Primary Care Medicine: Principles and Practice

October 11-13, 2017

Hotel Nikko
San Francisco, CA

Course Chair:
Robert B. Baron, MD, MS
University of California, San Francisco
Exhibitors

GILEAD SCIENCES
NOVO NORDISK
PLATEJOY
SALIX
SIMPLIFIMED, INC.

UCSF MEDICAL CENTER /
UCSF BENIOFF CHILDREN’S HOSPITALS
Primary Care Medicine: Principles and Practice

Overview:

Changing patterns of medical practice are placing greater emphasis on ambulatory medicine. Increasingly difficult management decisions must now be made in the outpatient setting. Greater emphasis is being placed on office-based preventive medicine, reduction of cardiovascular risk factors, care of elderly patients, special problems in women's health, application of behavioral medicine skills, and the rational use of diagnostic tests and new medications. Designed for practicing internists, family practitioners, and other primary care health professionals, this course will present a comprehensive review of new developments in outpatient medicine. Special attention will be paid to the day-to-day controversies of office practice. An audience response system will facilitate questions and discussion. An electronic course syllabus will be distributed to all participants prior to the meeting. This course is presented by the Division of General Internal Medicine, Department of Medicine, and is sponsored by the University of California, San Francisco School of Medicine.

Target Audience
Designed for practicing internists, family practitioners, and all other health professionals interested in providing high quality primary care, this course will present a comprehensive review of new developments in outpatient medicine.

Objectives:

The purpose of this course is to increase competence and improve clinician practice in primary care. We specifically anticipate improvements in skills and strategies to:

- implement new guidelines in office-based preventive medicine including new strategies for cancer screening, immunizations, prevention of coronary heart disease and stroke, prevention of serious allergic reactions, and detection of hepatitis C;
- manage common office problems including, lipid disorders, diabetes, coronary heart disease, valvular heart disease, heart failure, depression, hepatitis C, asthma, COPD, pneumonia, Parkinson's Disease, stroke, gout, shoulder and knee pain, sexually transmitted infections, and substance abuse;
- manage common specialty problems in neurology, cardiology, rheumatology, dermatology, orthopedics and sports medicine, gynecology, psychiatry, geriatrics, palliative care, and perioperative care;
- diagnose and treat common problems in women's health including cervical, breast and ovarian cancer, and osteoporosis,
- select the best diagnostic tests and enhance value in medical practice;
- use best evidence and optimize patient communication and shared-decision making;
- become a better health advocate with a deeper understanding of health disparities and the central role of primary care clinicians in providing equitable, patient-centered care;
- identify strategies to find satisfaction and joy in primary care practice.
Accreditation

The University of California, San Francisco School of Medicine (UCSF) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Physicians
UCSF designates this live activity for a maximum of 20.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity meets the requirements under California Assembly Bill 1195, Continuing Education and Cultural and Linguistic Competency.

Geriatric Medicine Credit
The approved credits shown above include 19.25 credits toward meeting the requirement under California Assembly Bill 1820, Geriatric Medicine.

Nurses
For the purpose of recertification, the American Nurses Credentialing Center accepts *AMA PRA Category 1 Credit™* issued by organizations accredited by the ACCME.

Physician Assistants
AAPA accepts category 1 credit from AOACCME, Prescribed credit from AAFP, and *AMA PRA Category 1 Credit™* from organizations accredited by the ACCME.

Pharmacists
The California Board of Pharmacy accepts as continuing professional education those courses that meet the standard of relevance to pharmacy practice and have been approved for *AMA PRA Category 1 Credit™*.

Family Physicians
Application for CME credit has been filed with the American Academy of Family Physicians. Determination of credit is pending.

Pharmacotherapeutics CEUs for Nurses
For the purposes of recertification the American Nurses Credentialing Center accepts *AMA PRA Category 1 Credits™*. issued by organizations accredited by the ACCME. This activity is designated for a maximum of 15.25 pharmacotherapeutic credits towards meeting the requirement for nursing pharmacology continuing education.

Nurses should claim 0.1 CEUs for each contact hour of participation in designated pharmacotherapeutic continuing education.

ABIM Maintenance of Certification Points
Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 20.25 MOC points in the American Board of Internal Medicine’s (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider’s responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.
General Information

**Attendance Verification / Sign-In Sheet / CME Certificates**
Please remember to sign-in on the sign-in sheet when you check in at the UCSF Registration Desk on your first day. You only need to sign-in once for the course, when you first check in.

After the meeting, you will receive an email from Qualtrics@ucsf.edu with a link to complete your online **Course Evaluation/Electronic CME Certificate**. Please make sure that you add this email to your safe senders list. Upon completing the online survey, your CME certificate will be automatically generated to print; you will also receive a copy by email. For smartphone users, you may want to take a photo of your certificate as some settings prevent you from emailing the certificate.

The link will be available for approximately 30 days after the last day of the course. However, after that date the link will expire and you will no longer be able to claim your credits online. You must then contact the Office of CME at registration@ocme.ucsf.edu to receive your certificate and a $15 administrative fee may be applied.

**Speaker Survey**
Your opinion is important to us – we do listen! The speaker survey is the bright yellow hand-out you received when you checked in. Please complete this during the meeting and turn it in to the registration staff at the end of the course.

**Security**
We urge caution with regard to your personal belongings and syllabus books. We are unable to replace these in the event of loss. Please do not leave any personal belongings unattended in the meeting room during lunch or breaks or overnight.

**Exhibits**
Industry exhibits will be available outside the ballroom during breakfasts and breaks, and the lunch periods.

**Final Presentations**
A link to PDF versions of the final presentations will be sent via e-mail approximately 3 – 4 weeks post course. Only presentations that have been authorized for inclusion by the presenter will be included.
Cultural and Language Competency

Federal and State Law
Regarding Linguistic Access and Services for Limited English Proficient Persons

I. Purpose.
This document is intended to satisfy the requirements set forth in California Business and Professions code 2190.1. California law requires physicians to obtain training in cultural and linguistic competency as part of their continuing medical education programs. This document and the attachments are intended to provide physicians with an overview of federal and state laws regarding linguistic access and services for limited English proficient (“LEP”) persons. Other federal and state laws not reviewed below also may govern the manner in which physicians and healthcare providers render services for disabled, hearing impaired or other protected categories.

The Federal Civil Rights Act of 1964, as amended, and HHS regulations require recipients of federal financial assistance (“Recipients”) to take reasonable steps to ensure that LEP persons have meaningful access to federally funded programs and services. Failure to provide LEP individuals with access to federally funded programs and services may constitute national origin discrimination, which may be remedied by federal agency enforcement action. Recipients may include physicians, hospitals, universities and academic medical centers who receive grants, training, equipment, surplus property and other assistance from the federal government.

HHS recently issued revised guidance documents for Recipients to ensure that they understand their obligations to provide language assistance services to LEP persons. A copy of HHS’s summary document entitled “Guidance for Federal Financial Assistance Recipients Regarding Title VI and the Prohibition Against National Origin Discrimination Affecting Limited English Proficient Persons – Summary” is available at HHS’s website at: http://www.hhs.gov/ocr/lep/.

As noted above, Recipients generally must provide meaningful access to their programs and services for LEP persons. The rule, however, is a flexible one and HHS recognizes that “reasonable steps” may differ depending on the Recipient’s size and scope of services. HHS advised that Recipients, in designing an LEP program, should conduct an individualized assessment balancing four factors, including: (i) the number or proportion of LEP persons eligible to be served or likely to be encountered by the Recipient; (ii) the frequency with which LEP individuals come into contact with the Recipient’s program; (iii) the nature and importance of the program, activity or service provided by the Recipient to its beneficiaries; and (iv) the resources available to the Recipient and the costs of interpreting and translation services.

Based on the Recipient’s analysis, the Recipient should then design an LEP plan based on five recommended steps, including: (i) identifying LEP individuals who may need assistance; (ii) identifying language assistance measures; (iii) training staff; (iv) providing notice to LEP persons; and (v) monitoring and updating the LEP plan.

A Recipient’s LEP plan likely will include translating vital documents and providing either on-site interpreters or telephone interpreter services, or using shared interpreting services with other Recipients. Recipients may take other reasonable steps depending on the emergent or non-emergent needs of the LEP individual, such as hiring bilingual staff who are competent in the skills required for medical translation, hiring staff interpreters, or contracting with outside public or private agencies that provide interpreter services. HHS’s guidance provides detailed examples of the mix of services that a Recipient should consider and implement. HHS’s guidance also establishes a “safe harbor” that Recipients may elect to follow when determining whether vital documents must be translated into other languages. Compliance with the safe harbor will be strong evidence that the Recipient has satisfied its written translation obligations.
In addition to reviewing HHS guidance documents, Recipients may contact HHS’s Office for Civil Rights for technical assistance in establishing a reasonable LEP plan.

The California legislature enacted the California’s Dymally-Alatorre Bilingual Services Act (Govt. Code 7290 et seq.) in order to ensure that California residents would appropriately receive services from public agencies regardless of the person’s English language skills. California Government Code section 7291 recites this legislative intent as follows:

“The Legislature hereby finds and declares that the effective maintenance and development of a free and democratic society depends on the right and ability of its citizens and residents to communicate with their government and the right and ability of the government to communicate with them.

The Legislature further finds and declares that substantial numbers of persons who live, work and pay taxes in this state are unable, either because they do not speak or write English at all, or because their primary language is other than English, effectively to communicate with their government. The Legislature further finds and declares that state and local agency employees frequently are unable to communicate with persons requiring their services because of this language barrier. As a consequence, substantial numbers of persons presently are being denied rights and benefits to which they would otherwise be entitled.

It is the intention of the Legislature in enacting this chapter to provide for effective communication between all levels of government in this state and the people of this state who are precluded from utilizing public services because of language barriers.”

The Act generally requires state and local public agencies to provide interpreter and written document translation services in a manner that will ensure that LEP individuals have access to important government services. Agencies may employ bilingual staff, and translate documents into additional languages representing the clientele served by the agency. Public agencies also must conduct a needs assessment survey every two years documenting the items listed in Government Code section 7299.4, and develop an implementation plan every year that documents compliance with the Act. You may access a copy of this law at the following url: http://www.spb.ca.gov/bilingual/dymallyact.htm
Program Faculty

Course Director

Robert B. Baron, MD, MS
Professor of Medicine
Associate Dean for Graduate and Continuing Medical Education
University of California, San Francisco

Speakers (University of California, San Francisco)

Douglas Bauer, MD
Professor of Medicine and Epidemiology & Biostatistics
Director, UCSF K Scholars Program

Brook Calton, MD
Assistant Professor of Medicine, Division of Geriatrics
Director, Bridges Home-Based Palliative Care Program

H. Quinny Cheng, MD
Professor of Medicine

Rena Fox, MD
Professor of Medicine

Jonathan Graf, MD
Professor of Medicine, Division of Rheumatology

Katherine Gundling, MD, FACP
Professor of Medicine, Division of Allergy and Immunology

Erick Hung, MD
Professor of Psychiatry
Vice Chair for Education and Psychiatry Residency Training Director
UCSF Weill Institute for Neurosciences

Rebecca Jackson, MD
Professor of Obstetrics, Gynecology & Reproductive Sciences and of Epidemiology and Biostatistics
Chief, Obstetrics, Gynecology & Reproductive Sciences
Zuckerberg San Francisco General

S. Andrew Josephson, MD
Chair, Department of Neurology
Carmen Castro Franceschi and Gladyne K. Mitchell Neurohospitalist Distinguished Professor

Katherine Julian, MD
Professor of Medicine
Director, Primary Care Internal Medicine Residency
Director Innovations and Outcomes, Graduate Medical Education

Maya Katz, MD
Assistant Professor of Neurology
Coleen Kivlahan, MD, MSPH  
Professor of Family and Community Medicine  
Executive Director, Primary Care Services  
UCSF Health

Ryan Laponis, MD  
Assistant Professor of Medicine  
Associate Program Director, Primary Care Internal Medicine Residency

Michael Peters, MD  
Assistant Professor of Medicine

Susan Philip, MD, MPH  
Assistant Professor of Medicine  
Director, Disease Prevention and Control Branch  
San Francisco Department of Public Health

Van Selby, MD  
Assistant Professor of Medicine, Division of Cardiology

Carlin Senter, MD  
Associate Professor of Medicine and of Orthopaedics  
Primary Care Sports Medicine

Bradley A. Sharpe, MD  
Associate Professor of Medicine  
Associate Chief, Medical Service  
Associate Program Director, Internal Medicine Residency Program  
Interim Chief, Division of Hospital Medicine

Kanade Shinkai, MD, PhD  
Associate Professor of Dermatology  
Program Director, Dermatology Residency Program

Krishan Soni, MD, MBA  
Assistant Professor of Medicine, Division of Cardiology  
Director of Value Improvement for Department of Medicine  
UCSF Health Subspecialty Services

Judith M.E. Walsh, MD, MPH  
Professor of Medicine and of Epidemiology and Biostatistics  
Associate Medical Director, UCSF Women’s Health Primary Care Practice

Lisa Winston, MD  
Professor of Medicine  
Vice Chief, Inpatient Medical Services and Hospital Epidemiologist  
Zuckerberg San Francisco General
Disclosures

The following individuals have disclosed they have no financial interest/arrangement or affiliation with any commercial interests who provide products or services relating to their presentation(s) in this continuing medical education activity:

Robert B. Baron, MD, MS
Douglas Bauer, MD
Brook Calton, MD
H. Quinny Cheng, MD
Jonathan Graf, MD
Katherine Gundling, MD
Erick Hung, MD
Rebecca Jackson, MD
S. Andrew Josephson, MD
Katherine Julian, MD
Maya Katz, MD
Coleen Kivlahan, MD, MSPH
Ryan Laponis, MD
Van Selby, MD
Carlin Senter, MD
Bradley Sharpe, MD
Kanade Shinkai, MD, PhD
Krishan Soni, MD, MBA
Judith Walsh, MD, MPH
Lisa Winston, MD

The following individuals have disclosed having a financial interest/arrangement or affiliation during the past twelve months with a commercial interest who provides products or services relating to their presentation(s) in this continuing medical education activity. All conflicts of interest have been resolved in accordance with the ACCME Standards for Commercial Support:

Rena K Fox, MD
Michael Peters, MD MAS
Susan Philip, MD MPH
Gilead Sciences Inc
Merck
Melinta Therapeutics
GlaxoSmithKline
Grant/Research Support
Advisor or Reviewer
Grant/Research Support
Grant/Research Support

This UCSF CME educational activity was planned and developed to: uphold academic standards to ensure balance, independence, objectivity, and scientific rigor; adhere to requirements to protect health information under the Health Insurance Portability and Accountability Act of 1996 (HIPAA); and, include a mechanism to inform learners when unapproved or unlabeled uses of therapeutic products or agents are discussed or referenced.

