in those given the standard-dose vaccine, the number needed to treat to prevent one influenza infection was about 200 with the high-dose vs the standard-dose vaccine; to prevent one case of pneumonia, more than 270 would need to be treated.

The current price differential as well as the high number needed to treat to prevent one infection may discourage the use of the high-dose vaccine. Medicare Part B pays for one dose of either influenza vaccine per season. For patients who paid out of pocket, the 2014–2015 season cost at a typical pharmacy was about $32 for the standard-dose vaccine and $55 for the high-dose.

PNEUMOCOCCAL VACCINATION

Conjugate vaccine now recommended for seniors

The 23-valent polysaccharide vaccine (Pneumovax) has been available since 1983 and is recommended in the United States for all adults age 65 and over. A 13-valent pneumococcal diphtheria conjugate vaccine (Prevnar 13) has been available since 2010. Until recently, the conjugate vaccine was recommended for children; the only adults for whom it was recommended were those age 19 and over who either were immunocompromised or had a cochlear implant, asplenia, a cerebral spinal fluid leak, or renal failure.

The CAPITA trial[2] (Community-Acquired Pneumonia Immunisation Trial in Adults) randomized nearly 85,000 people (most 65 and older, and some children) in the Netherlands to receive either the conjugate vaccine or placebo. It found a 46% reduction in community-acquired pneumonia (P = .0006), a 45% reduction in nonbacteremic nonvaccine-type community-acquired pneumonia (P = .0067), and a 75% reduction in vaccine-type invasive pneumococcal disease (P = .0005). Common side effects included pain, swelling at the injection site, limitation of arm movement, fatigue, headache, decreased appetite, chills, and rash.

Based on this one study, the Advisory Committee on Immunization Practices[3] recommended that all adults 65 and older receive the conjugate vaccine.

The recommendations for the conjugate vaccine for all ages are complicated. Limited to those age 65 and older, current recommendations are:

- For those who have *already* received the polysaccharide vaccine: get the conjugated vaccine at least 1 year later
- For those who have *never* received the polysaccharide vaccine: get the conjugate vaccine now, then the polysaccharide vaccine 6 to 12 months later.

Whether the Netherlands findings fully apply to the United States is under question. At the time of the study, Dutch infants but not adults had received pneumonia conjugate vaccinations since 2002 with a high compliance rate. Unlike in the United States, the polysaccharide pneumococcal vaccine had not been routinely recommended in the Netherlands. There may have been some indirect immunity due to the "herd" effect, but no direct immunity. With a likely higher background immunity to pneumonia in the United States, the dramatic reduction in infection noted in the Netherlands may not be duplicated here.

For those without Medicare coverage, the 2014–2015 winter season cost at a pharmacy was about $95 for the polysaccharide vaccine

Number needed to treat with the high-dose vs the standard-dose vaccine to prevent one case of influenza: 200

and about $200 for the conjugate vaccine. As of February 2, 2015, the Centers for Medicare and Medicaid Services are implementing Medicare Part B coverage to allow initial pneumococcal vaccine for Medicare patients who never received a pneumococcal vaccine under Medicare Part B, and then a different, second pneumococcal vaccine, 1 year after the first vaccine was administered.

HEART FAILURE

Eplerenone's new role in mild heart failure

Aldosterone antagonists have been recommended for moderate to severe heart failure (New York Heart Association [NYHA] classes III and IV) for some time. The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines also recommend them for mild heart failure (NYHA II).[4]

The EMPHASIS trial[5] (Eplerenone in Patients With Systolic Heart Failure and Mild Symptoms) randomized 2,737 patients, median age 69, with NYHA class II heart failure and an ejection fraction of no more than 35% to receive the aldosterone antagonist eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy. The trial was stopped early, after a median follow-up of 21 months, when the treatment group was found to have a significantly lower risk of cardiovascular death or hospitalization for heart failure or for any cause.

2013 ACC/AHA guidelines recommend aldosterone antagonism for mild heart failure

Of note: hyperkalemia occurred in 11.8% of the eplerenone group vs 7.2% in the placebo group ($P < .001$). The high frequency of hyperkalemia in the placebo group may have been due to concomitant use of angiotensin-converting enzyme (ACE) inhibitors.

