Updates in Outpatient Medicine

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Topics

- Lung cancer screening
- Shingles vaccine
- Glycemic targets
Lung Cancer Screening
Case #1

A 60-year-old woman comes for follow-up regarding essential hypertension. She has no symptoms other than mild, long-standing dyspnea on exertion; she specifically reports that she has no cough or chest pain and that her weight has not changed. There is no personal history of cancer or family history of lung cancer. She reports smoking one pack of cigarettes per day since 16 years of age. On prior visits, she declined assistance with smoking cessation, citing her stressful life situation as the primary caretaker for her disabled husband. Should you advise lung-cancer screening with low-dose computed tomography (CT)?
A brief word about screening considerations

- The burden of suffering caused by the condition
- The performance of the screening test
- The effectiveness, safety, and cost of the preventive intervention or treatment
Lung Cancer

- Cigarette smoking responsible for 85-90% of cases
- 234,000 new cases annually in US
- 1.6 million deaths annually worldwide
- Leading cause of cancer related deaths in men and women
- 154,000 deaths annually in US (more than breast, colorectal, and prostate cancer combined)
- Only 18% 5-year survival rate
- Outcomes for non-small cell lung cancers directly related to stage at the time of diagnosis
Why screen for lung cancer

- Significant prevalence
- Identified risk factors allow targeting of high risk individuals
- Lengthy pre-clinical phase
- High morbidity and mortality
- Therapy is more effective in early stage disease
  - Increased cure rate
  - Allow more limited surgical resection to achieve cure
Screening modalities

- Chest x-ray/sputum cytology
  - 7 large scale controlled clinical trials
  - None of these trials showed mortality benefit
  - Not recommended

- Low-dose chest CT (LDCT)
  - Low dose helical CT
  - Non-contrasted study obtained during a single maximal inspiratory breath hold for at least 6 seconds
  - Generate high-resolution images with significantly less radiation than diagnostic CT scanning
National Lung Screening Trial (NLST)

- Randomized trial comparing screening by LDCT with chest radiography for 3 years in 53,454 high risk patients
  - 33 US medical centers
  - Men and women 55-74 years of age
  - ≥30 pack years of smoking
  - Current smokers and those who had discontinued within 15 years
  - Randomly assigned to 3 rounds of annual screening
National Lung Screening Trial (NLST)

- Trial stopped after 6.5 years
- Statistically significant benefit for LDCT
  - LDCT- 645 cases of lung cancer/100,000 person-years (1060 cancers)
  - CXR- 572 cases of lung cancer/100,000 person years (941 cancers)
National Lung Screening Trial (NLST)

- LDCT - 247 lung cancer deaths
- CXR - 309 lung cancer deaths
- 20% lung cancer mortality reduction (CI 3.8-26.7)
- 6.7% all-cause mortality reduction (CI 1.2-13.6)
National Lung Screening Trial concerns

- 39% LDCT group had at least one false positive
- Most with positive screening test required follow up imaging
- Invasive tissue sampling
  - 2% had needle biopsy
  - 4% had bronchoscopy
  - 4% underwent surgery
National Lung Screening Trial concerns

- 24% of surgical biopsies were performed in patients with benign nodules
- 1% had one complication related to invasive testing
National Lung Screening Trial concerns

- High number of false positive scans (only 6% of positive scans lead to diagnosis of lung cancer)
- Radiation exposure of long term annual screening
- Overdiagnosis- 10-20% of lung cancers diagnosed by LDCT might have never been detected in the patient’s lifetime in the absence of screening
- Incidental findings
Comparing sources of radiation exposure with a single LDCT scan:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Radiation Exposure (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air travel, 10 hours</td>
<td>0.04 mSv</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>0.1 mSv</td>
</tr>
<tr>
<td>Screening mammogram</td>
<td>0.4 mSv</td>
</tr>
<tr>
<td>LDCT scan</td>
<td>1.4 mSv</td>
</tr>
<tr>
<td>Average background radiation in the United States (1 year)</td>
<td>3.0–5.0 mSv</td>
</tr>
<tr>
<td>Diagnostic CT</td>
<td>7.0 mSv</td>
</tr>
</tbody>
</table>

mSv = millisievert, a measure of the amount of radiation absorbed by the body.
Uncertainties

Are the NLST results applicable to routine practice?