This activity has been reviewed and approved by members of the UCSF CME Governing Board in accordance with UCSF CME accreditation policies. Office of CME staff, planners, reviewers, and all others in control of content have disclosed they have no relevant financial relationships.
WEDNESDAY, OCTOBER 11, 2017

7:30 am  Course Registration and Continental Breakfast
8:20  Welcome ................................................................. Robert B. Baron, MD, MS

KEYNOTE ADDRESS
8:30  The Present and Future of Primary Care: Optimizing Payment, Quality, Equity, and Joy
 ................................................................. Coleen Kivlahan, MD, MSPH
9:10  Discussion

PREVENTIVE MEDICINE
9:20  Cancer Screening 2017:  Current Issues for Breast, Colon, Prostate, and Lung Cancer
 ..................................................................................... Judith M.E. Walsh, MD, MPH
10:00  Discussion
10:10  Break
10:30  Vaccinations for Adults and Adolescents ..............................Lisa Winston, MD
11:10  Discussion
11:20  Allergy and Immunology: Pearls and Prevention........... Katherine Gundling, MD, FACP
12:00 pm  Discussion
12:10  Lunch on Your Own
1:30  Cancer Screening 2017:  Current Issues for Cervical, Ovarian, and Endometrial Cancer
 ..................................................................................... Rebecca Jackson, MD
2:10  Discussion

CLINICAL STRATEGIES IN PRIMARY CARE I
2:20  Gout: New Guidelines for an Old Disease.................................Jonathan Graf, MD
3:00  Discussion
3:10  Break
3:30  Parkinson’s Disease for the Primary Care Clinician .................Maya Katz, MD
4:10  Discussion
4:20  Caring for Patients Who Need Surgery: Updates in Perioperative Medicine
 ..................................................................................... H. Quinny Cheng, MD
5:00  Discussion
5:10 pm  Adjourn

G - Geriatric Credit
THURSDAY OCTOBER 12, 2017

7:30 am  Continental Breakfast

CLINICAL STRATEGIES IN PRIMARY CARE II
8:30  Advances in Prevention and Treatment of Stroke: What Every Primary Care Clinician Should Know.................................................................S. Andrew Josephson, MD
9:10  Discussion
9:20  Dermatology in Primary Care: Recognition and Treatment of Common Disorders of the Skin..............................................................Kanade Shinkai, MD, PHD
10:00 Discussion
10:10 Break
10:30  New Drugs for Diabetes: Which Ones, For Which Patients?.....Robert B. Baron, MD, MS
11:10 Discussion
11:20 Diagnosis and Treatment of Osteoporosis: What New in 2017 .....Douglas Bauer, MD
12:00 pm Discussion
12:10 Lunch on Your Own

CLINICAL STRATEGIES IN PRIMARY CARE III
1:30  Clinical Dilemmas in Outpatient Psychiatry.................................Erick Hung, MD
2:10  Discussion
2:20  Advances in Heart Failure Management ........................................Van Selby, MD
3:00  Discussion
3:10 Break
3:30  Sexually Transmitted Diseases: What’s New in the Guidelines and Beyond..............................................................Susan S. Philip, MD, MPH
4:10  Discussion
4:20 Management of Hyperlipidemia and Cardiovascular Risk: Balancing Benefits and Harms..........................................................Robert Baron, MD MS
5:10 pm Adjourn

G - Geriatric Credit
FRIDAY OCTOBER 13, 2017

7:30 am  Continental Breakfast

CLINICAL STRATEGIES IN PRIMARY CARE IV

8:30 G  Updates on Asthma and COPD .................................................... Michael Peters, MD
9:10  Discussion
9:20 G  Preventing, Recognizing, and Managing Opiate Use Disorders .......Kathy Julian, MD
10:00  Discussion
10:10  Break
10:30 G  Interventional Cardiology for the Non-Cardiologist: New Innovations and New Guidelines
............................................................................................................................................. Krishan Soni, MD, MBA
11:10  Discussion
11:20 G  Optimizing Communication to Improve Patient and Provider Outcomes Ryan Laponis, MD
12:00 pm  Discussion
12:10  Lunch on Your Own

CLINICAL STRATEGIES IN PRIMARY CARE V

1:30 G  Palliative Care Pearls and Pitfalls ................................................. Brook Calton, MD
2:10  Discussion
2:20 G  Hepatitis C: New Medications, New Hope, and New Opportunities for Primary Care
............................................................................................................................................. Rena Fox, MD
3:00  Discussion
3:10  Break
3:30 G  Update in Hospital Medicine ....................................................... Bradley A. Sharpe, MD
4:10  Discussion
4:20 G  Common Sports Injuries of the Knee and Shoulder..................... Carlin Senter, MD
5:00  Discussion
5:10 pm  Adjourn

G - Geriatric Credit
Primary Care Medicine: Principles and Practice

The Present and Future of Primary Care: Optimizing Payment, Quality, Equity, and Joy
Coleen Kivlahan, MD, MSPH


Stand Up and Vote

The Present
- Burnout high but stable
- Practice and Care Redesign
- Experimentation
- EHR use Asynchronous and telehealth visits
- PC Shortage
- Collection of Social Determinants data

YOU ARE HERE
What is Burnout?

Exhaustion, depersonalization, low sense of accomplishment

Nearly half of all U.S. nurses and physicians

Contributes to lower patient satisfaction, worse patient safety, more likely to leave jobs, take sick leave, depression and relationship problems

How Do we Fix It?

System fixes:

Burnout improved with workflow interventions, and with targeted QI projects.

Interventions in communication or workflow led to greater improvements in clinician satisfaction, and with a trend toward lower intention to leave.

Linzer, M. A Cluster Randomized Trial of Interventions to Improve Work Conditions and Clinician Burnout in Primary Care: Results from the Healthy Work Place (HWP) Study. JGIM Aug 2015 30(8): 1105-11

Resilience to Burnout

Reasons we practice medicine: patient interaction and the intellectual challenge

Deploying curiosity is an opportunity with each patient

Curiosity (continuous learning) is sensed by the patient and family, leading to improvements in both patient and physician satisfaction

Curiosity, mindfulness and reflection, as daily renewal behaviors, may constitute an effective antidote to burnout.

Schattner, A. Measuring Burnout in Primary Care Staff. JGIM Aug 2015 30(8): 1062

It's Not Just Us

Overall prevalence of burnout was 41%

Rates of burnout in our teams: physicians (49%), nurse care managers (42%), MAs, LPNs (32%), and admins (30%)

Clinicians and staff are more likely to suffer burnout when we are part of under-staffed teams with frequent turnover, and when we have an over-capacity patient panel.

Burnout prevalence was 30% lower for those working on fully staffed teams with no turnover and caring for an appropriate panel compared other practices

Helfrich CD et al, The Association of Team-Specific Workload and Staffing with Odds of Burnout Among VA Primary Care Team Members. JGIM July 2017 32(7): 760-66
Germany, U.S., UK, and Swedish primary care doctors reported higher-than-average levels of dissatisfaction compared with other countries. The vast majority of primary care doctors in the world are satisfied with their practice and income, but frustrated with administrative burden and insurance hassles. It is far worse in countries with multipayer private insurance systems.


What is the Common Denominator?

Addressing burnout is necessary, but not sufficient.

We all believe that health is more than the absence of disease.
Well, joy in work is more than the absence of burnout.
Joy in work is a shared responsibility at all levels of our organization.

(IHI President and CEO Derek Feeley Aug 2017)

JOY HAS TO BE OUR PRIORITY

Practice Redesign
We Spend More Time Online

Over 31M EHR transactions 2011–14 by 471 PCPs on 765,000 patients’ EHRs.

Doctors logged an ave. of 3.08 hours on F2F office visits and 3.17 hours on desktop medicine daily.

Desktop medicine=communicating with patients through a secure patient portal, responding to patients’ online requests for prescription refills or medical advice, ordering tests, sending staff messages, and reviewing test results.

Over the study years, there was a decline in the time allocated to F2F visits, and an increase in time allocated to desktop medicine.

Staffing and scheduling in the physician’s office, as well as provider payment models for primary care practice, must account for this new work.
Observing Physician Time Use

4 specialties in 4 states (IL, NH, VA, WA). 57 doctors in FM, IM, Card, and Ortho observed for 430 hours

Overall, daily physicians spent 27% on direct clinical face time with patients and 49% of their time on EHR and desk work.

In the exam room: 53% on direct clinical face time and 37% on EHR and desk work.

For every hour physicians provide F2F time with patients, nearly 2 additional hours is spent on EHR and desk work within the clinic day.

Outside office hours, physicians spend another 1 to 2 hours of personal time at night doing additional computer and other clerical work.


Telehealth

Three types of services: store-and-forward (asynchronous communication), real-time video (synchronous conversation), and remote patient monitoring.

Wearables

Home-Based Diagnostics

Convenience, cost and interpretability improve, highly aligned with accountability
**Do Video Visits Cost Less?**

RAND study: commercial claims data on over 300,000 patients from three years.

Total annual spending (costs to insurers and out-of-pocket payments by patients) was $45 more per patient for people who used telehealth to treat acute URI than it was for patients who saw doctors for the same condition.

**WHY?** 88% of the telehealth visits represented people who would not have gone to a doctor otherwise (NEW utilization).

Only 12% of the telehealth sessions, the researchers concluded, amounted to a substitute for seeing the doctor.


---

**Patient Perceptions of Telehealth Video Visits**

Interviews with adult patients following video visits with their primary care clinicians at a single academic medical center.

All patients reported overall satisfaction with video visits, with the majority interested in continuing to use video visits as an alternative to in-person visits.

Primary benefits were convenience and decreased costs. Some patients felt more comfortable with video visits than office visits and expressed a preference for receiving future serious news via video visit, because they could be in their own supportive environment.


---

**Barriers To Adoption Of Online Care**

**Payment System:** The current visit-based payment system

**Lack Of Integrated Tools:** Some tools are not integrated with electronic records

**Financial Incentives:** Pay for individual online visits, management fees to compensate for time spent in online patient care

**Chronic Disease Management:** Treatment and management of chronic diseases such as obesity, diabetes, high blood pressure, and high cholesterol
2017 MATCH data:
IM programs with 98% positions filled and 45% filled with U.S. allopathic seniors.
FM programs 96% positions filled and 45.1% filled with U.S. allopathic seniors.

1/3 of all doctors are in primary care; yet 51% of all outpatient visits are in PCPs.

FM docs reduce high-volume OB Care

50% decrease in family physicians providing high-volume obstetric care
The decline in low and moderate volume OB is nearly as great
Reduced access for OB, especially in rural areas.
Racial Disparities In Geographic Access To Primary Care

Ratios of adults per primary care provider for each census tract to assess variation in primary care access in Philadelphia, PA.
The average ratio was 1:1,073; the supply of primary care providers varied widely across census tracts, ranging from 1:105 to 10,321.
Six areas of the city have much lower accessibility to primary care relative to the rest.
After adjustment for sociodemographic and insurance characteristics, the odds of being in a low-access area were twenty-eight times greater for census tracts with a high proportion of African Americans than in tracts with a low proportion of African Americans.


Primary Care’s Preparation for Complex Patients

For complex patients <70% of PC practices state that they are well prepared
For mental health or substance use–related problems, <50% reported their practice to be well prepared; and in the United States, <16% are well prepared.
50% of German, New Zealand, Dutch, US, and Swedish doctors said that their patients use e-mail to contact them about medical questions.
60% of US doctors (more than twice as high as the other 9 countries) provide their patients with online access to view, download, or transmit information from their medical record.


IOM’s Social Determinants of Health Recommendations for EHRs

Integrating Social Determinants of Health into EHRs

Integrating SDH data into EHRs could:
inform clinical decision making (eg, indicate the urgency of screening, medications, or behavioral counseling; augment clinical risk scores)
enable teams to tailor services, facilitate appropriate referrals, and coordinate care across community organizations
facilitate active panel management approaches that identify and prioritize patients for focused outreach

New Competencies in Primary Care

A new level of medical generalism demands:
- Instant access 24/7 to our patients
- Direct/concierge care
- Broader use of more team members
- More use of technology and wearables
- Provide integrated data that patients value
- Attention to our communities
- Focus on social determinants of health
The CareMore Care Center is a care model for pro-active, integrated health that redefines the way in which senior health care is delivered. It is a breakthrough model of care that combines wellness and medical supervision. We do this with a team approach and with giving our members access to providers at the very forefront of medical knowledge and research.

We believe meaningful, caring relationships are the key to good health. Our lower health is related to the unique healthcare needs of people with Medicare. Our doctors use fewer doctors than most doctors so they spend more time with you. This allows us to take the time to understand your individual circumstances and develop a comprehensive care plan for you.

We are committed to the communities we serve. We are proud to reflect the diversity of the patients we serve through our community clinics. Our clinic features a community room with unique programming including fitness classes, computer classes, and movie nights. Many of our patients take advantage of our door-to-door transport.
Need for a New Vision

In the U.S., financing has focused almost exclusively on transactional care, **Fee for Service**

RVUs for primary care **undervalue** the work of PC doctors in the health of our communities

Primary care faces work life balance, high burnout, workforce shortages and lower salaries

And PCMH is not going to fix it all

---

Defining a New Vision

1. **Payment must support primary care and reward non-visit-based care** in order to encourage population-based care strategies.
2. Relationships will provide value and will be fostered by teams and technology. **Task redistribution** is now required in primary care. Workforce shortages will mandate **panel size increases**.
3. **Generalist physicians will increasingly focus on high acuity/high complexity patients**, involving end of life care, severe illness, and atypical presentations; other team members will manage lower acuity patients.
4. **Primary care will address health behaviors and social determinants of health for their patients.**

---

“I want to thank you for today. Our time with you was open, inspiring and calming. Your approach was spot on with my husband and left him with newfound hope and possibilities. You helped normalize things that have been otherwise elusive. Thank you for taking the time to really get to know us and understand our crazy journey. You are such a breath of fresh air.”
Cancer Screening 2017

New Recommendations,
New Controversies

Judith M.E. Walsh, MD, MPH
Division of General Internal Medicine
Women’s Health Center of Excellence
University of California, San Francisco

Disclosures

• I have no conflicts of interest

Selected Controversies

• Breast Cancer Screening
  – Guideline confusion
  – Implications of “dense breasts”
  – New screening technologies

• Colorectal Cancer
  – What test and how often?
  – New options?

