Internal Medicine Update

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Topics

• Outline of talk
  – Prostate cancer screening
  – Type 2 diabetes mellitus
  – Bone scans for osteoporosis screening
  – Hepatitis C

PSA debate

• 1970 Prostate-specific antigen is a normal component of the prostate.
• 1986.1 first commercial PSA test, the Hybritech Tandem-R PSA test developed
• 1986 PSA test approved by FDA to aid in the care of patients who already had been diagnosed with prostate cancer.
  – "The PSA test by itself cannot be relied on to determine whether a man has prostate cancer. It must be used in conjunction with other diagnostic procedures, including the digital rectal exam, to rule out prostatitis or other benign prostatic conditions that can elevate the PSA."
• 2009 The Prostate, Lung, Colorectal and Ovarian (PLCO) trial, started in 1993 in the United States N≈77000, and the European Randomized Study of Screening for Prostate Cancer (ERSPC), started in 1994, N≈182,000 men randomly assigned to receive screening or not.
  – The plco trial - no difference in mortality from combined screening with the psa test and dre through 10 years
  – the erspc trial - psa screening without dre was associated through 9 years with a 20% reduction in mortality from prostate cancer.
• October 11, 2011, the US Preventive Services Task Force (USPSTF) released its draft recommendation on prostate cancer screening.
  – The common perception that PSA-based early detection of prostate cancer prolongs lives is not supported by the scientific evidence.
  – Although about 90% of men are currently treated for PSA-detected prostate cancer in the United States—usually with surgery or radiotherapy—the vast majority of men who are treated do not have prostate cancer death prevented or lives extended from that treatment, but are subjected to significant harms.
  – The USPSTF concludes that there is moderate certainty that the harms of PSA-based screening for prostate cancer outweigh the benefits.

Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement

While early detection of prostate cancer is important, the potential harms of PSA screening are significant. The U.S. Preventive Services Task Force (USPSTF) recommends against routine screening for prostate cancer with PSA (Grade B), with the following exceptions:

• Men aged 50 to 69 years who are at average risk of prostate cancer and have a life expectancy of at least 10 years

What Are the Clinical Implications of the Evidence and Recommendation?

Regardless of what the final USPSTF recommendation may be, some men will continue to request prostate cancer screening and some physicians will continue to offer it. An individual who is informed about the possibility of benefits and harms may choose to be screened because he places a higher value on the possibility of benefit, however small, than the known harms that accompany screening and subsequent treatment—particularly harms related to overdiagnosis and overtreatment. No man should be screened without his explicit consent.

In addition, clinicians and health systems performing screening should demonstrate that they can in fact reduce avoidable harms by being more selective about use of potentially curative treatments for patients with low-risk prostate cancers, ideally informed by results from computed tomography and continuing to tailor treatment for screen-detected cancers.

The controversies behind prostate cancer screening may never be fully resolved, but a solid grounding in what the evidence demonstrates—and using it to thoughtfully inform health policy and individual screening decisions—can help provide a rational basis for moving forward.
"A man needs to make a choice for himself, realizing the benefits exist in theory, but the harms have been shown in every study that we’ve ever done in prostate cancer," said Dr. Olis Brawley, chief medical officer of the American Cancer Society. "If there is an overall mortality benefit from prostate screening it is very, very small."

American Urological Association, president, John Barry, "psa testing for prostate cancer remains a valuable screening tool and should be appropriately offered to men"

European Randomized Study of Screening for Prostate Cancer (ERSPC)

- 182,160 men, age 50-74 years at entry, with predefined core age group of 162,388 men age 55-69; 8 European countries
- Randomly assigned to PSA-based screening vs. no screening
- Primary outcome mortality from prostate cancer

• After median f/u of 11 years in the core age group, RR in risk of death from prostate cancer in PSA screening group 21% [RR 0.79, 95% CI 0.68,0.91, P=0.001]
• 29% RR after adjustment for non-compliance
• Absolute risk reduction in mortality 0.1 deaths per 1000 person-years or 1.07 deaths per 1000 men
• To prevent 1 death from prostate cancer at 11 years of f/u, 1055 men would need to be screened and 37 cancers would need to be detected

European Randomized Study of Screening for Prostate Cancer (ERSPC), Anthony B. Miller, M.D.