- Medicare Evidence Development and Coverage Advisory Committee voted in 2014 that they had low confidence in applicability of NLST results to Medicare population.

- The lung cancer reduction in mortality has not been confirmed by other studies.

- Can LDCT scanning be implemented as effectively and safely in routine clinical practice with less expertise and resources compared to NLST?
I asked what our VA radiology does?

- There is no specific order for a low dose CT
- We order non-contrasted CT and put indication in comments field
- Radiologist protocols the request and some patients end up getting full dose CT
- Scanning time dependent on height of patient
- Rarely get adequate images in patients over 215#
- If any movement artifact, they need to repeat the scan
Costs

- Estimated screening cost of
  - $126,000-$269,000 per QAYL
  - $81,000 per QAYL

- Smoking cessation programs are more cost effective for reducing lung cancer mortality
Future directions

- Lung CT Screening Reporting and Data System (Lung-RADS) is a standardized system for interpreting and reporting LDCT results
- Targeted screening might be more cost effective
  - 60% of participants at highest risk accounted for 88% of all screening prevented lung cancer mortality
- Use of lung cancer screening program
  - Standardized practices for acquisition and interpretation of LDCT
  - Patient and provider notification
  - Evaluation of nodules and abnormalities
Back to our case

- Our patient meets NLST and USPSTF eligibility criteria for LDCT screening
- Will her insurance cover it?
- Consider PFTs to evaluate DOE and determine extent of possible COPD
- Shared decision making where provider gives information about potential risks and benefits of LDCT screening
- Take advantage of opportunity to discuss smoking
- Remind patient that negative screening test is not a reason to continue smoking
Benefits and Harms Experienced by People Ages 55–74 Who Were Screened for Lung Cancer With Low-Dose CT Scans Once a Year for 3 Years as Compared to Those Who Were Not Screened*

**SCREENED (1000 PEOPLE)**

**BENEFITS ADDED by Screening**
- 18 PEOPLE DIED from lung cancer in a group of 1000 people who are screened. This was **3 FEWER DEATHS** from lung cancer compared to the **NOT SCREENED** group.

**HARMS ADDED by Screening**
- 365 IN 1000 PEOPLE SCREENED experienced a **FALSE POSITIVE** result.
- 25 of those false positive results led to an **INVASIVE PROCEDURE**.
- 3 PEOPLE developed a **MAJOR COMPLICATION** from the invasive procedure.

**NOT SCREENED (1000 PEOPLE)**

- 21 PEOPLE DIED from lung cancer in a group of 1000 people who were not screened. This was **3 ADDITIONAL DEATHS** from lung cancer compared to the group that was screened.

*The benefits and harms were measured after an average of 6.5 years.

The information in this graphic was obtained from Patient and Physician Guide, National Lung Screening Trial (NLST). See: http://www.cancer.gov/newscenter/qap2003/NLStudyGuidePatients/Physicians

Not everyone places the same amount of value on these benefits and harms. Think about how you value the benefits and harms described in this picture.
Shingles vaccine

Shingles vaccine is now available for people age 50 and over. Get yours today!
Case #2

72 yo healthy man on no medications comes in for routine follow up. He states he feels well and wants to stay that way. His golfing buddies told him he should get the shingles shot. He remembers getting one a few years ago but wonders if he needs a booster. How do you advise him?
Background

- Varicella-zoster virus (VZV) causes two clinically distinct diseases
  - Primary infection, commonly called chickenpox, is characterized by vesicular lesions of the face and trunk predominantly
  - Herpes zoster, commonly called shingles, is characterized by a painful, unilateral vesicular eruption in a restricted dermatomal distribution resulting from reactivation of latent VZV in neurons of sensory ganglia

- Cell mediated immunity plays critical role in controlling VZV latency and limiting reactivation

- Decline in CMI with aging and lymphoproliferative disorders can result in reactivation of latent VZV
Epidemiology of Shingles in the United States