Selected Controversies

• Lung Cancer
  – Why not Chest X Ray?
  – Who should we screen?

• Prostate Cancer
  – The ongoing question- should we screen?
Principles of screening

• Detection while patient is asymptomatic
  – High sensitivity

• Early detection reduces the risk of death from the cancer – randomized trials

• The number of false positives is acceptably low
  – High specificity
  – Reasonably high prevalence of disease

• Ideally few harms

USPSTF

• Rigorous review of existing peer-reviewed evidence

• Ratings reflect the strength of the evidence on the benefits and harms of a preventive service

• No consideration of costs

• ACA: Must cover A or B ratings

USPSTF Grades

<table>
<thead>
<tr>
<th>Grade</th>
<th>Evidence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High certainty of substantial net benefit</td>
<td>Provide</td>
</tr>
<tr>
<td>B</td>
<td>High certainty of moderate net benefit Moderate certainty of moderate/substantial net benefit</td>
<td>Provide</td>
</tr>
<tr>
<td>C</td>
<td>Moderate certainty that net benefit is small</td>
<td>Selectively offer/provide</td>
</tr>
<tr>
<td>D</td>
<td>No net benefit or harms outweigh benefits</td>
<td>Do not provide</td>
</tr>
<tr>
<td>I</td>
<td>Insufficient evidence regarding balance of benefits and harms</td>
<td></td>
</tr>
</tbody>
</table>

Breast Cancer Screening

• Breast cancer is the most common cancer in women and the second leading cause of cancer death

• Screening mammography reduces breast cancer mortality

• Risk increases with age

• Pre-menopausal breast tissue is dense
  – Decreased sensitivity
Breast Cancer Screening

- Maggie Graham is a 50 year old woman with no family history of breast cancer. She has been reading news articles about the “increased accuracy” of screening ultrasound or MRI in women with dense breasts.
- You perform a clinical breast examination, which is normal.

Breast Cancer Screening

- What do you recommend to Maggie?
  - Add ultrasound
  - Add breast MRI
  - Mammogram alone
  - Add ultrasound and MRI

U.S. screening guidelines: no agreement

<table>
<thead>
<tr>
<th>Organization</th>
<th>Starting age</th>
<th>Stopping age</th>
<th>Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States Preventive Services Task Force (USPSTF)</td>
<td>50</td>
<td>74</td>
<td>Biennial</td>
<td>Screening for age 40-49 = Grade C recommendation</td>
</tr>
<tr>
<td>American Cancer Society (ACS)</td>
<td>45</td>
<td></td>
<td>Annual</td>
<td>Biennial for age 50-59 on life expectancy &gt; 10 yrs.</td>
</tr>
<tr>
<td>American College of Obstetricians and Gynecologists (ACOG)</td>
<td>40</td>
<td></td>
<td>As appropriate based on life expectancy</td>
<td>Annual if good health and life expectancy ≥10 yrs.</td>
</tr>
</tbody>
</table>

USPSTF vs American Cancer Society Recommendations

<table>
<thead>
<tr>
<th>Age</th>
<th>USPSTF 2015</th>
<th>ACS 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-44</td>
<td>None (or biennial)</td>
<td>None</td>
</tr>
<tr>
<td>45-49</td>
<td>None (or biennial)</td>
<td>Annual</td>
</tr>
<tr>
<td>50-54</td>
<td>Biennial</td>
<td>Annual</td>
</tr>
<tr>
<td>55-74</td>
<td>Biennial</td>
<td>Biennial</td>
</tr>
<tr>
<td>75+</td>
<td>Insufficient evidence for or against</td>
<td>Biennial if good health and life expectancy ≥10 yrs</td>
</tr>
</tbody>
</table>

American Cancer Society Guidelines. JAMA 2015;314(15):1590-1614
Harms Of Screening

- **Over-diagnosis**
  - Cancers diagnosed that never would cause symptoms:
    - Patients receive all the costs and harms of treatment
  - Estimates: 10% to 30% of invasive breast cancers plus much of DCIS

- **False positives**
  - Anxiety
  - Additional tests including biopsies
  - One-third of total screening cost

- **Radiation exposure**
  - One breast cancer for 3000 women screened annually for 10 years

Jørgensen, BMJ, 2009

Impact of mammographic screening in U.S.

Screening has also led to large increase in detection of ductal carcinoma in situ (DCIS)

Breast Cancer Deaths
Randomized Trials, all ages

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Deaths Averted Screening 1,000 Women Over 10 Years</th>
<th>95% confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 to 49</td>
<td>0.3</td>
<td>0.0 to 0.9</td>
</tr>
<tr>
<td>50 to 59</td>
<td>0.8</td>
<td>0.2 to 1.7</td>
</tr>
<tr>
<td>60 to 69</td>
<td>2.1</td>
<td>1.1 to 3.2</td>
</tr>
<tr>
<td>70 to 74</td>
<td>1.3</td>
<td>0.0 to 3.2</td>
</tr>
<tr>
<td>75+</td>
<td>Unknown</td>
<td>--</td>
</tr>
<tr>
<td>50 to 69</td>
<td>1.3</td>
<td>0.6 to 2.2</td>
</tr>
</tbody>
</table>

Bottom line: Greatest screening benefit in women aged 60-69; smaller, and possibly no, screening benefit in women aged 40-49
False-Positive Results and Breast Biopsies per 1000 women

<table>
<thead>
<tr>
<th>Outcome</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-74</th>
</tr>
</thead>
<tbody>
<tr>
<td>False-positive mammogram</td>
<td>121</td>
<td>93</td>
<td>81</td>
<td>70</td>
</tr>
<tr>
<td>Breast biopsies recommended</td>
<td>16</td>
<td>16</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Biopsies per cancer diagnosed</td>
<td>10</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Harms of One-Time Mammography Screening, by age

Estimated annual mammography screening costs in the US

Screening the 40 million women in the US aged 50-74 costs $4.72 billion per year

Screening the 22 million women in the US aged 40-49 costs an additional $1.32 billion per year


State breast density legislation

- Requires notification of women with heterogeneously dense or extremely dense breasts
- Exact wording specified by law: decreased sensitivity and increased risk for BC
- No mandate for insurance coverage of supplemental screening in most states

New Breast Technologies

- Digital Mammography
- Digital Breast Tomosynthesis
- Breast MRI
- Breast Ultrasound
**Digital mammography**

- Higher sensitivity, same specificity in women < 50 years old, dense breasts
  - Sensitivity 78% versus 51% film
  - Specificity 90%
- Worse in women 65 and older
  - Sensitivity 53% versus 69% film

**Digital Breast Tomosynthesis**

- Digital Breast Tomosynthesis (DBT) as a primary screening strategy

**USPSTF: DBT**

- Digital Breast Tomosynthesis (DBT) as a primary screening strategy
  - Benefit: Reduces recall rate and increases cancer detection rates compared to conventional mammography
  - Harm: twice as much radiation; unknown rate of over diagnosis. May increase biopsy rates
- No evidence on mortality, morbidity, or QOL
- "Insufficient evidence to fully assess benefits and harms

**MRI Screening**

- Does MRI have a role for screening in high risk women?
  - MRI is a very sensitive method of breast imaging and has been used as a diagnostic tool in women with breast cancer
  - Not influenced by breast density
  - Specificity is variable
  - Expensive
### Sensitivity And Specificity Of Breast Cancer Screening Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>77%</td>
<td>95%</td>
</tr>
<tr>
<td>Mammography</td>
<td>36%</td>
<td>99.8%</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>33%</td>
<td>96%</td>
</tr>
</tbody>
</table>

### Supplemental screening: better outcomes?

<table>
<thead>
<tr>
<th></th>
<th>MRI</th>
<th>Ultrasound (US)</th>
<th>Tomosynthesis (DBT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>Most sensitive</td>
<td>Well-tolerated</td>
<td>Similar cancer detection rate, fewer false positives</td>
</tr>
<tr>
<td></td>
<td>No radiation</td>
<td>Relatively</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>inexpensive</td>
<td></td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>High false positive rate</td>
<td>High false positive rate (low PPV)</td>
<td>Not as sensitive as MRI</td>
</tr>
<tr>
<td></td>
<td>Overdiagnosis</td>
<td>Operator-</td>
<td>Limited evidence base (newer)</td>
</tr>
<tr>
<td></td>
<td>IV contrast</td>
<td>dependent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Claustrophobia</td>
<td></td>
<td>Limited availability</td>
</tr>
<tr>
<td></td>
<td>Expensive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**USPSTF Grade I: January 2017**

### Impact For Clinical Practice

- MRI may be useful in screening high risk women
- The effect of MRI screening on mortality is not known
- MRI is not currently recommended for screening average risk women
- Ultrasound adds little to mammography
- Tomosynthesis is promising

### Bottom Line: Breast Cancer

- 40-49 informed consent
  - Digital if decide to screen: now standard
- 50-74 screen every 2 years
- 75+ informed consent - don’t if life expectancy less than 10 years
- Don’t promote SBE, promote breast awareness
- BRCA risk equivalent: MRI
Lung Cancer Screening

Question?

- Mr. Nico Teen is a 69 year old man with a 50 pack-year history of smoking and COPD. You have previously been unsuccessful in encouraging him to quit smoking. He comes in for a check-up, is worried about developing lung cancer and wants to know what test you think he should have. What do you recommend?
  - Chest X ray
  - Sputum cytology
  - LDCT
  - None of these tests

Lung Cancer Screening: Systematic Review of Chest X-rays

- 7 trials of lung cancer screening
- Frequent screening with chest x-rays was associated with an increase in mortality
  - RR 1.11 (95% C.I. 1.00-1.23)
- No difference in chest X-ray plus cytology versus chest X-ray alone

Manser, Thorax, 2003

PLCO: Lung Cancer Screening

- PCLO randomly assigned 154,901 adults aged 55 through 74 to annual CXR for 4 years vs. usual care
- Followed for 13 years
- Cumulative lung cancer mortality
  - 14.0/10,000 py screening group vs. 14.2/10,000 py control group
  - Rate ratio: 0.99 (95% CI 0.87-1.22)

Oken MM. JAMA 2011;306:1865
Low Dose Spiral Computed Tomography

- Scans lung in < 20 seconds (single breath)
- No IV contrast
- More radiation exposure than CXR but less than conventional CT
- Can detect much smaller lesions than chest X-ray

The National Lung Screening Trial (NLST)

53,454 participants randomized to CT or CXR
- Current or former heavy smokers: ≥ 30 pack-years
- Ages 55 to 74
- Annual CT scans x 3 years. 6.5 years follow-up

RR (95% CI)
- Lung cancer death: .80 (.73-.93)
- Any death: .93 (.86-.98)

20% reduction in lung cancer death; 7% all deaths!

Number needed to invite to screen

- NNI to prevent one lung cancer death in 6.5 years = 320
- NNI to prevent one death from any cause in 6.5 years = 218

Summary from NLST

<table>
<thead>
<tr>
<th></th>
<th>Low-dose CT</th>
<th>Chest X-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit: How did CT scans help compared to chest X-ray, an ineffective screening test?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 in 1,000 fewer died from lung cancer</td>
<td>13 in 1,000</td>
<td>17 in 1,000</td>
</tr>
<tr>
<td>6 in 1,000 fewer died from all causes</td>
<td>79 in 1,000</td>
<td>79 in 1,000</td>
</tr>
<tr>
<td>Harm: What problems did CT scans cause compared to chest X-ray?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>223 in 1,000 more had at least one false alarm</td>
<td>385 in 1,000</td>
<td>142 in 1,000</td>
</tr>
<tr>
<td>15 in 1,000 more had a false alarm leading to an invasive procedure, such as bronchoscopy, biopsy, or surgery</td>
<td>25 in 1,000</td>
<td>7 in 1,000</td>
</tr>
<tr>
<td>3 in 1,000 more had a major complication from invasive procedures</td>
<td>3 in 1,000</td>
<td>1 in 1,000</td>
</tr>
</tbody>
</table>
**NLST Harms**

- **False positives**
  - At least 1 positive test in 39% CT
- **Possible over diagnosis**
  - Higher cancer incidence with CT
  - 1060 vs. 941 cancers
  - Rate ratio 1.13 (95% CI 1.03–1.23)
- **Radiation exposure**
- **Incidental findings**

---

**Guidelines and recommendations**

- Recommend for those meeting NLST entry criteria at specialized centers
  - ACCP / ASCP / ATS
  - ACS
  - ALA
  - NCCN
  - AATS

---

**The NLST Setting**

- 76% of sites were NCI designated cancer centers
- 82% were large academic medical centers
- All likely to have specialized thoracic radiologists and board certified thoracic surgeons on site
- CT scanners extensive quality control
- Nodule management algorithm but not mandated
USPSTF Recommendation

- USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in persons at high risk for lung cancer based on age and smoking history
  - Grade B recommendation
  - Published December 31, 2013

USPSTF

- Age
  - 55-79
- Total exposure to tobacco smoke
  - 30 pack years or more
- Years since quitting
  - Those who have smoked within the past 15 years are at highest risk
- Consider other comorbidities

Medicare Coverage Decision

- Annual lung cancer screening with LDCT for age 55-77, asymptomatic, at least 30 pack year history and currently smoking or quit within past 15 years
- Written order for lung cancer screening written during lung cancer screening shared decision making visit furnished by physician or certified non-physician practitioner
  - February, 2015

Primary Prevention Of Lung Cancer

- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation!!!!!
Implications

• Smoking cessation
• Strict adherence to guidelines
  – 55-79 years, 30+ pack years
• Use experienced centers / demonstration projects to ensure quality and effectiveness