Sodium restriction reasonable

Although sodium restriction has been standard practice in heart failure for decades, restricting sodium in the elderly was given only a IIa ("reasonable") classification, based on level C (very limited) evidence.[4]

Strong evidence exists that middle-aged and young older adults with heart failure (with preserved or reduced ejection fraction) should reduce their sodium intake by about 1 g per day or aim for a mean 24-hour urinary sodium excretion of about 2.3 g per day. However, little evidence exists to support a specific long-term target intake, and no evidence exists for "old-old" patients (loosely defined as older than 75 or 80).

Caution with digoxin

Use of digoxin has been recommended in patients with heart failure with reduced ejection fraction to reduce hospitalizations,[4] but more recent publications have raised questions regarding its safety and efficacy.

Freeman et al,[6] in a prospective study, followed 2,891 patients with newly diagnosed systolic heart failure over 2.5 years, of whom 529 were prescribed digoxin. The digoxin group had a higher rate of death (14.2 vs 11.2 per 100 patient-years) and heart failure-related hospitalization (28.2 vs 24.4 per 100 person-years).

The study was unable to determine if the digoxin level influenced the results, since about 30% of patients had no digoxin level drawn, and an additional 27% had only one level drawn during the study. For those with measured blood levels, the mean digoxin level for men was 0.83 ng/mL and 1.12 ng/mL for women. Risks and benefits of this medication should be weighed carefully.

Simultaneous interventions beneficial

The following evidence-based interventions are recommended for patients with heart failure with reduced ejection fraction:

- Heart failure education
- A beta-blocker
- An ACE inhibitor
- An aldosterone antagonist for NYHA class II–IV symptoms
- Anticoagulation for atrial fibrillation in patients with added risks (eg, hypertension, diabetes, prior transient ischemic attack or cerebrovascular accident, age at least 75)
- An implantable cardioverter-defibrillator and cardiac resynchronization therapy for select patients with symptoms, increased QRS duration, and left bundle branch block.

Fonarow et al[7] studied these interventions in an analysis of a prospective study of outpatients with diagnosed heart failure or myocardial infarction and reduced left ventricular ejection fraction. Their nested case-control study compared 1,376 patients, mean age 72, who had died within 24 months and 2,752

propensity-matched controls who survived to 24 months. The survival rate was 37% higher with two simultaneous interventions than with one, and 70% higher with four simultaneous interventions than with one. Benefits plateaued with four to five interventions.

LIPID-LOWERING THERAPY FOR SENIORS

The 2013 ACC/AHA cholesterol guideline[8] included new recommendations specifically relevant to the elderly. It advocates using a new cardiovascular disease risk calculator that provides an estimate of 10-year risk of atherosclerotic cardiovascular disease (ASCVD), based on data from multiple community-based populations and applicable to African American and non-Hispanic white men and women ages 40 through 79. Primary prevention with a statin is encouraged for those with a 10-year risk of 7.5% or higher. The tool generated controversy from the moment it was announced and may overestimate ASCVD risk by 67% in women and 86% in men.[9]

Emphasis on tolerability

The guideline focuses on statins as the main treatment and de-emphasizes the adjunctive use of other drugs to further lower lipids such as niacin, ezetimibe, and fenofibrate.

Statin tolerability is now stressed rather than specific lipid level targets. The guideline recommends reassessing statin choice and intensity according to pain, tenderness, stiffness, cramping, weakness, and fatigue (class IIa recommendation ["reasonable"], level of evidence B ["limited"]). Also recommended is reassessment of statin choice and intensity for patients older than 75 or for those taking multiple medications, drugs that alter metabolism, and conditions requiring complex medications (class IIa, level of evidence C ["very limited"]). For patients with confusion, statin and nonstatin causes should be considered as the source of the problem (class IIb ["consider"], level of evidence C).

Initiating high-intensity statin therapy is not recommended after age 75. However, continuing such treatment is reasonable for patients already receiving and tolerating the therapy for an appropriate indication. Initiation of moderate-intensity statin therapy in this age group is recommended for those with either clinical atherosclerotic cardiovascular disease or a low-density lipoprotein cholesterol (LDL-C) level of at least 190 mg/dL.

No specific guidance is provided for patients older than age 75 without ASCVD, with LDL-C less than 190 mg/dL, or with diabetes. In these groups, statin therapy may be initiated, continued, or intensified (class IIb, level of evidence C).

HYPERTENSION: LESS AGGRESSIVE GOALS FOR ELDERLY

The eighth Joint National Committee (JNC 8)[10] made nine recommendations for managing high blood pressure, only one of which specifically addresses people 60 and older.