- 1 million cases of shingles in United States annually\(^{[a,b]}\)
- \(\approx 4\) cases per 1000 people aged 50 to 60 years\(^{[c]}\)
- > 10 cases per 1,000 people \(\geq 80\) years\(^{[c]}\)
- Incidence of shingles and complications, such as PHN, increases with age\(^{[c]}\)

Approximately **1 of every 3 people** in the United States will develop shingles in their lifetime.\(^{[a]}\)

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c. CDC website. Herpes zoster background 2016.
Vaccination

▶ Boosts VZV specific CMI resulting in prevention or attenuation of herpes zoster

▶ Two major formulations
  ▶ Live attenuated vaccine designated as zoster vaccine live (ZVL) sold as Zostavax since 2006
  ▶ Non-live recombinant glycoprotein E designated recombinant zoster vaccine (RZV) sold as Shingrix since 2018
RZV (Shingrix)

- Zoster Efficacy Study in Adults 50 Years of Age or Older (ZOE-50) and ZOE-70
- Efficacy in preventing herpes zoster
  - 96.6% (95% CI = 89.6–99.3) aged 50-59
  - 97.4% (95% CI = 90.1–99.7) aged 60–69
  - 91.3% (95% CI = 86.8–94.5) age ≥70
- Vaccine efficacy in the first year after vaccination was 97.6% and was 84.7% (95% CI = 69.0–93.4) or higher for the remaining 3 years of the study in persons aged ≥70 years.
- Efficacy in preventing PHN
  - 91.2% (95% CI = 75.9–97.7) aged ≥50 years
  - 88.8% (95% CI = 68.7–97.1) aged ≥70 years
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<thead>
<tr>
<th></th>
<th>Shingrix</th>
<th>Zostavax</th>
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<tbody>
<tr>
<td>Efficacy for prevention of shingles</td>
<td>&gt;91%</td>
<td>51%</td>
</tr>
<tr>
<td>Efficacy for prevention of PHN</td>
<td>&gt;88%</td>
<td>67%</td>
</tr>
<tr>
<td>Dose</td>
<td>2 IM doses (2-6 months apart)</td>
<td>1 SQ dose</td>
</tr>
<tr>
<td>Reactions</td>
<td>Occasional muscle soreness which may be more severe due enhanced immunogenicity</td>
<td>Occasional muscle soreness</td>
</tr>
<tr>
<td>Recommended age of administration</td>
<td>&gt;50</td>
<td>&gt;60</td>
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</tbody>
</table>
Recommendations of the CDC

- Healthy adults ≥50 years should get two doses of Shingrix separated by 2 to 6 months, to prevent shingles and PHN.
- Shingrix is the preferred vaccine over Zostavax.
- Zostavax remains a recommended vaccine adults aged ≥60 years but Shingrix preferred.
- Consider revaccination with Shingrix in patients who have received previous Zostavax.
If It's Longer Than 6 Months

Don't Restart -- Pick Up

Advice from the CDC\(^a\)

- If a patient returns after 6 months:
  - Administer the second dose
  - Do not restart the series
- If there's a Shingrix shortage:
  - Prioritize patients who need a second dose over those who need a first dose
  - Don't substitute Zostavax for the second dose

Why the 6-month timeframe?\(^b\)

- After 6 months, there's a drop in antibody response

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\(^a\) CDC website. Shingrix FAQs 2018.
Back to our case

- No role for revaccination with Zostavax
- Revaccination with Shingrix is not contraindicated
- Shingrix will lessen chance of zoster, PHN and provide longer standing immunity
- Based on expert opinion, Shingrix should not be given <2 months after receipt of Zostavax
Glycemic targets for pharmacologic treatment of Type 2 DM
Case #3

A 59 yo man with HTN and DM comes in for routine follow up. His medications are chlorthalidone 12.5 mg qd, lisinopril 40 mg qd, and glargine 20 u hs. He reports that he is very frustrated because all of his doctors keep changing his blood pressure and diabetes goals. Do you commiserate with him?
Hemoglobin $A_1c$ Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians

- Reviewed guidelines from AACE/ACE, ADA, ICSI, NICE, SIGN, and VA/DoD
- Six coauthors independently reviewed and assessed each guideline using the AGREE II instrument
- 23 questions in 6 domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence
- Reviewed five large, long-term randomized controlled trials of intensive versus less intensive treatment target strategies in adults with Type 2 DM (VADT, ACCORD, ADVANCE, UKPDSx2)
American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE)

- Recommends HbA$_1c$ level in most adults $\leq 6.5\%$ if it can be achieved safely
- Higher target 7-8\% is recommended in patients with multiple chronic conditions or shorter lifespan
- ACP’s take- This guideline is a consensus, expert-based guideline, with no systematic review of evidence
American Diabetes Association (ADA)

- HbA$_{1c}$ targets should be <7% in most adults
- HbA$_{1c}$ goal <6.5% for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment
- HbA$_{1c}$ goal <8% in patients with multiple chronic conditions
- ACP’s take- This guideline does not clearly present methods or details about the systematic reviews that were used to develop the recommendations
Scottish Intercollegiate Guidelines Network (SIGN)

- \( \text{HbA}_1\text{c} < 7.0\% \) among people with type 2 diabetes is reasonable to reduce risk of microvascular disease and macrovascular disease.
- \( \text{HbA}_1\text{c} < 6.5\% \) may be appropriate at diagnosis.
- Targets should be set for individuals in order to balance benefits with harms, in particular hypoglycemia and weight gain.
- ACP’s take- The SIGN guideline is based on a clear description of the benefits and harms of tight glycemic control.
HbA$_1c$ 6.0-7.0% for patients with a life expectancy greater than 10-15 years and absent or mild microvascular complications, if it can be safely achieved

HbA$_1c$ 7.0-8.5% is appropriate for most with established microvascular or macrovascular disease, comorbid conditions, or 5-10 years life expectancy, if it can be safely achieved

HbA$_1c$ 8.0-9.0% for patients with life expectancy <5 years, significant comorbid conditions, advanced complications of diabetes, or difficulties in self-management

ACP’s take- The VA/DoD guideline is based on a description of the benefits and harms of glycemic control. It emphasizes the importance of shared decision making in setting HbA$_1c$ goals and recommends target ranges based on comorbid conditions, life expectancy, and other factors rather than setting a fixed target HbA$_1c$ level.
National Institute for Health and Care Excellence (NICE)

- HbA$_1c$ <6.5% when only diet and exercise are used to manage diabetes
- HbA$_1c$ <7% when patients are treated with monotherapy associated with hypoglycemia
- HbA$_1c$ <7.5% when they are treated with combination therapy
- ACP’s take- The NICE guideline is based on a clear description of the benefits and harms of tight glycemic control. It encourages patients to be involved in decisions about their HbA$_1c$ target.
Clinician should personalize goals with patients to achieve glycemic control with a HbA$_1^c$ < 7% to < 8% depending on individual patient factors.

HbA$_1^c$ <8% may be more appropriate than <7% in persons with cardiovascular disease, history of severe hypoglycemia requiring assistance, polypharmacy issues, limited life expectancy, cognitive impairment, or extensive comorbid conditions.

ACP’s take- The ICSI clearly presents the evidence and methodology behind their clinical recommendations.
ACP summary of VADT, ACCORD, ADVANCE, & UKPDS results

- Main effect of more intensive glycemic control is small absolute reductions in risk for microvascular surrogate events, such as retinopathy detected on ophthalmologic screening or nephropathy defined by development or progression of albuminuria.

- Studies have not consistently shown that intensive glycemic control to HbA$_1c$ <7% reduces clinical microvascular events, such as loss or impairment of vision, end-stage renal disease, or painful neuropathy, or reduces macrovascular events and death.