Colorectal Cancer

Question

• What do you most commonly recommend for colorectal cancer screening?
  – Fecal occult blood test (FOBT)
  – Fecal immunochemical Test (FIT)
  – Sigmoidoscopy
  – Colonoscopy
  – Virtual Colonoscopy
  – Fecal DNA

Guidelines

Guidelines, Guidelines
Joint Guideline: ACS, ACR,…

- FOBT annually
- Fecal immunochemical test annually
- Flexible sigmoidoscopy every 5 years
- DCBE every 5 years
- CT colonography every 5 years
- Colonoscopy every 10 years
- Stool DNA testing (interval uncertain)

Levin, Gastroenterology, 2008

Joint Guideline Recommendation

- Clinicians should make patients aware of the full range of screening options
- Offer patients a choice between a screening test that is effective at both early cancer detection and cancer prevention through the detection and removal of polyps and a test that is primarily effective at cancer detection
- CRC prevention should be the primary goal of screening

American College of Gastroenterology

- American College of Gastroenterology guidelines for colorectal cancer screening (Rex DK. Am J Gastroenterol 2009;104:739)
  - Colonoscopy… remains the preferred CRC screening strategy

American College of Physicians 2015

- Annual high sensitivity gFOBT or FIT
- Flex sigmoidoscopy every 5 years
- High sensitivity gFOBT or FIT every 4 years plus flex sigmoidoscopy every 5 years
- Colonoscopy every 10 years

» Ann Int Med 2015
USPSTF 2016

• USPSTF: "A" recommendation (2016)
  - Routine screening from age 50 until 75
• USPSTF "C" recommendation (2016)
  - Individualized decisions age 76 to 85
    • Greater benefit in those not previously screened
• No screening after 85

USPSTF 2016

• Screening for CRC in average risk patients age 50-75 is of substantial net benefit
• Multiple screening strategies available
  - Different levels of evidence
  - Strategies reviewed include colonoscopy, FOBT, FIT, flex sig, CT colonography, fecal DNA and methylated SEPT9 DNA test
  - No evidence that any strategy provides greater net benefit

Colonoscopy: RCTs in progress

• VA
  - Colonoscopy versus fecal immunochemical test in reducing mortality from colorectal cancer
• Spain
  - Colorectal cancer screening in average-risk population: immunochemical fecal occult blood testing versus colonoscopy
• Netherlands
  - Colonoscopy or colonography for screening

Newer Tests

• Virtual Colonoscopy
• Stool based molecular testing
  - Fecal DNA
• Combined FIT and Stool DNA
• Septin-9
Computed Tomographic Colonography (Virtual Colonoscopy)

• Non-invasive radiological technique
  – Radiation dose similar to barium enema
• Bowel preparation similar to colonoscopy
  – Prep-less technique is being evaluated
• Does not require sedation
• Colon distended with carbon dioxide or air
• Breath holding for 20-50 seconds
• Colonoscopy to remove polyps

Laxative-Free CT Colonography

• Low fiber diet, orally ingested contrast material and specialized processing software “electronic cleansing”
• 605 adults underwent CTC and OC
• CTC was more accurate in detecting adenomas 10 mm or larger and less so for smaller lesions
  – 91% sensitivity vs 70% for adenoma 8 mm or larger
• Patients preferred it

Potential Harms

• Radiation Exposure
  – 1/1000 could develop solid cancer or leukemia
• Procedure related harms
  – Perforation rate low
• Extra-colonic findings

Extra-colonic Findings

• Extra-colonic findings common: 27 – 69%
• “High” clinical significance require surgical or medical treatment or intervention or further investigation
  – 5 - 11%
• 7-16% of individuals need additional evaluation for extra-colonic findings, but very few abnormalities ultimately required definitive treatment
Fecal DNA Testing

• PCR test for DNA mutations in the stool
• Potential advantages
  – Non-invasive
  – No preparation
  – Detection along entire length of the colon

Multi-target Stool DNA Testing

• Multi-target DNA test (and hemoglobin), FIT, and colonoscopy 9989 average risk adults in multiple centers
• Fecal DNA detects more neoplasms than FIT, but with more false positive results
  – Sensitivity for CRC 92.3% vs 73.8%
  – Specificity for CRC 86.6% vs 94.9%
• Problems with sample collection or assay application greater with DNA test
  – 6.3% vs 0.3%

Fecal Immunochemical Testing (FIT)

• Uses labeled antibodies that attach to antigens of any human globin present in the stool
• Globin does not survive passage of the upper GI tract
• No dietary restrictions (easier than FOBT)

Imperiale, 2014

Fecal Immunochemical Testing

• FIT is more sensitive in detecting CRC and large adenomas (>1 cm) than FOBT
• FIT is a little less specific than FOBT
**Combined FIT-Stool DNA**

- Cologuard is the only combined stool DNA with FIT available in the U.S.
- Colorectal cancer detection
  - Sensitivity 92%
  - Specificity 84%
- More sensitive than FIT but less specific
  - More false positives

**Septin 9**

- Second generation serum assay to detect circulating Septin 9
  - Septin 9 hypermethylated in CRC
  - FDA approved 2016
- Use for those refusing guideline recommended strategies?

**Colorectal Cancer Screening: Choices**

- Randomized trial offering colonoscopy, FOBT, or choice of colonoscopy/FOBT
- 997 subjects ages 50 to 79
- 12-month follow up
  - Inadomi JM. Arch Intern Med 2012;172:575
- Recommending only colonoscopy led to lower adherence

**Screening Completion**

Inadomi JM. Arch Intern Med 2012;172:575
**Colorectal Cancer Screening: Conclusions**

- Offer testing
- Any screening is better than no screening for reducing colorectal cancer mortality
- Increase awareness of the importance of colorectal cancer screening

**Implications for Practice**

- Recognize importance of patient preferences
  - "The best test is the one that gets done"
- Positive fecal blood tests must be evaluated with diagnostic colonoscopy

**QUESTION**

- What is your usual practice for PSA screening for men aged 50-70?
  - Usually order PSA
  - Sometimes order PSA
  - Rarely order PSA
  - Never order PSA
Prostate Cancer: Should We Screen?

- Disease has high prevalence
  - 10% lifetime risk
  - 30% of men have prostate cancer at autopsy
- Disease has serious consequences
  - Sometimes but may be a benign disease for many men
- Detectable preclinical phase- ?? PSA
- Treatment for preclinical disease is more effective?
  - Complications of prostate cancer treatment
    - 8.4% incontinence
    - 60% impotence
      > Prostate Cancer Outcomes Study 24 month follow up Screening
- Screening reduces cancer mortality?

SCREENING TESTS: PSA

- PSA testing has increased dramatically since 1988
- Observational studies have had conflicting findings about the benefits of screening
- Two large randomized controlled trials of PSA screening and mortality
  
  PLCO Cancer Screening Trial

  - 76,693 men randomized to annual PSA for 6 years plus rectal examination for four years vs usual care
  - High rates of screening in the control group
  - No significant difference in death between the two groups at 7 year follow-up
    - 2.6 deaths per 10,000 person years in the screening group
    - 1.7 deaths per 10,000 person years in the controls
  - Similar results after 10 years
    > Andriole, NEJM 2009

  European Randomized Study of Screening for Prostate Cancer (ERSPC)

  - 182,160 men aged 50-74 in eight European countries
  - PSA screening at least once every four years vs no screening
  - Mortality lower in the screened group at 9 year follow up
    - 7 fewer prostate cancers per 10,000 screened men
  - To prevent one prostate cancer death at 11 year follow up
    - 1,410 men needed to be screened
    - 48 additional prostate cancers treated
  - To prevent one prostate cancer death at 13 year follow up
    - 781 men screened
PSA Screening: Conclusions

- PSA screening may lead to a modest reduction in mortality
- To achieve this mortality reduction, there is a substantial amount of over-diagnosis and over-treatment

USPSTF Recommendations 2012

- Recommended against PSA based screening for prostate cancer
  - PSA can detect early prostate cancer, but inconclusive evidence about whether early detection improves health outcomes.
  - Harms include frequent false positives and unnecessary anxiety, biopsies and potential complications of treatment of some cases of cancer that may never have affected a patient’s health.
  - Grade “D” recommendation

USPSTF Draft Recommendations 2017

- Clinicians should inform men age 55-69 about the potential benefits and harms of PSA screening
  - Grade C
- Decision to screen should be individualized
- No screening in men aged 70 and over
  - Grade D

USPSTF

- Persistent mortality reduction and new evidence to suggest decrease in metastatic prostate cancer with screening
  - 3 fewer cases per 1000 men over 13 years
- No specific recommendations for high risk men
  - Family history, African American
- Public commentary period closed in May, 2017
American Cancer Society

- Men with at least a 10 year life expectancy should have an opportunity to make an informed decision with their health care provider about whether to be screened
- Screening should not occur without an informed decision making process
- Men at average risk should receive the information beginning at age 50
- Information should be provided at age 45 for men at higher risk and age 40 for very high risk

- American Cancer Society, 2016

American Cancer Society

- For men unable to decide, the decision can be left to the discretion of the health care provider
- Men with less than a 10 year life expectancy should not be offered screening
  - At age 75, only half of men have a life expectancy of 10 years or more
- Men without access to regular care should be tested only if high quality informed decision making is available through community based programs

- American Cancer Society, 2016

American Cancer Society

- For those who choose to be screened
  - PSA with or without DRE
  - Screening yearly for men whose PSA is 2.5 ng/ml or greater
  - If PSA <2.5 ng/ml, screening can be extended to every 2 years
  - PSA of 4.0 ng/ml or greater - referral
  - PSA of 2.5-4.0 ng/ml individualized risk assessment

- Age, African American, family history, previous negative biopsy

- American Cancer Society, 2016

American Urological Association Guidelines

- The decision to use PSA testing should be individualized
  - Inform men of the potential benefits and risks
- No routine screening for men aged 40-54
- Shared decision making for men aged 55-69
- No routine screening for men aged 70 and over
- Screening intervals can be individualized based on baseline PSA level

- American Urological Association, 2013
ACP Guidance Statement

- Derived from an appraisal of available guidelines
  - ACPM, ACS, AUA, USPSTF
- Inform men aged 50-69 about limited potential benefits and substantial harms of screening for PSA
  - Base decision on risk for prostate CA, discussion of benefits and harms, health and life expectancy and preferences
  - Do not screen in those who do not have a clear preference for screening

ACP Guidance Statement

- Do not screen average risk men under age 50, over age 69 or with a life expectancy of less than 10-15 years

Prostate Cancer Screening: Summary

- PSA testing may reduce prostate cancer mortality but the benefit is small
- Risks of early detection and treatment
- Shared decision making is key

Summary Of Recommendations

- Women aged 50 to 74 should undergo mammography every 2 years
- Screening decisions for women in their forties and for women and for women aged 75 and older should be individualized
- All men and women aged 50-75 should be screened for colorectal cancer
  - Any screening is better than no screening
Summary Of Recommendations

• Screening for lung cancer with low-dose CT reduces mortality
  – USPSTF Recommends screening high risk individuals
• A shared decision making approach is recommended for prostate cancer screening

Questions?

“Today I ate two bowls of dog food, a sandwich crust, some spaghetti that fell on the floor, half of your cat food, a used tea bag, three bugs and the inside of a sneaker. How many grams of fat is that?”
Diseases/Pathogens with Vaccines Generally Available in the U.S.

- Tetanus
- Diphtheria
- Pertussis
- Measles
- Mumps
- Rubella
- Varicella
- Meningococcus
- Pneumococcus
- Hepatitis B
- Hepatitis A
- Haemophilus influenzae type B
- Human papillomavirus
- Polio
- Influenza
- Rabies
- Typhoid
- Yellow fever
- Japanese encephalitis
- Rotavirus
- Cholera

Key Resource
Centers for Disease Control and Prevention
http://www.cdc.gov/vaccines/
http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/index.html
Outline - vaccines to be covered

- Vaccine-related news
  - Hepatitis A
  - Yellow fever
  - Pneumococcal
  - Meningococcal
  - Pertussis (Tdap)
  - Influenza
  - Varicella (Zoster)
  - Human Papillomavirus

Hepatitis A outbreak

- Outbreak in CA, mostly in persons who are homeless and/or use illicit drugs (injection and non-injection)
  - San Diego – 421 cases, 16 deaths
  - Santa Cruz – 69 cases
- Recommendation to vaccinate at risk population
  - Vaccinate occupational groups with close contact
  - New - expanded use of hepatitis A vaccine for post exposure prophylaxis
  - When using IM immune globulin for pre or post exposure prophylaxis, use higher dose

Yellow fever vaccine shortage

- Due to manufacturing problems, currently using an imported vaccine
- Available at fewer locations

- Recent report of New York resident who died from yellow fever acquired in northern Peru – not vaccinated
  - https://www.cdc.gov/mmwr/volumes/66/wr/mm6634a5.htm
Pneumococcal Vaccines

- Two vaccines now used routinely in adults 65 and older
- Pneumococcal polysaccharide vaccine
  - PPSV-23 (Pneumovax); 23 valent
  - In use since 1983
  - Efficacy against pneumonia in older adults is unclear
- Pneumococcal protein conjugate vaccine
  - PCV-13 (Prevnar); 13 valent
  - Recommended for selected adults in U.S. in 2012
  - Additionally recommended for 65 and older in 2014
  - In adults, only one-time dose indicated

Pneumococcal 13-Valent Conjugate Vaccine for Adults

- Clinical trial in the Netherlands: 84,496 adults > 65 randomized to PCV13 vs. placebo – (CAPITA trial)
  - 46% fewer first cases of vaccine type pneumococcal community acquired pneumonia (CAP) - primary outcome
  - 75% fewer first cases vaccine type invasive pneumococcal disease
  - No difference CAP from any cause


---

### Single dose PPSV-23 (< age 65)

<table>
<thead>
<tr>
<th>Condition</th>
<th>PCV-13 single dose</th>
<th>PPSV-23 single dose</th>
<th>PPSV-23 revaccinate 5 years after 1st dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Lung disease – including asthma</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholism</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term care resident</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native populations with high risk</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Single dose PCV-13 and single dose PPSV-23 (< age 65)

<table>
<thead>
<tr>
<th>Condition</th>
<th>PCV-13 single dose</th>
<th>PPSV-23 single dose</th>
<th>PPSV-23 revaccinate 5 years after 1st dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF leak</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cochlear implant</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Single dose PCV-13 and repeat PPSV-23 five years after first dose (≤ age 65)

<table>
<thead>
<tr>
<th>Condition</th>
<th>PCV-13 single dose</th>
<th>PPSV-23 single dose</th>
<th>PPSV-23 revaccinate 5 years after 1st dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell disease</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Asplenia</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HIV</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Renal failure</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Leukemia</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hodgkin disease</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Generalized malignancy</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Other immunosuppression</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Sequencing pneumococcal vaccines in adults

- If PCV-13 and PPSV-23 both indicated, give PCV-13 first
  - For 65 and older: wait at least one year before administering PPSV-23
  - Wait at least 8 weeks for less than age 65
- If PCV-13 and PPSV-23 both indicated and PPSV-23 has already been administered
  - Wait at least one year before PCV-13

Meningococcal Vaccines - MenACWY

- Two tetravalent protein conjugate vaccines (Menactra, Menveo) covering strains A, C, Y, W-135
  - Menactra: 9 months – 55 years; Menveo – 2 months – 55 years
  - Advantages compared to polysaccharide vaccine
    - Longer lasting antibody titers
    - Good antibody response to revaccination
    - Serogroup B not covered by tetravalent vaccines (B, C, and Y circulate in U.S.)