- We are left with an unsatisfactory situation, in which many practitioners will think there are insufficient data to recommend abandoning PSA screening for prostate cancer. However, the findings of the PLCO trial are more applicable to the situation in the United States, since the ERSPC was conducted in a largely PSA-naive population. Therefore, an intensification of PSA screening would be unwise, and I think it would be advisable to follow the preliminary recommendations of the U.S. Preventive Services Task Force."
Diabetes Update

- April 19, 2012 The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) issued a joint position statement
  - The last guidelines specific to management of hyperglycemia were published about 4-5 years ago
  - Guidelines focus on type 2 DM
    - management more complicated
      - Greater available pharmacotherapy
      - issues regarding potential adverse effects
      - new uncertainties concerning the effects of intensive glycemic control on macrovascular complications.

T2D Guidelines - Highlights

- ADA has set the HbA1c goal at 7% in general, but with some individualization (ACCORD).
  - Higher HbA1C for patients with advanced cardiovascular disease, reduced life expectancy, and multiple medical problems
  - Lower HbA1C for patients with newly diagnosed T2D and the “very motivated”

Key Recommendations

- Targets and treatments to lower glucose must be individualized according to specific patient characteristics.
- The mainstream of any type 2 diabetes treatment program is still diet, exercise, and education.
- Metformin is the preferred first-line drug, in the absence of contraindications. Data are limited regarding use of agents other than metformin. A reasonable approach is combination therapy with 1 to 2 additional oral or injectable agents, with the goal of minimizing side effects to the extent possible.
- To maintain glycemic control, many patients will ultimately need insulin monotherapy or in combination with other medications.
- Whenever possible, the patient should participate in all treatment decisions, focusing on their preferences, needs, and values.
- A major treatment goal must be comprehensive cardiovascular risk reduction.
Research Question

- The U.S. Preventive Services Task Force stated in 2011, “Because of limitations in the precision of testing, a minimum of 2 years may be needed to reliably measure a change in BMD; however, longer intervals may be necessary to improve fracture risk prediction.” No U.S. study has addressed this clinical uncertainty.

### Table 1: Interval between Baseline Testing and the Development of Osteoporosis in 100% of Study Participants, According to the Result of Baseline Testing

<table>
<thead>
<tr>
<th>Result of Baseline Test</th>
<th>Interval between Baseline Testing and Development of Osteoporosis</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal BMD</td>
<td>17.4 (11.5-23.3)</td>
<td>19.3 (13.5-24.8)</td>
<td></td>
</tr>
<tr>
<td>Mild osteopenia</td>
<td>16.3 (13.6-19.2)</td>
<td>13.3 (11.2-15.5)</td>
<td></td>
</tr>
<tr>
<td>Moderate osteopenia</td>
<td>4.6 (3.1-6.5)</td>
<td>4.7 (4.2-5.2)</td>
<td></td>
</tr>
<tr>
<td>Advanced osteopenia</td>
<td>1.0 (0.8-1.1)</td>
<td>1.1 (1.0-1.3)</td>
<td></td>
</tr>
</tbody>
</table>

*Osteoporosis was defined as a T score of -2.5 or lower at the femoral neck or total hip. Normal BMD was defined as a T score of -1.0 or higher. Mild osteopenia was defined as a T score between -1.0 and -2.5. Moderate osteopenia was defined as a T score between -2.5 and -4.0. Advanced osteopenia was defined as a T score between -4.0 and -5.0.*

- The estimated BMD testing interval was 16.8 years (95% confidence interval [CI], 11.5 to 24.6) for women with normal BMD, 17.3 years (95% CI, 13.9 to 21.1) for women with mild osteopenia, 4.7 years (95% CI, 4.2 to 5.2) for women with moderate osteopenia, and 1.1 years (95% CI, 1.0 to 1.3) for women with advanced osteopenia.