Drug therapy should be initiated if the blood pressure is 150/90 mm Hg or higher, and the blood pressure should be treated to less than that level (grade A recommendation, ie, strong). If treated systolic blood pressure is less than 140 mm Hg without adverse effects, it should be sustained (grade E recommendation, ie, based on expert opinion).

Tension between guidelines

The higher threshold for hypertension treatment and the lower threshold for statin therapy create tension between guidelines, and between guidelines and epidemiologic data.

Statin tolerability is now stressed rather than specific lipid level targets

For example, in a 67-year-old woman without diabetes and with a favorable lipid profile (eg, total cholesterol 130 mg/dL, high-density lipoprotein cholesterol 55 mg/dL), the ACC/AHA ASCVD risk calculator predicts a 10-year risk of less than 7.5% if her systolic blood pressure is 147 mm Hg. If the patient's blood pressure were 148 or 149 mm Hg and all the other variables were the same, the JNC 8 would not recommend treatment with antihypertensive medication, but the ACC/AHA guidelines would recommend preventive statin therapy.

Another example is the relationship between heart failure and antihypertensive drugs. Multiple studies[11,12] demonstrate a reduction in heart failure incidence with hypertension treatment. A 70-year-old man whose systolic blood pressure is 140 mm Hg has about a 15% lifetime risk of heart failure. If his systolic pressure were 160 mm Hg, his lifetime heart failure risk would be more than 50%.[13] If his systolic pressure were 149, his

lifetime risk of heart failure would be between 15% and 50%, but the JNC 8 criteria do not recommend antihypertensive therapy.

EXERCISE SLOWS PROGRESSION TO FRAILTY

In the absence of a gold standard, frailty has been operationally defined as meeting three out of five phenotypic criteria: diminished grip strength, low energy, slow gait, low physical activity, and unintentional weight loss. A "prefrail" stage, in which one or two criteria are present, identifies a vulnerable subset at high risk of progression to frailty.

About 42% of older adults in the community are considered vulnerable, or prefrail, and about 11% are frail.[14] Interventions at the prefrail stage may prevent progression to frailty, but it is rare, without intervention, for a person to re-achieve the stronger stage once diagnosed with frailty.

Pahor et al[15] randomized 1,635 sedentary adults ages 70 to 89 who met the criteria of prefrailty to either a moderate-intensity exercise program (consisting of aerobic, resistance, and flexibility exercises for 150 minutes per week, performed in a center and at home) or to a health education program with workshops on topics relevant to older adults and upper-extremity stretching exercises. Adherence to the exercise program was verified by questionnaire and an accelerometer device. Participants were assessed every 6 months for an average of 2.6 years.

About 42% of community-dwelling older adults are considered 'prefrail,' and 11% are frail

The primary outcome measure was the development of major mobility disability as defined by the loss of ability to walk 400 m without assistance (a cane was acceptable, but not a walker). The primary outcome occurred in 30.1% of those in the exercise group and 35.5% of the health education group (hazard ratio 0.82, $P = .03$). Those in the exercise group also had one third fewer falls. No differences were found in death rates. The number needed to treat was about 19 to prevent one person from developing major disability. Those most likely to benefit were those who walked slowly at baseline (< 1.8 mph), were more mobility-impaired, and were more cognitively healthy.

SLOWING DEMENTIA IS STILL AN ELUSIVE GOAL

Vitamin E modestly improves cognitive function but may have a cost

Before new information emerged in 2014 regarding vitamin E and dementia, the best data were from a 1997 study[16] that randomized patients with moderate dementia to either daily vitamin E 2,000 IU, the monoamine oxidase inhibitor selegiline 10 mg, both, or placebo for 2 years. No benefit of treatment for cognitive function was found. However, after adjusting for the baseline Mini-Mental State Examination score, the investigators found that either treatment was associated with a delay of about 7 months in the primary outcome (death, institutionalization, loss of activities of daily living, or severe dementia).