Who should get MenACWY vaccines?

- Recommended as routine for ages 11 - 18 – ideally given at age 11-12 visit
- “Catch up” at high school or college entry if not given at age 11-12
- Second doses now routine for adolescent and teenage vaccinees
### MenACWY vaccine - summary table

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Primary series</th>
<th>Booster dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 11-18</td>
<td>1 dose, preferred age 11 or 12</td>
<td>16, if primary dose age 11 or 12; 16-18, if primary dose age 13-15; No booster if primary dose on or after age 16</td>
</tr>
<tr>
<td><em>Also, 1st yr. college students in residence halls up to age 21</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 2-55 with complement deficiency or functional or anatomic asplenia</td>
<td>2 doses, 2 months apart</td>
<td>Every 5 years</td>
</tr>
<tr>
<td>Age 2 - 55 with prolonged increased risk of exposure</td>
<td>1 dose</td>
<td>Age 2-6: after 3 years; Age 7 and older: after 5 years</td>
</tr>
</tbody>
</table>

*MMWR. January 28, 2011;60:72-76*

### Who else should get MenACWY vaccine?

- In June 2016, ACIP voted to recommend MenACWY to all HIV-positive persons age 2 months and above
  - 5 – 24 fold increased risk invasive meningococcal disease
  - 2-dose primary series, doses given 8-12 weeks apart
  - Booster dose every 5 years
  - If Menactra will be used, complete PCV-13 series first and wait at least 4 weeks before MenACWY
- Expert opinion – data only in infants regarding immune interference

*MMWR 2016;65(43):1189-94*

- Clusters in New York City and Southern California among men who have sex with men – vaccine may be recommended before travel

- San Francisco Department of Public Health recommends MenACWY locally for MSM, especially if multiple partners, partners sought via websites or digital applications, visit crowded venues such as bars or parties, smoke, spend time in smoky settings

*Who else should get MenACWY vaccine?*

- Given to military recruits, travelers/residents with geographic risk, microbiologists
- Other notes:
  - Meningococcal polysaccharide vaccine is recommended for those 56 years and older if a single dose of vaccine is indicated; MenACWY is preferred if previously vaccinated with MenACWY or if multiple doses are anticipated
  - Vaccination required for pilgrims going to Hajj or Umrah in Saudi Arabia
Epidemiology meningococcal disease
United States

- Incidence of all serogroups has declined
  - Decline occurred prior to routine MenACWY vaccine
  - In 2013: 564 culture and PCR confirmed cases
  - Historically, only 2-3% of US cases occur in outbreaks, i.e. most cases are sporadic
  - Serogroup B now causes about 40% of cases in adolescents and young adults

Recent serogroup B outbreaks linked to college campuses

- Princeton 2013-2014: 9 cases (1 death)
- UC Santa Barbara 2013: 4 cases (no deaths)
- University of Oregon 2015: 7 cases (1 death)
- Santa Clara University 2016: 3 cases (no deaths)

Two meningococcal serogroup B vaccines available in US

- Both approved ages 10-25 years
- MenB-FHbp (Trumenba) approved Oct 2014
  - 2 or 3-dose series (high risk – 3 doses preferred)
  - Contains two recombinant factor H binding protein antigens
    - One from each subfamily A and B
- MenB-4C (Bexsero) approved Jan 2015
  - 2-dose series
  - Contains four components
- Cover most but not all serogroup B strains
- Local and systemic reactions common
  - More common than with other adolescent vaccines

Recommendations for MenB vaccines

- Recommended for persons 10 years and older at elevated risk due to
  - Persistent complement component deficiencies
    - Including taking drug eculizumab
  - Anatomic or functional asplenia
  - Routine exposure (microbiologists)
  - Serogroup B outbreak

- Additional category B recommendation (individual decision making): MenB vaccine may be given to adolescents and young adults ages 16-23 to provide short-term protection; preferred age range 16-18

MMWR 2015. 64(22):608-612
Pertussis Vaccine

- Vaccine combinations:
  - Childhood DTaP: diphtheria toxoid, tetanus toxoid, and acellular pertussis
  - Adult/adolescent Td and Tdap: tetanus toxoid and reduced dose diphtheria toxoid +/- reduced dose acellular pertussis antigens

Pertussis Vaccine

- Pertussis immunity wanes over time
- Peaks every 2-5 years in U.S., including:

Acellular pertussis vaccine in adults and adolescents - how well does it work?

- 2781 subjects 15 – 65 yrs received reduced dose acellular pertussis vaccine or hepatitis A placebo
- Followed for 2.5 yrs
- Based on primary pertussis definition, vaccine 92% effective

Waning immunity after acellular vaccination

- California outbreak 2010:
  - Most pediatric cases were vaccinated as recommended
  - High levels of disease in pre-adolescents, especially 10-year-olds  *J Pediatr 2012;161:1091-6*
  - Kaiser Permanente study in CA kids: odds of pertussis increased by 42% per year in the 5 years after completing DTaP  *New Engl J Med 2012;367:1012-19*
  - Kaiser Permanente study:
    - 263,496 persons 8-20 years old who received acellular vs. whole-cell vaccine (at least one dose)
    - 8.6 relative risk of pertussis for 5 doses acellular vaccine  *Clin Infect Dis 2013;56:1248-54*
Why is acellular vaccine less protective?

- Fewer antigens
  - Acellular vaccines – up to 5 antigens
  - Whole cell vaccines - ~3000 antigens
  - Priming more robust with whole cell
  - Different type of T cell response
- Antigen balance
  - High levels of antibody to pertussis toxin may have blocking effect on antibodies to other antigens
- Genetic changes in *Bordetella pertussis*
  - Especially pertactin deficiency

**Caveat**

- Pertussis rates began increasing in 1980s
  - Well before acellular vaccines
- Rate today estimated 20-fold less than pre-vaccine era and reported rates influenced by
  - More testing
  - More sensitive tests – PCR
  - False positives, e.g. due to other *Bordetella* species
- When acellular vaccine fails in children, illness less severe than in unvaccinated

**Tdap - Recommendations**

- For adolescents, give Tdap instead of Td at routine 11-12 yr visit
- For adults 19 and older, give single dose Tdap to replace a dose of Td
- Can be given at any interval from last tetanus-containing vaccine
- Recommended for every pregnancy at 27 – 36 weeks

**Tdap - pregnancy**

- Multiple studies showing Tdap is safe in pregnancy, including with short interval between vaccine doses
- Maternal immunization results in high levels of pertussis antibody in infants and does not impair response to DTaP
- High vaccine effectiveness (observational) when Tdap given at least 28 days before birth
- Some debate re exact timing – recent data suggest targeting 27 weeks may be optimal
  - JAMA 2015;314(15):1581-7
  - JAMA 2014;311(17):1760-9
  - Lancet 2014;384(9953):1521-8
  - Clin Infect Dis 2017;64(1):3-8
  - Clin Infect Dis 2017;64(1):9-14
Influenza Vaccine

- Indicated for all people older than 6 months
  - Unless there is a contraindication...
    - Egg allergy – no longer a contraindication
    - Severe previous reaction
    - Guillain-Barre – relative contraindication

Influenza Vaccine - egg allergy

- Only hives after exposure to egg – any influenza vaccine appropriate for age and health status
- Other reactions to egg (including angioedema and respiratory distress) – any influenza vaccine appropriate for age and health status; administer in a medical setting with ability to treat allergic reactions
- No need to observe for 30 minutes
  - 15 minutes already recommended for all, especially adolescents (syncope)

MMWR 2016;65:1-54

2017-18 Influenza Vaccine

- A/Michigan/45/2015 (H1N1)pdm09-like (new)
- A/Hong Kong/4801/2014 (H3N2)-like (same)
- B/Brisbane/60/2008-like (B/Victoria lineage) (same)
- For quadrivalent vaccine add:
  B/Phuket/3073/2013-like (B/Yamagata lineage) (same)

Recent Influenza Seasons

- 2016-17: (interim estimate)
  - Estimated vaccine effectiveness 48%
  - Influenza A H3N2 (predominant virus): 43%
  - Influenza B virus: 73%
- 2015-16: relatively mild
  - Estimated vaccine effectiveness 59%
  - Late peak (March), long duration
  - Vaccine good match for circulating strains
- 2014-15: moderately severe
  - Rate of hospitalization for age 65+ highest since surveillance began 2005-6
  - Estimated vaccine effectiveness 19%
Inactivated, quadrivalent, standard dose
- Fluarix Quadrivalent
- Flulaval Quadrivalent
- Fluzone Quadrivalent
- Fluzone Intradermal Quadrivalent

Inactivated, quadrivalent, cell culture-based, standard dose
- Flucelvax Quadrivalent

Inactivated, trivalent, standard dose
- Afluria (adults by jet injector)
- Fluvarin

Adjuvanted, inactivated, trivalent, standard dose
- Fluaad

Inactivated, trivalent, high dose
- Fluzone High-Dose

Recombinant
- Flublok Trivalent and Quadrivalent

---

**Inactivated standard dose vaccines given IM**

- Quadrivalent: 2 influenza A strains, 2 influenza B strains
- Trivalent: 2 influenza A strains, 1 influenza B strain

---

**High-dose inactivated vaccine**

- Trivalent
- Licensed for ages 65 and older
- 60 μg hemagglutinin per virus strain compared with 15 μg in regular dose
- Enhanced immune response in those 65 and older and other populations, including people living with HIV
- Local reactions (mild to moderate) more common

*J Infect Dis 2009;200:161-3*

---

**High dose inactivated vaccine**

- Studies with clinical outcomes:
  - 2-year study with 31,989 participants randomized to high dose vs. standard dose: 1.4% vs. 1.9% with confirmed influenza (relative efficacy 24.2%)
  - Retrospective study at VA 2010-2011; 25,714 veterans high dose, 139,511 standard dose. No difference in hospitalization for influenza or pneumonia, except in those 85 and older
  - Clin Infect Dis 2015;61:171-6
  - Cluster randomized trial in 823 nursing homes 2013-2014; respiratory-related hospital admission 3.4% vs. 3.9%
### Adjuvanted inactivated vaccine
- Trivalent
- MF-59 adjuvant: oil-in-water emulsion of squalene oil
- Has been used widely in Europe, licensed in Canada
- Licensed in U.S. November 2015 for ages 65 and older
- Approved based on safety and immunogenicity data
- Clinical trials in progress

### Recombinant Influenza Vaccine
- Recombinant vaccine (Flublok) uses baculovirus vectors carrying genes that encode for hemagglutinin
- Vaccine with new antigens can be produced in 6 – 8 weeks
- 2014-2015 influenza season: 8855 participants 50 years and older received either quadrivalent recombinant vaccine (45 µg HA per strain) or quadrivalent standard vaccine (15 µg HA per strain)
- RT-PCR confirmed influenza attack rate 2.2% vs. 3.2%


### Live Attenuated Influenza Vaccine (LAIV)
- Trade name FluMist
- Quadrivalent
- Heat sensitive and cold adapted
- Approved for healthy persons ages 2 – 49
- *Not recommended 2016-17 or 2017-18*

### Additional influenza vaccines licensed in U.S.
- Cell culture derived vaccine using canine kidney cells (Flucelvax)
  - Quadrivalent; ages 4+
- One vaccine can be administered by jet injector (Afluria)
  - Ages 18-64
- Intradermal vaccine (Fluzone intradermal)
  - Quadrivalent; ages 18-64; needle one-tenth standard length; more local reactions
Influenza vaccination in pregnancy

- Multiple studies with reduction in infant influenza-like illness (ILI) and confirmed influenza after maternal vaccination in pregnancy
- Recently published:
  - Observational study of 249,387 infants in Utah for first 6 months of life
  - 658 infants with laboratory confirmed influenza: 0.84/1000 if mother immunized, 2.83/1000 if mother not immunized
  - Risk reduction 64% ILI, 70% laboratory confirmed influenza, 81% influenza hospitalization

Varicella Vaccine (Varivax)

- Recommended for all adults without immunity (history of varicella or laboratory evidence)
- Avoid in pregnancy and with most immunocompromise
- Given as 2 dose series for all ages
  - Two doses 98% effective in children
- Average annual mortality has declined 88% overall and 96% under age 50
  
  Shapiro et al, Journal Infect Dis 2011;203:312-15
  Marin et al, Pediatrics 2011;128:214-20

Varicella Vaccine – Zoster (Zostavax)

- Recommended a single dose of zoster vaccine for adults age 60 and above, even if prior history of zoster
- Contraindicated in many, but not all, immunocompromised persons (e.g. okay in HIV if clinically well and CD4 count > 200)

Varicella Vaccine – Zoster (Zostavax)

- Oxman et al, NEJM, June 2005
- Randomized trial 38,546 adults ≥ age 60
  - Excluded if history of zoster, immunocompromise
- Potency much greater (at least 14x) than vaccine to prevent primary varicella
- Zoster incidence reduced by > 50%; post herpetic neuralgia reduced by > 65%
- Injection site reactions common
Varicella Vaccine – Zoster (Zostavax)

- Main questions concern cost effectiveness – multiple studies
  - Vaccine cost ~ $150 per dose
  - Societal costs $27,000 – 112,000 per QALY

- Follow up subjects in Shingles Prevention Study
  - Efficacy for zoster prevention estimated to last 8 years

  Clin Infect Dis 2015;60(6):900-9

Varicella Vaccine – Zoster (Zostavax)

- Two most frequently asked questions:
  - Why is zoster vaccine given to people with a recent history of zoster?
  - How soon can vaccine be given after an episode of zoster?