- Patients randomly assigned to more intensive therapy required more antiglycemic medications at higher doses, which led to more adverse events than in the less intensive groups.
Guidance Statement 1

- Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.
Guidance Statement 1
Rationale

- All of the assessed guidelines recommend personalizing HbA$_1c$ goals for individual patients

- The benefits and harms of more versus less intensive glycemic control may be finely balanced for many persons and vary according to expected duration of treatment, comorbid conditions, risk factors for hypoglycemia, and choice of medication

- The choice of glycemic target also depends on consideration of other variables, such as risk for hypoglycemia, weight gain, and other drug-related adverse effects, as well as the patient's age, life expectancy, other chronic conditions, functional and cognitive impairments, fall risk, ability to adhere to treatment, and medication burden and cost
Guidance Statement 2

Clinicians should aim to achieve an HbA$_{1c}$ level between 7% and 8% in most patients with type 2 diabetes.
Guidance Statement 2
Rationale

- Most of the guidelines referred to 5 trials as the rationale for their HbA\textsubscript{1c} targets of 7% or 8%.

- These trials showed that treating to targets of 7% compared with targets of 8% did not reduce death or macrovascular events over about 5 to 10 years of treatment but did result in substantial harms, including but not limited to hypoglycemia.

- Of the 3 trials achieving an HbA\textsubscript{1c} <7%, none showed a reduction in all-cause or cardiovascular-related death.
Guidance Statement 3

Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA$_{1c}$ levels less than 6.5%
Guidance Statement 3
Rationale

- No trials show that targeting HbA$_{1c}$ levels below 6.5% in diabetic patients improves clinical outcomes, and pharmacologic treatment to below this target has substantial harms.

- The ACCORD trial, which targeted an HbA$_{1c}$ level less than 6.5% and achieved the lowest level of the included studies (6.4%), was discontinued early because of increased overall and cardiovascular-related death and severe hypoglycemic events.

- The ADVANCE study also failed to find a statistically significant clinical benefit and had more adverse effects with an achieved median HbA$_{1c}$ level of 6.4% than with 7.0%.
Clinicians should treat patients with type 2 diabetes to minimize symptoms related to hyperglycemia and avoid targeting an HbA$_{1C}$ level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residence in a nursing home, or chronic conditions (such as dementia, cancer, end-stage kidney disease, or severe chronic obstructive pulmonary disease or congestive heart failure) because the harms outweigh the benefits in this population.
Guidance Statement 4
Rationale

- All of the evaluated guidelines suggest relaxing HbA$_1^c$ targets for patients with multiple comorbid conditions, limited life expectancy, or increased risk for hypoglycemia.

- The ACP guidance statement in persons with a life expectancy less than 10 years is based on the small death or cardiovascular benefit of lower HbA$_1^c$ targets through at least 10 years, which should be balanced with treatment harms, including but not limited to hypoglycemia and patient views of treatment burden.
The ADA was not happy

- Everyone seems to agree with Guidance Statement 1.
- The ADA is deeply concerned by the new guidance from the ACP published in the Annals of Internal Medicine on March 5, 2018.
- ACP’s new guidance does not consider the positive legacy effects of intensive blood glucose control confirmed in multiple clinical trials and, therefore, are not reflective of the long-term benefits of lower A1C targets. There is clear, convincing evidence of a long-term reduction in diabetes complications with A1Cs at and below 7 percent.
- ADA is also concerned by the missing consideration of the positive impact of several newer medication classes (SGLT2 inhibitors and GLP-1 receptor agonists) that are associated with low risk for hypoglycemia, have favorable effects on weight and improved cardiovascular disease outcomes.
ACP defends their position

- There is no high quality evidence that achieving an HbA$_{1c}$ of $<7\%$ improves clinical outcomes, and it leads to harms, medication burden, and costs.
- Evidence does not support an HbA$_{1c}$ of $<6.5\%$, but rather demonstrates that this leads to no benefit and substantial harms and costs.
Takeaways

- All of these organizations are coming to different conclusions from the same studies and data.
- Agreement that diet and lifestyle, including exercise, weight loss, blood pressure control, and smoking cessation, are the cornerstones of primary care treatment to control diabetes.
- Agreement that care should be individualized and that the focus should be on patients.
- Shared medical decision making.
Back to our case

- After commiserating with the patient
  - Engage in shared medical decision making
  - Consider age, life expectancy, duration of disease, comorbid conditions, risks, benefits, cost of therapy, patient preferences, resources and support systems
  - Regularly re-evaluate treatment plan and goals of care