Unfortunately, selegiline is often poorly tolerated, causing dyskinesia in more than 10% of patients, nausea in 20%, and confusion, hallucinations, and syncope. Although vitamin E is better tolerated, in high doses it can cause fatigue, headache, and bleeding, with increased risk of hemorrhagic stroke. Studies conflict as to whether it increases the risk of death from any cause.[17,18]

Dysken et al,[19] in a study reported in 2014, randomized 613 patients with mild to moderate Alzheimer disease, all of whom were taking an acetylcholinesterase inhibitor, to either daily vitamin E 2,000 IU, memantine 20 mg, both, or placebo. The primary outcome measure was an activities of daily living score (0–78, higher being better), which included the ability to perform such tasks as dressing oneself. Each task was scored from 0 (totally dependent on help) to 4 (able to perform completely independently).

Scores fell in both groups over the mean 2.7 years of the study, but the decrease was slightly slower in the vitamin E group: 3 points less at the end of the study compared with placebo. The groups taking memantine, vitamin E, or both did not differ significantly from one another. No significant differences were found in the secondary outcome of cognitive, neuropsychiatric, functional, and caregiver measures.

Based on the 1997 study, vitamin E may defer the time to important clinical outcomes by 7.5 months over a 2-year period in patients

with moderate dementia. Based on the 2014 study, vitamin E may preserve half an activity of daily living over 2.7 years in patients with mild to moderate dementia. On the other hand, high doses of vitamin E may increase the risk of bleeding and falling, and whether they increase the risk of death is unclear.

Antidepressants for behavior issues

Other common problems in patients with major neurocognitive disorders include disturbed perception, thought content, mood, and behavior, collectively called behavioral and psychological symptoms of dementia. No known nondrug intervention is consistently effective for these problems, and no drug approved by the US Food and Drug Administration (FDA), except for a fixed-dose combination of dextromethorphan and quinidine, addresses any specific symptom.

Porsteinsson et al[20] randomized 186 patients with Alzheimer disease and agitation to a psychological intervention plus either the selective serotonin reuptake inhibitor citalopram (titrated from 10 to 30 mg per day based on response and tolerability) or placebo. Agitation was reduced with citalopram compared with placebo, based on the agitation subscale of the Neurobehavioral Rating Scale.

Of those taking citalopram, 40% were much or very much improved, compared with 26% of those taking placebo. These results are comparable to or better than those with antipsychotic drugs, which should be avoided for treating dementia-related psychosis in elderly patients because of black-box warnings.

No differences were found in activities of daily living. An interesting finding, not seen in other studies, is that the Mini-Mental Status Examination score declined by 1 point in the treatment group vs no change in the placebo group ($P = .03$).

Prolonged QTc was found in 12.5% in the citalopram group vs 4.3% in the placebo group ($P = .01$). The FDA issued a warning in 2012 of a dose-dependent effect of citalopram on QTc and recommended a maximum dose of 20 mg for those over age 60; for "poor metabolizers" of cytochrome P450 2C19 (CYP 2C19); and for those taking medications that inhibit CYP 2C19, including proton pump inhibitors, cimetidine, fluvoxamine, fluoxetine, indomethacin, ketoconazole, modafinil, and probenecid. The United Kingdom has extended this warning to escitalopram. Unfortunately, in the Porsteinsson study, nearly 80% of the treatment group received the 30-mg dose and only 15% received the 20-mg dose, which provided insufficient data for independent analysis.

Possibly, citalopram cannot be administered in a dosage sufficient to produce the benefits seen in the study. Using escitalopram may also be risky. Based on this study, it would be prudent to monitor QTc when using these drugs.

Dextromethorphan and quinidine

A fixed-dose combination of dextromethorphan and quinidine (Nuedexta) was recently approved by the FDA for treatment of pseudobulbar affect in individuals with stroke, traumatic brain injury, or dementia. Pseudobulbar affect has been defined as a condition of contextually inappropriate or exaggerated emotional expression that often occurs in adults with neurologic damage.

Using a 20/10-mg dose combination, a small 12-week noncomparative trial demonstrated measurable improvement in pseudobulbar symptoms after 30 days (as measured by the Center for Neurologic Study-Lability Scale).[21] Though individuals enrolled in this trial appeared to tolerate this dose, additional trials still need to be conducted to more clearly determine its long-term safety and efficacy. It is not approved for dementia with agitation, but a phase 2 trial suggests a benefit compared with placebo in reducing agitation and caregiver burden.[22]

Although vitamin E may delay important outcomes in dementia, high doses may increase the risk of bleeding and falling

RISKS OF MILD COGNITIVE IMPAIRMENT

The spectrum of cognitive impairment ranges from mild cognitive impairment (MCI), in which deficits are evident on neuropsychological testing but the person maintains overall function, to the different stages of dementia (mild, moderate, and severe). MCI was documented in the Cardiovascular Health Study in 22% of adults 75 and older.[23]