---

**Varicella Vaccine – Zoster (Zostavax)**

- Phase 3 study; 7698 received vaccine, 7713 placebo
- Adults 50 and older stratified by age
- Two dose series
- 6 cases zoster in vaccine group, 210 in placebo group
  - Mean follow up 3.2 years
  - 97% efficacy
  - No difference in efficacy by age
- Mild-moderate systemic and local reactions common

---

**Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults**

- NEJM 2015;372:2087-96
- 13,900 participants age 70 and older
- 2 doses adjuvanted subunit vaccine or placebo
- Follow up 3.7 years
- Vaccine efficacy against zoster 89.8%
  - 23 cases vaccinated vs. 223 cases placebo
- No difference in efficacy by age
- More injection site and systemic reactions with vaccine
- Serious adverse events similar
- Long-term follow up both studies in progress
Human Papillomavirus (HPV) Vaccines

• Genital HPV most common sexually transmitted infection in the U.S.
• Quadrivalent HPV vaccine (Gardasil)
  ▫ Contains major capsid protein L1 from types 6, 11, 16, 18
  ▫ Phased out in 2016
• Bivalent HPV vaccine (Cervarix) protects against types 16 and 18
  ▫ Only licensed in females
• Types 16 & 18 associated with 66% cervical cancer
• Types 6 & 11 associated with 90% genital warts

Nine-valent HPV vaccine

• Protects against 6, 11, 16, 18 plus 31, 33, 45, 52, 58 (high risk types)
  ▫ ~ 97% reduction in cervical, vaginal, vulvar pre-cancers due to types 31, 33, 45, 52, 58 compared with quadrivalent vaccine
  ▫ 5 additional types account for about 20% of cervical cancers

HPV Vaccines Recommendations for Use

• Routine vaccination beginning at age 11-12
  ▫ Okay to start as young as age 9
• Females: vaccinate through age 26
  ▫ Use bivalent vaccine (Cervarix), 4-valent vaccine (Gardasil), or 9-valent vaccine (Gardasil 9)
• Males: vaccinate routinely through age 21
  ▫ Extend to age 26 for MSM or immunocompromise
  ▫ Use 4-valent vaccine (Gardasil) or 9-valent vaccine (Gardasil 9)
• Okay to continue series with a different vaccine

HPV vaccine: two dose series

• October 2016: ACIP and CDC recommended two-dose HPV series if started before age 15
  ▫ 9 – 14 years olds should receive two doses at least 6 months apart
• If started at 15+ years, three doses still needed

MMWR 2015;65(11):300-304
HPV Vaccines

- Excellent efficacy in studies (nearly 100%) in preventing infection with HPV types included in vaccine, if not previously infected
- Prevent cervical and anal intraepithelial neoplasia
- Greatest benefit before onset of sexual activity / infection with HPV
- No protection against types with which already infected at time of vaccination
- Some partial cross protection against non-vaccine serotypes

HPV Vaccine: External Genital Lesions

- 4065 healthy men and boys ages 16 – 26
- Randomized, double-blind, placebo controlled
- 36 external genital lesions in vaccine group, 89 in placebo group (intent to treat efficacy 60%)
- In seronegative group with all doses received, vaccine was 90% effective against genital lesions due to HPV types 6, 11, 16, 18 (mostly 6 and 11)

HPV Vaccines - questions

- Relatively expensive
- Not clear what long-term effect will be on risk of cancer
- No recommendation to change cervical cancer screening based on vaccination status

HPV Vaccines - uptake

- In 2015, 62.8% of girls and 49.8% of boys ages 13 – 17 had received one of more doses of HPV vaccine
  - Girls: small improvement; boys: greater increase
  - Lower than coverage with Tdap and MenACWY
  - MMWR 2016;65:850-58
- HPV infections due to vaccine types are dropping in 14-19 year old girls even with limited uptake - J Infect Dis 2013;208:385-93
Allergy and Immunology
*Pearls for Clinical Practice*
2017
Katherine Gundling, MD FACP
Professor, Section Chief
Allergy and Immunology
UCSF

Nothing to declare
No discussion of non-FDA approved medication use

Update in Drug Adverse Reactions (2)
Intermission (with 2 Cool Immunology videos)!
Hygiene hypothesis update
*News flash*

Perioperative Anaphylaxis
*Reactions can be severe or fatal*
Perioperative Anaphylaxis

Exposure to many agents occurs during a short time period:
- Antibiotics
- Neuromuscular blocking agents
- Propofol
- Latex
- **Chlorhexidine**
- Dyes
- Opioids
- Blood transfusions
- Benzodiazepines
- Others

Commercial products that contain chlorhexidine (to name a few):
- Antiseptic mouthwashes
- Antiseptic sore throat lozenges and sprays
- Antiseptic toothpastes
- Topical eczema creams
- Acne creams
- Antiseptic powders such as athletes foot powder
- Antiseptic creams
- Antiseptic wipes

More chlorhexidine containing products
- Antiseptic dressings
- Skin washes/cleansers
- Topical disinfectants
- Bladder washouts
- Eye drops
- Contact lens solution
- Anesthetic gels for catheterization
- Some creams and sprays (such as nasal sprays) include chlorhexidine as a preservative
- Some sunscreens

Clinical Pearls

****Chlorhexidine is embedded in some central line catheters****

If your patient develops a rash upon exposure to chlorhexidine, consider avoiding its use during the perioperative period.
Clinical Pearls

For any severe anaphylactic reaction history, consider obtaining serum tryptase level to help rule out a mast cell disorder.

A patient with a previous allergic reaction to which agent is most likely to experience a drug allergic reaction to furosemide?

A. Acetazolamide  
B. Atenolol  
C. Penicillin  
D. Trimethoprim-sulfamethoxazole

Reactions to sulfonamide non-antibiotics are likely due to predisposition to allergic reactions, not due to cross-reactivity with sulfonamide antibiotics!

On the sulfonamide molecule it is the arylamine component that is most allergenic, hence the vast majority of patients who react to arylamine sulfonamides will not react to non-arylamine sulfonamides.

Partial list of sulfonamide medications

<table>
<thead>
<tr>
<th>Arylamine Sulfonamides</th>
<th>Non-arylamine Sulfonamides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfamethoxazole</td>
<td>Carbonic anhydrase inhibitors</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>Sulfonureas</td>
</tr>
<tr>
<td>Sulfacetamide</td>
<td>Loop diuretics</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Thiazide diuretics</td>
</tr>
<tr>
<td>Sulfonamide antiretrovirals</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>Others</td>
</tr>
<tr>
<td>Fosampranavir</td>
<td></td>
</tr>
</tbody>
</table>
From the furosemide package insert, noted in 2017: “patients allergic to sulfonamides may also be allergic to furosemide.”

Updated recommendations: “The weight of evidence suggests that withholding non-antibacterial sulfonamides from patients with prior reactions to antibacterial sulfonamides or other non-antibacterial sulfonamides is not clinically justified.”

N Engl J Med 349;17
Am J Health-Syst Pharm 70:1483-94

The Drug Allergy Practice Parameters from the AAAAI state:

“There is no evidence to suggest allergic cross-reactivity between sulfonamide antibiotics and nonantibiotic sulfonamides.”

AAAAI.org Drug Allergy: An Updated Practice Parameter

Clinical Pearls

The term “sulfa” allergy should be dropped!

- Endeavor to determine and report the exact medication to which a reaction occurred.
- When that information is not available, inquire as to the condition that was being treated, and document the information.

Adverse Drug Reactions

Intermission (with 2 Cool Immunology videos)!

Hygiene hypothesis update

News flash
Adverse Drug Reactions
Intermission (with 2 Cool Immunology videos)!

**Hygiene hypothesis update**

*News flash*

---

Early life exposure to which of the following is *most* associated with the *prevention* of atopic disease (atopic dermatitis, food allergy, allergic rhinitis, asthma)?

A. A household dog  
B. An older brother  
C. Barn animals  
D. Dust mites in the pillow

---

**Answer:** Barn animals

Early exposure to barn animals is strongly associated with less atopy

Exposure to pets from infancy might also be helpful, as are older siblings

Exposure to dust mites is associated with increased atopic conditions (is this still true??)

*Von Mutius E. Proc Am Thorac Soc 2007; Vol 4 pp 212-216*
Environmental exposures and development of asthma

Background:
- Environmental exposure in early life appears to play an important role in the pathogenesis of childhood asthma
- What exposures can be modified to decrease the likelihood of developing asthma?

- 442 high risk, inner-city children
Evaluated the relationship of prenatal and early-life environmental factors to the occurrence of asthma at 7 years.

J Allergy Clin Immunol; Sept 2017
Higher indoor levels of pet or pest allergens in infancy were associated with lower risk of developing asthma.

The abundance of a number of bacterial taxa in house dust was associated with increased or decreased asthma risk.

*Sampling of the association with taxa:*
- Homes without asthma: *Kocuria* genus more abundant; produces kocurin, a potent macrolide with activity against *Staphylococcus* species
- Homes with asthma: potent pathogens such as *Staphylococcus, Haemophilus, Corynebacterium, (others)*

- It may not be just about diversity of the microbiome (popular theory)
- Much work to be done to define cause and effect.....

Other risk factors for the development of childhood asthma that confirmed previous observations:

- Prenatal tobacco smoke exposure (umbilical cord cotinine concentration)
- Higher maternal stress and depression scores

Prevention of atopic conditions

Clear:
- Infants should be breast fed
- Early exposure to animals and a broad variety of proteins is associated with decreased likelihood of developing asthma
- Allergen immunotherapy can prevent the development of new sensitization and asthma

Gathering data:
- Influence of food/microbiome of the gut and airways
- Role of early exposures to pollution, infections, medications
News Flash

Dust mite sublingual tablets have just been approved to treat allergic respiratory disease!

Consider this type of immunotherapy for patients who:
- have year round allergy symptoms
- who have a limited number of allergic triggers
- who are tired of taking medication
- who don’t have time to dedicate 3-5 years to allergy shots

Summary of Key Points

- Watch out for sneaky exposures to chlorhexidine, which can be associated with severe anaphylaxis
- “Sulfa allergy” is a term that should be dropped
- Immune cells at work are truly awe inspiring
- Early life exposures play a key role in training a healthy immune system
- For those people who already have allergy to dust mites, immunotherapy tablets are a new option to retrain the immune system
Gynecologic Cancer Screening 2017: Updates and Controversies

Rebecca Jackson, MD
Professor, Ob/Gyn & Reproductive Sciences
Epidemiology & Biostatistics
University of California, San Francisco

I have no financial interests to disclose

Lecture Plan

1-2 questions for each gyn cancer

- **Cervix**: Brand new USPSTF guidelines: what changed and why? How do you help patients choose between different screening algorithms?
- **Endometrium**: It’s the 4th most common cancer in women, why don’t we screen for it?
- **Ovary**: New RCT’s are conflicting: should we be screening for it? Why has it been so difficult to screen for ovarian cancer?

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Ovary</th>
<th>22,440</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cervix</td>
<td>12,820</td>
</tr>
</tbody>
</table>

Incidence (2016)

<table>
<thead>
<tr>
<th>Mortality</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>246,660</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>106,470</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>63,670</td>
</tr>
<tr>
<td>Urine corpus</td>
<td>60,050</td>
</tr>
<tr>
<td>Thyroid</td>
<td>49,350</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>32,410</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>29,510</td>
</tr>
<tr>
<td>Leukemia</td>
<td>26,050</td>
</tr>
<tr>
<td>Pancreas</td>
<td>25,400</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>23,050</td>
</tr>
<tr>
<td>All Sites</td>
<td>943,620</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mortality</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td></td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>72,160</td>
</tr>
<tr>
<td>Breast</td>
<td>45,450</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>23,170</td>
</tr>
<tr>
<td>Pancreas</td>
<td>20,330</td>
</tr>
<tr>
<td>Ovary</td>
<td>14,260</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>10,470</td>
</tr>
<tr>
<td>Leukemia</td>
<td>10,270</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>8,890</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>8,830</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>6,810</td>
</tr>
<tr>
<td>All Sites</td>
<td>281,480</td>
</tr>
</tbody>
</table>

Mortality (2016)
Pap smears are the most effective screening test ever invented....

Adding screening to naïve populations reduces incidence by 60-90% within 3 years of implementation.

Why does pap screening work?

- Sensitivity of pap/cytology not great
  BUT
- The organ is easily accessible for screening
- Natural history is favorable:
  - precursor exists that is detectable and treatable;
  - time course before cancer develops is long (>10yr)
  - many opportunities to detect. Even if one test is false negative, get another chance.
- It is cost-effective: many years of life are saved because cancer is actually prevented.
As with many other cancers, higher incidence and death rate in Black women.

In Hispanic women, high incidence partly due to poor screening in immigrants’ home countries

Cervical Cancer is preventable with screening

– Let’s not forget this as we strive to fine tune screening guidelines

Racial Disparities

• Higher rates of adenocarcinoma in Black women (less easily detected by screening and poorer prognosis)

But that is not the whole story….

• Black women are screened at similar or higher rates than whites

• Inadequate follow-up and unequal treatment contribute to the differences in outcomes

• Implicit bias in our care?

Implicit Association Test: https://implicit.harvard.edu/implicit/

Terminology clarification

HPV reflex test: With ASCUS, HPV is reflexively sent to determine whether or not to do colpo.

HPV co-test: HPV and cytology done at same time. HPV is adjunct to cytology

Primary HPV screening: only HPV test is done. HPV is alternative to cytology

Cytology reflex: HPV is primary, cytology sent if HPV+

HPV genotyping: Specifically identifies HPV 16 and 18 DNA. Can be used as reflex test after positive hrHPV screen

• HPV reflex test: With ASCUS, HPV is reflexively sent to determine whether or not to do colpo.