- Osteoporosis would develop in less than 10% of older, postmenopausal women during rescreening intervals of approximately 15 years for women with normal bone density or mild osteopenia, 5 years for women with moderate osteopenia, and 1 year for women with advanced osteopenia.

### Bone-Density Testing Internal and Transition to Osteoporosis in Older Women

Morgan L. Gooley, M.D., M.P.H., Jason P. Fire, Sc.D., John S. Prucnal, Ph.D., Ryan C. May, Ph.D., Cheni Li, Ph.D., LiYung Liu, M.S., David F. Randhoff, M.D., Jane A. Cauley, Dr. P.H., and Kristine E. Ensrud, M.D., M.P.H., for the Study of Osteoporotic Fractures Research Group

**Abstract**

Less-frequent bone scans may be OK

**Research Question**

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Hepatitis C

- Hepatitis C (HCV) is a flavivirus related to Yellow Fever and West Nile Virus
- Most common chronic bloodborne infection in the US
- Contagious liver disease causing mild illness to serious, lifelong illness or death

Hep C Transmission

- Spread by blood to blood contact:
  - IV drug use
  - Mother to child transmission
  - Can be sexually transmitted but less common
- Since 1992, screening has limited spread through transfusions and transplants
- For most, acute infection leads to chronic infection
- There is no vaccine for Hepatitis C

Hepatitis C Trends

- Most patients infected 20-40 years ago before virus identification and screening
- Incidence decreasing but number of patients developing cirrhosis, cancer & end stage liver disease increasing (peak 2020 to 2030)
- Total cost of care for untreated Hep C will continue to increase over next 20 years
Current Hepatitis C Treatment

• PEG-Interferon
  – Increases expression of proteins that interfere with Hep C viral replication
• Ribavirin
  – Enhances the antiviral effect of interferon
  – Precise mechanism of action uncertain
• Treatment lasts for one year; if successful, induces cure

Side Effects Current Hep C Treatment

• INTERFERON - Hematologic complications (i.e., neutropenia, thrombocytopenia), neuropsychiatric complications (i.e., memory and concentration disturbances, visual disturbances, headaches, depression, irritability), flu-like symptoms, metabolic complications (i.e., hypothyroidism, hyperthyroidism, low-grade fever), gastrointestinal complications (i.e., nausea, vomiting, weight loss), dermatologic complications (i.e., alopecia), and pulmonary complications (i.e., interstitial fibrosis)

• RIBAVIRIN - Hematologic complications (i.e., hemolytic anemia), reproductive complications (i.e., birth defects), and metabolic complications (i.e., gout)

New Hepatitis C Treatment

• FDA recently approved two new protease inhibitors for treatment of Hep C
  – Boceprevir
  – Telaprevir
• Are added to, do not replace, original therapy
• Indications:
  – treatment of chronic Hep C genotype 1
  – with compensated liver disease, including cirrhosis
  – previously untreated or who have failed previous interferon and ribavirin therapy.
New Hepatitis C Treatment

- In previously untreated patients, 79% of those receiving telaprevir experienced a sustained virologic response (SVR) compared with less than 50% with peginterferon alfa and ribavirin treatment alone.
- Cure rate for patients treated with telaprevir across all studies, and across all patient groups, was between 20-45% higher than current regimen.
- Course of treatment decreased from 48 weeks to 24 weeks.

Challenges of New Treatment

- Cannot be given alone or resistance will develop
- Same side effects plus additional side effects
  - Anemia
  - Neutropenia
  - Thrombocytopenia
  - Severe Rash
- Logistical Challenges in administration
  - Must be given at same time every day
  - Must be given with fatty food (e.g., ice cream)
- Cost
  - Both boceprevir and telaprevir are priced for cure
  - $45,000 to $75,000 per patient

Summary

- PSA Screening – the debate continues
- Individualized treatment of type 2 DM
- Osteoporosis screening in older women
- 2 new hepatitis C drugs