Despite presenting with apparently normal function, elderly people with MCI have a higher risk of falls, rehospitalization, and delirium. Screening is not typically performed for MCI in primary care. No study has com-

pared clinical outcomes after screening vs not screening for cognitive impairment (whether MCI or dementia), and the US Preventive Services Task Force maintains that there is insufficient evidence for screening.[24]

Unrecognized cognitive impairment affects discharge outcomes

Nazir et al,[25] in a 1-year longitudinal study, compared 976 patients age 65 and older who upon admission to a public hospital were either diagnosed with cognitive impairment (defined as scoring 7 or less on the 10-question Short Portable Mental Status Questionnaire) or not. They found that 42.5% were cognitively impaired on admission. Overall, 36.5% of patients were discharged to a facility rather than home; those who were cognitively impaired, older, and sicker were more likely to be discharged to a facility.

Interestingly, among those discharged to a facility, patients with cognitive impairment were less likely to be subsequently rehospitalized or die within 30 days of hospital discharge than those without cognitive impairment. Whether this can be explained by differences in comorbidities between the groups was not explored. Those discharged home had similar rates of death and rehospitalization whether or not they were cognitively impaired.

The elderly population is heterogeneous

Patel et al[26] screened 720 older patients upon discharge after hospitalization for heart failure with the Mini-Cog (a 3-minute test that consists of recall of three words and the ability to draw a clock face). About a quarter of patients were diagnosed with cognitive impairment based on this test.

Among those discharged home (about two-thirds of the group overall), patients were much more likely to be rehospitalized or die within 30 days if they were cognitively impaired. Among those discharged to a facility, the rates between the two groups were similar for the first 20 days; after that, people in the cognitively impaired group were much more likely to die or be readmitted to a hospital.

Dodson et al,[27] in a study of 282 hospitalized patients with heart failure (mean age 80), identified 47% as having cognitive impairment at the time of hospitalization based on a score of less than 25 on the Mini-Mental State Examination. Of those found to have mild cognitive impairment (score 21–24), only 11% had documentation of a cognitive deficit in the medical record, and 39% of those found to have moderate to severe cognitive impairment (score < 21) had documentation of it in the medical record. Those with unrecognized impairment were 1.5 times more likely to die or be rehospitalized within 6 months than those with documented impairment.

Do interventions help?

It is unclear whether developing specific interventions tailored to cognitive impairment improves outcomes.

Davis et al[28] studied 125 patients hospitalized for heart failure who were identified as having mild cognitive impairment based on a Montreal Cognitive Assessment score of 17 to 25 (out of 30) points. Patients were randomly assigned to either a targeted self-care teaching intervention or usual discharge care. The intervention included education and customized instruction on self-care tasks such as managing symptoms, organizing medications, and measuring fluid and sodium intake.

Thirty days after discharge, the intervention group had greater knowledge about heart failure than the control group, but no significant difference was found in ability to care for themselves or in readmission rates.

Interventions that target the patient-caregiver dyad may have more success. A pilot project in Indiana[29] that developed an integrative care model for older people with mild cognitive impairment, dementia, or depression that targeted patients as well as their caregivers found that compared with patients from area primary care clinics, their patients had lower rehospitalization rates within 30 days of discharge (11% vs 20%) and higher rates of achieving a hemoglobin A_{1c} of less than 8% (78% vs 51%). Results of an expanded innovations demonstration project awarded by the Centers for Medicare and Medicaid Services are pending.

The following more recently published data show promise for prevention of dementia through nonpharmacologic interventions.

The FINGER trial[30] (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) screened 2,654 Finnish individuals ages 60 to 77 us-

ing the Cardiovascular Risk Factors, Aging and Dementia risk tool, identifying 1,260 individuals with higher levels of cognitive impairment and randomizing them to a 2-year intervention consisting of exercise, cognitive training, and vascular risk monitoring (n = 631), or a control group provided with general health advice only (n = 629). Neuropsychological testing was conducted to measure differences between the groups, and at the end of the study, the mean Z-score difference in the total testing score between the intervention and control group was 0.22 (P = .30). This trial demonstrated that if cognitive impairment were identified, a multimodal intervention could improve or maintain cognitive function in at-risk elderly individuals.

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