• HPV co-test: HPV and cytology done at same time. HPV is adjunct to cytology

• Primary HPV screening: only HPV test is done. HPV is alternative to cytology

– Cytology reflex: HPV is primary, cytology sent if HPV+

• HPV genotyping: Specifically identifies HPV 16 and 18 DNA. Can be used as reflex test after positive hrHPV screen
Why the difference between <30 and >30 yo?

HR-HPV co-testing only clinically useful after age 30. Why?

- In <30yo: HPV often positive, usually transiently. Cancer risk very low. CIN usually regress spontaneously. Therefore, HPV testing not clinically useful and leads to excess colpo and treatment without improving outcomes
- > Age 30: HPV positivity more likely to represent persistent HPV which is a significant risk factor for dysplasia/cancer. AND, HPV negativity is a strong negative predictor.

2017 USPSTF: What's different?

- No more co-testing (ie pap + HPV at same time)
  - <30yo: cytology alone q 3 yrs (rec unchanged)
  - >30yo: EITHER cytology alone q 3 yrs or HPV alone q 5 years

2012 Rec for >30yo was cytology alone q 3 yrs or co-test (cyto+HPV) q 5 years

Why did USPSTF change recs?

- Minimal differences in mortality/incidence between screening algorithms
- Majority of cervix cancer in US is in unscreened or inadequately screened women
- 11% of US women inadequately screened*
- Picking a more sensitive or specific screening process will not help these women
- USPSTF Goal: Simplify screening process in order to get more women adequately screened and followed-up

How to choose: Cyto q3 vs HPV q5?

- With either method, chance of cervical cancer while being screened is extremely low
- Depends how women value the benefits/harms and timing.
- More psychological distress and lower sexual satisfaction when women told have +HPV vs abnormal pap
- Cytology alone: slightly less sensitive and more specific so less dysplasia detected (but fewer colpos)
- HPV alone: slightly more sensitive but less specific so more colpo for each case detected
Trade-offs: Women age 30-65 yo

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cytology Alone q 3yr</th>
<th>Cyto q 30y, HPV Alone q 5yr*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevent 16.5 cases and 7.6 deaths</td>
<td>Prevent 17.8 cases and 8.0 deaths</td>
</tr>
<tr>
<td></td>
<td>Gain 0.26 life years/person</td>
<td>Gain 0.27 life years/person</td>
</tr>
<tr>
<td></td>
<td>39 colpos per cancer averted</td>
<td>82 colpos per cancer averted</td>
</tr>
<tr>
<td></td>
<td>False+ or True+ = 3</td>
<td>False+ or True+ = 6.4</td>
</tr>
<tr>
<td></td>
<td>Less distress with abnormal pap vs with HPV</td>
<td>640 additional colpos per additional cancer averted compared with cyto alone</td>
</tr>
<tr>
<td></td>
<td>Simpler screening and f/u algorithms</td>
<td>*Using cytology triage after HPV</td>
</tr>
</tbody>
</table>

Is it safe to decrease amount of screening?

- Over the past decade we've seen a progression of recs from annual pap to q3 yr pap to q5yr co-test and now q5 yr single test (HPV).
- 1yr vs 3 yr cytology: No appreciable gain in life years with marked increase in colpos and treatments
- Co-test vs HPV alone:
  - In RCTs, doubled the number of f/u tests with no increase in detection.
  - In modeling study, per 1000 women over lifetime, 7500 more tests, exactly the same detection and life years gained

Follow-up after primary HPV screening

Easier to remember and implement
Follow-up of abnormal screen

- USPSTF recommends using standard guideline for follow-up and surveillance. No preference for which f/u algorithm to use
- For primary HPV, options include reflex test with either cytology or HPV16/18 genotyping.
  - Modeling studies show equivalent detection but fewer colpos with cytology follow-up compared with HPV genotyping.

How are we doing in f/u after abnormal?

- Follow-up is as important as screening
- How are we doing? Among 10K women in BCCEDP:
  - Only 44% of women with 2 sequential abnormal pap tests got colpo
  - >half did not get followed according to guidelines
- Even for women with insurance/access to services, clinician adherence to guidelines varies greatly across specialty, geography, personal characteristics

All US guidelines mostly similar

- All strongly recommend against starting before age 21
- None recommends annual screening
- All recommend against HPV alone or as a co-test in women <30 (ok as a reflex test after abnormal pap per ASCCP)
- None recommend screening after hysterectomy (as long as no history of CIN2+)
- All recommend stop at age 65 (if adeq screening)
- None recommend changes in screening for those who’ve had HPV vaccine

What’s different between guidelines?

- ACS/ASCCP/ASCP & ACOG: >30yo prefer co-test with 5 yr interval; acceptable to do cyto alone q3yr
- Interim update 2015 ASCCP & SGO:
  Primary HPV screening starting at age 25 years ok as an alternative to cytology alone or cotesting.
  - ACOG agreed in 2016
Why <25yo for primary HPV?

Alternative to PAP Test is Approved by F.D.A.  
Cobas detects 14 high risk HPV types plus genotyping for 16 & 18  
FDA approved Roche Cobas HPV test as primary screen (no pap) in >25yo

Primary HPV at 25yo vs 30yo?

• Many more positive HPV in 25-30yo vs >30yo and usually transient infection which is not clinically significant.

• Over the lifetime of 1000 women:
  • Benefit: 18 cancers averted vs 17.8. Similar number of life years gained (compared to no screening, gain 274yr/1000 women at >25yo and 272yr/1000 at >30yo)
  • Cost: 8500 more total tests (8.5 per woman). 400 extra colpos. 112 colpo per cancer averted. 8.5 false positives for every true positive
  
  —Concordant over-diagnosis and over-treatment

ACS/ACSSP/ACP guidelines

• Co-testing “preferred” method
• Preferred by whom?

Looking more deeply into the “preferred” recommendation…. Supplemental page

Co-testing “preferred”

• Weak recommendation
  • “substantial uncertainty surrounding the balance of benefits and harms, and further research is needed to increase confidence in the results, or that benefits and harms are closely balanced, with decisions based largely on individual preferences and values”

• Why didn’t the authors more clearly disclose that the designation of co-testing as “preferred” was a weak recommendation?
Beware guideline bias

- ACS/ASCCP/ACSP: Approximately 25% of committee members reported financial conflicts of interests with companies that make HPV tests

Can we do better?

- Over half of cervical cancers occur in women who are not screened or inadequately screened. These women tend to be poor, uninsured, with lack of access to care
  - More sensitive algorithms will not fix this problem!
  - If we really want to decrease cervical cancer, this is where we should focus
- We need to solve the racial disparities—especially those related to improper follow-up

Cobas HPV test Ipad App
Direct to consumer: scare tactics.

Racial disparities in endometrial cancer

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>All races</td>
<td>All races</td>
</tr>
<tr>
<td>White</td>
<td>White</td>
</tr>
<tr>
<td>Black</td>
<td>Black</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>Asian/Pacific Islander</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>American Indian/Alaska Native</td>
</tr>
<tr>
<td>Hispanic</td>
<td>Hispanic</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>Non-Hispanic</td>
</tr>
</tbody>
</table>

Endometrial cancer is the most common female reproductive cancer, so why don't we hear more about it?

Gwen Ifill, PBS NewsHour co-anchor
September 29, 1955 – November 14, 2016
Endometrial Cancer

- 4th most common cancer in women
- Average age 61 but 25% occur pre-menopausally
- Presents at early stage with bleeding; rare in the absence of bleeding.
- Majority effectively treated with simple hysterectomy
- Risk Factor = Increased estrogen (long h/o anovulation eg PCOS, obesity).

What’s the evidence for EmCa screening?

- 2 options: endometrial biopsy (emb) and transvaginal ultrasound (TVUS) to measure endometrial stripe
  - EMB sensitive and specific, but uncomfortable and invasive
  - TVUS: sensitive in postmenopausal women WITH bleeding, but less sensitive without bleeding and specificity poor (60%) leading to many biopsies
- No RCT’s have been done of routine screening (with either EMB or TVUS) of asymptomatic women with mortality as outcome
- Nonetheless, because of the favorable disease characteristics, all guidelines recommend against screening

Why don’t we screen for EmCa?

- Although prevalence is high, mortality is low (case fatality rate is low)
- Majority of patients (75-90%) present with abnormal uterine bleeding and 2/3 have disease confined to uterus with 95% 5-year survival
  - Would yet earlier detection offer any advantage?
  - What are the harms of screening and is it acceptable?
- Given the already good outcomes, it is easier to shift the balance toward harm

Other EmCA screening Q’s

1. Should women on Tamoxifen be screened?
   No. Same natural history as other EmCa so do EMB or TVUS only if bleeding occurs
2. Should women with Lynch syndrome be screened?
   Yes-per expert opinion. Annual EMB starting at age 35y
3. What about TVUS with incidental thickened endometrium in asymptomatic post-meno women?
   Based on decision analysis, >11mm in asymptomatic woman carries same EmCa risk as women with PMB and >5mm stripe.
Can we do better--EmCa?

• Given that the reason for low mortality is that the cancer presents early with symptoms, patients/public should know symptoms and when to seek care
  – Very little public health messaging about EmCa or the need to get all postmenopausal bleeding evaluated (10% of PMB=cancer).

• Given that irregular bleeding is characteristic of perimenopause and of EmCa, how do patients now when to come in to be evaluated?
  – Rule of 2's: come in if more than 2 periods in one month or more than 2 continuous weeks of bleeding.

What about Em Ca Education?

• This is only 1 found in Google search in US
• It says nothing about early warning symptoms, ie bleeding

Ovarian Cancer Screening?

• The answer for a long time has been….Don’t screen.

But….  

• A new RCT from UK reportedly shows mortality benefit
• The PLCO RCT from US showed no mortality benefit
**PLCO: Ovarian Cancer Arm**

**PLCO RCT:** Annual screening with CA-125 + TVUS for 6 yrs, 12 yr f/u

(PLCO=pro, lung, colon, ovarian screening trial)

<table>
<thead>
<tr>
<th>Ovarian Cancer (per 10K person-yrs)</th>
<th>Screen</th>
<th>Control</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ov Ca</td>
<td>212 (8.7)</td>
<td>176 (4.7)</td>
<td>1.2 (1.0-1.5)</td>
</tr>
<tr>
<td>Stage 3&amp;4</td>
<td>77%</td>
<td>78%</td>
<td>ns</td>
</tr>
<tr>
<td>Deaths</td>
<td>118 (3.1)</td>
<td>100 (2.6)</td>
<td>1.2 (0.8-1.7)</td>
</tr>
</tbody>
</table>

20% increase in diagnosis AND death

**UK Collaborative Trial of Ovarian Cancer Screening**

- Primary analysis: No mortality benefit.
  - Multimodal screen (MMS) 0.85 (0.7-1.03)
  - TVUS 0.89 (0.73-1.07)
- However, mortality benefit was seen for MMS if exclude peritoneal cancers and prevalent ovarian cancers: This is what — 0.80 (0.65-1.02) p=0.02
- False positive surgeries: 14 per 10,000 screens in MMS, and 50 per 10K in TVUS

**Ovarian Cancer Screening**

- No changes from prior 2012 recommendation

**Ov ca Screening Harms**

**PLCO Conclusion:**

“Screening does not reduce mortality but does increase medical procedures and associated harms.”

- PLCO: 3285 women (8%) with false positive screens
  - 1080 surgical follow-up
  - 163 serious surgical complications (15%)
  - PPV=6% (94% of those with + test did NOT have cancer)
- UK study: For each cancer detected, 2 women in MMS and 10 in TVUS had a false positive surgery. Complication rate 3%
Why can’t we screen for ovarian cancer?
Even though we have very sensitive and specific tests....

1. No known histologic precursor lesions
2. Unknown time for development or for progression from Stage 1 to Stage 4
   – mathematical models suggest 8 months for development which would be impossibly short to detect by screening
3. For false positives, about 1/3 undergo surgery as the confirmatory test which is more morbid than confirmatory tests for others types of cancer screening

4. Very low prevalence compared to other cancers
   – Peak prevalence(age 55), 50/100,000 (yearly incidence=14/100k)
   – Breast cancer: 6/1000; cervical dysplasia and colonic adenomas: ~4%
5. Given low prevalence, even if a test had a specificity of 99.5%, PPV would only be 7%.
   – Large number would undergo unnecessary surgery to detect 1 case of ovarian cancer
   – In practice, specificity always lower than in research studies

Last words
• Preventive interventions (including screening) require a high burden of proof: the “do no harm” principle.
• Screening is complex—it’s not detection we care about—its decrease in mortality and that can only be determined by RCT
• Choose your guidelines and evidence carefully: beware vested interests in guideline groups.
• Some racial disparities in outcomes are within our control (eg unequal follow-up or treatment)—we need to openly analyze our practices to correct
Gout and its place in ancient history

“Persons affected with the gout who are aged, have tophi in their joints, who have led a hard life, and whose bowels are constipated are beyond the power of medicine to cure” – Hippocrates c. 400 BCE

James Gillray; 18th Century

Gout and its place in world history

David Wells 15th perfect game in Major League history 1998
Benjamin Franklin co-drafted Declaration of Independence 1776
Henry VIII King of England 1509-1547

Gout and its place in prehistory

The New York Times
May 22, 1997

Pity a Tyrannosaur? Sue Had Gout
By MALCOLM W. BROWNE

For all the suffering she probably caused her Cretaceous prey, a tyrannosaur named Sue seems to have paid dearly. Scientists have determined that the big dinosaur probably was a victim of agonizing gout and other debilitating ailments.
Why give a primary care update on gout?

1. Gout is prevalent: 2007-2008 NHANES 3.9% (8.3 million)\(^1\)
   - Men = 5.9% (6.1 million)\(^1\)
   - Women = 2.0% (2.2 million)\(^1\)
   - Prevalence has increased by 1.2 percentage points (30%) in past two decades\(^1\)
   - Crystalline arthritis accounted for 2.3% (39 million) admissions\(^2\)
   - Gout responsible for 5% (5 million) outpatient visits 2010\(^2\)


Why give a primary care update on gout?

In 2002, What percentage of outpatient visits specifically for gout were to rheumatologists?

A. 1.3%
B. 13%
C. 33%
D. 53%
E. 73%

Why give a primary care update on gout?

In 2002, What percentage of outpatient visits specifically for gout were to rheumatologists?

2. Gout is treated primarily by PCP’s in U.S.

   - Only 1.3% of all outpatient visits for gout treated by rheumatologists\(^1\)
   - 70% of patients with gout are under the care of primary care physicians
   - Only 3% of gout patients are referred by PCP’s to rheumatologists

Why give a primary care update on gout?

3. Gout is generally mismanaged
   – Underuse of uric acid lowering therapy (ULT) in eligible patients likely to benefit
   – Under-dosing of allopurinol in patients on ULT (40% with serum uric acid ≥6 on current dose)
   – Initial overdosing of allopurinol in some patients at risk for hypersensitivity

Why give a primary care update on gout?

4. Plethora of urate lowering therapies currently available or coming to market

Gout in recent general medical literature

ACP Guidelines 2017:
Extraordinary disappointment
Gout guidelines published by rheumatology societies

US: ACR 2012

Europe: EULAR 2016


2016 EULAR Recommendations for the Management of Gout. EULAR Task Force on Gout, EULAR Committee of Evidence-Based Clinical Practice Guidelines.}

Acute Gout

• Acute, usually self limited monoarticular inflammatory arthropathy

• Inflammatory response directed against monosodium urate crystals in synovium

• Usually but not always associated with hyperuricemia

• Monosodium urate crystals precipitate around at a concentration of 6.8 mg/dL, within reference range in most US populations

Test Center

Uric Acid

<table>
<thead>
<tr>
<th>Gender</th>
<th>2.5-7.0 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>219 Years</td>
</tr>
<tr>
<td>Female</td>
<td>219 Years</td>
</tr>
</tbody>
</table>

Clinical Significance

Serum uric acid measurements are useful in the diagnosis and treatment of numerous renal and metabolic disorders, including renal failure, gout, leukemia, prostate, elevation or other existing conditions, and in patients receiving cytotoxic drugs.

Distribution of Serum Uric Acid Levels in Japan: 34,000 People

Fig. 1. Distribution of serum uric acid levels: Males: n = 15,712, x = 3.42 mg/dL, SD = 1.14 mg/dL; Females: n = 19,258, x = 4.03 mg/dL, SD = 0.91 mg/dL (SD conversion: mmol/L = mg/dL × 0.0595).
Acute Gout Diagnosis

- **Definitive:** Crystal identification – the only way!
  - Joint fluid examination under polarized microscopy with red compensator
  - Strongly negatively birefringent needle shaped crystals
- **Suspected:** Characteristic radiographic “gouty” corticated erosions away from joint space
- **Possible:** Classic clinical picture with elevated serum urate
- **However** – presence of hyperuricemia alone is not diagnostic of gout

Therapy for Acute Gouty Flares

- **Acute gout attacks** are often self limited (3-5 days)
- **Goals:** reduce both severity and duration of attack
- **NSAIDs**
  - Effective and rapid relief of symptoms
  - Contraindicated in patients with GI, Renal, or hypersensitivity concerns
- **Corticosteroids** (intra-articular and/or systemic use)
- **Colchicine**:
  - Low dose only (0.6 mg BID)! Not every hour until patient gets sick
  - Must be used within 48 hours of attack onset (blocks leukocyte migration)
  - Likely not as effective as either NSAIDs or corticosteroids

Colchicine: How Effective for Acute Gout??

Table 2. Efficacy analysis (intent-to-treat population, n = 104)∗

<table>
<thead>
<tr>
<th>Colchicine dose</th>
<th>Primary end point</th>
<th>Treatment response based on target joint pain score 24 hours after the first dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (n = 52)</td>
<td>17 (32.7)</td>
<td>26 (50.0) 9 (17.3)</td>
</tr>
<tr>
<td>Low (n = 52)</td>
<td>10 (19.2)</td>
<td>15 (28.8) 10 (19.2)</td>
</tr>
<tr>
<td>Placebo (n = 50)</td>
<td>10 (20.0)</td>
<td>15 (30.0) 5 (10.0)</td>
</tr>
</tbody>
</table>

Fewer than 40% of patients achieve primary endpoint
High dose no more efficacious and more toxic

Managing Chronic Gout: 2012 ACR Guidelines
**Question I**

- 55 year old male with a history of known gout awakens with right knee pain and swelling one morning that worsens over next 48 hours until he has difficulty walking on that knee. On a recent Chem. 20 panel, uric acid level was elevated at 10.7. He denies any other joint pains, IVDU, or recent sexual contacts.

After undergoing arthrocentesis confirming the diagnosis of gout and ruling out an infectious process, the patient is started on indomethacin and allopurinol 300 mg/day and sent home. Which of the following actions in this case was a mistake?

- A. Allopurinol dose
- B. Indomethacin therapy
- C. The patient was not admitted and treated with antibiotics until synovial fluid cultures were negative for 5 days
- D. Use of allopurinol during acute phase of gout

---

**Chronic Gout - Progression**

- More frequent inflammatory arthritic attacks
  - Monoarticular attacks
    - Same joint
    - Spread to other joints
  - Polyarticular attacks of arthritis as disease progresses
- Attacks blend together/ No longer completely self-limited
- Chronic synovitis resembling rheumatoid arthritis
- Destructive arthritis/Tophaceous gout:
  - Uric acid containing tophi deposit in joints/tendons/soft tissues, can lead to erosions and deformities

---

**Chronic Gout – 2012 ACR guidelines**

- Goal: Treat to target uric acid level
  - Lower serum uric acid levels are associated with fewer attacks
  - Target serum urate levels below crystallization concentration (< 6.0 or even 5.0 in severe gout) to reabsorb tophi and remove UA stores
  - 1st line Urac acid lowering therapies: allopurinol and Febuxostat
  - Other therapies now available to get uric acid levels to target for patients who fail or are contraindicated/intolerant to 1st line meds
- Prophylaxis
  - Prophylax against acute gout flares when initiating or adjusting uric acid lowering therapy (Europeans recommend six months)
  - Colchines does work well for this (0.6 mg/day usually suffices)
  - NSAIDs and prednisone work as well
Treating hyperuricemia: ACR 2012 guidelines

- Do not treat asymptomatic hyperuricemia
  - Primary hyperuricemia may someday be linked to cardiovascular or metabolic syndromes
- General goal is:
  - To reduce frequency and severity of subsequent attacks of gout
  - To resorb tophacous uric acid deposits that can cause joint damage
- Allopurinol and febuxostat are considered first-line therapies for hyperuricemia associated with gout
- It’s now considered acceptable to initiate urate-lowering therapy during acute flares provided adequate treatment of flare is begun and prophylaxis against future flares is maintained for at least three months after flare

ACP Guidelines: Key failure

- The ACP expert panel couldn’t bring itself to recommend treating to a serum uric acid target
- Cited lack of evidence to recommendation (formal randomized prospective trials comparing treating to specific target on outcomes of gout flares, tophus reduction, metabolic syndrome, etc…)
- Cited clinical trials of urate lowering therapy with increased gout flares (lacked adequate prophylaxis)
- Ignored its own cited mountains of other literature/evidence (2 RCTs post-hoc analysis and 8 retrospective cohort studies) supporting long term reduction in gout flares and complications of hyperuricemia with treatment to serum urate <6 and better if <5.
- Ignored common sense: “The guideline…..imperils good outcomes, and could set optimal treatment of the disease back decades.” – R. Turkeltaub MD UCSD

Addressing co-morbid conditions in gout patients with hyperuricemia

Addressing co-morbid conditions in gout patients with hyperuricemia

<table>
<thead>
<tr>
<th>Table 2. Specific recommendation of a comorbidity checklist for gout patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration to consider in the clinical evaluation, and if clinically indicated, to evaluate evidence C for all?</td>
</tr>
<tr>
<td>Obesity, dietary habits</td>
</tr>
<tr>
<td>Metabolic syndrome, type 2 diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension, modifiable risk factors for coronary artery disease or stroke</td>
</tr>
<tr>
<td>Severe osteoarthritis medication disposable</td>
</tr>
<tr>
<td>History of nephrolithiasis</td>
</tr>
<tr>
<td>Chronic kidney, glomerulonephritis, or interstitial renal disease (e.g., analgesic nephropathy, polycystic kidney disease)</td>
</tr>
<tr>
<td>In selected cases, potential genetic or acquired cause of uric acid overproduction (e.g., adenine over production or purine, xanthine oxidase, or hyperuricemic disease, respectively)</td>
</tr>
<tr>
<td>Local consultation</td>
</tr>
</tbody>
</table>

Non-pharmacologic treatments for hyperuricemia

- Patient education about hyperuricemia, diet, and lifestyle modifications
- Consideration given to uric acid-elevating medications
  - Key culprits are thiazide and loop diuretics, niacin, and cyclosporine
  - Obviously if drug benefits outweigh small improvement in uric acid, then do not adjust or discontinue
A 62 YO male patient of yours with gout comes to your office asking what dietary changes he should make in helping to treat his gout and hyperuricemia. According to the ACR guidelines, you recommend that he avoid which of the following?

A. Modest alcohol intake  
B. Foods and beverages with high fructose corn syrup  
C. Chicken and turkey  
D. Low fat dairy products

**Diet recommendations:**  
*Fairly Meager evidence*

<table>
<thead>
<tr>
<th>Avoid</th>
<th>Limit</th>
<th>Encourage</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>High purine content e.g., meats, poultry</em></td>
<td><em>Avoid</em></td>
<td><em>Encourage</em></td>
</tr>
<tr>
<td><em>High fructose corn syrup, beverages</em></td>
<td><em>Restrict</em></td>
<td><em>Encourage</em></td>
</tr>
<tr>
<td><em>Alcohol more than 2 servings per day</em></td>
<td><em>Encourage</em></td>
<td><em>Encourage</em></td>
</tr>
</tbody>
</table>

Khanna et al. Arth Care and Research 2012: 64;10 1431-1446

**Chronic Gout: Uric Acid Lowering Therapies**

- **Allopurinol**
  - Xanthine Oxidase Inhibitor (blocks metabolism of purines to uric acid)
  - Effective for both under-excreters and overproducers of uric acid
  - Now acceptable to start many gout patients on allopurinol during a flare if they are responding appropriately to anti-inflammatory agents
  - Don’t stop therapy during an acute attack
Allopurinol is a purine derivative: a dead ringer for hypoxanthine

Allopurinol competes with Hypoxanthine for xanthine oxidase

Using allopurinol properly

• Do not start patients on more than 100 mg/day
• Dose reduce ALL patients with moderate to severe renal insufficiency
• Gradually up-titrate the dose, which in some cases, can be more than 300 mg/day if needed
• Treat to Target: serum urate concentration <6 if treating tophi, and <5 ideally.
• Push the allopurinol dose over 300 mg/day if necessary!!

EULAR 2016 Treat to Target Recommendations

Table 2. Recommendations are in line with prior joint expert recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level</th>
<th>Grade</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Start with a moderate dose of allopurinol to reduce the risk of gout flares.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Gradually increase the dose to achieve the target serum urate level.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. If necessary, increase the dose to achieve the target serum urate level.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. Monitor serum urate levels to ensure target levels are achieved.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. Adjust the dose as needed to achieve target serum urate levels.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F. Consider using additional medications if target serum urate levels are not reached.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EULAR 2016 Treat to Target: Recommendations for the Management of Gout

Allopurinol Toxicities

- Careful use in patients with renal failure
  - Metabolites are renally cleared
  - Hypersensitivity reactions are more common in patients with renal insufficiency
- Purine-associated hypersensitivity syndrome is DIFFERENT from allergic rash
  - Systemic and sometimes life threatening illness
- Fever, Steven's-Johnson/TEN, hepatitis, marrow suppression, nephritis, DRESS

(Drug Rash with Eosinophilia and Systemic Symptoms) The Role of HLA 5801 and Allopurinol Hypersensitivity is unquestioned
- All patients from populations with a high allele frequency for HLA 5801 and high hazard ratio for developing hypersensitivity should be screened!

HLA B5801 and Allopurinol Hypersensitivity
Hung et al. PNAS 2005

<table>
<thead>
<tr>
<th>Allelic Extender</th>
<th>Allopurinol SCAR</th>
<th>Tolerant control</th>
<th>Odd ratio</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a = 5801)</td>
<td>(a = 100)</td>
<td></td>
<td>1.07</td>
<td>0.0005</td>
</tr>
<tr>
<td>HLA B5801</td>
<td>119 (30)</td>
<td>102 (100)</td>
<td>1.15</td>
<td>0.02</td>
</tr>
<tr>
<td>HLA DRB1*1502</td>
<td>119 (30)</td>
<td>100 (100)</td>
<td>1.21</td>
<td>0.01</td>
</tr>
<tr>
<td>HLA DRB1<em>1502, A</em>1101</td>
<td>119 (30)</td>
<td>100 (100)</td>
<td>1.21</td>
<td>0.01</td>
</tr>
</tbody>
</table>

1. B5801 confers nearly 600 fold increased risk of allopurinol hypersensitivity
2. Allele and association is particularly important in Han Chinese patients, Thai, and Korean patients

Allopurinol Pharmacogenetics
Bench Clinic

1. The Role of HLA 5801 and Allopurinol Hypersensitivity is unquestioned
2. All patients from populations with a high allele frequency for HLA 5801 and high hazard ratio for developing hypersensitivity should be screened!

The Present State of Gout Therapy: What to do with a More Challenging Case?

You are seeing a 56 year old male with long standing diabetes, hypertension, chronic renal insufficiency, and destructive tophaceous gout. His gout originally began as episodic podagra that became more frequent and involved more joints over time. In the past few years, his tophi have grown larger and more numerous, and acute episodes of inflammatory arthritis have begun to blend together into a chronic, painful, polyarticular inflammatory synovitis in his hands, elbows, knees, and feet from which he has come to your office seeking relief.
Gout: Findings

- He has chronic swelling, synovitis, and deformities reminiscent of rheumatoid arthritis
- Numerous tophi scattered on arms, legs, and ears
- Serum creatinine is 1.8
- Uric Acid 10.2

Managing the Chronic Disease

Which of the following options is best suited to treat his hyperuricemia to target:

A. Starting allopurinol 300/day
B. Colchicine 0.6 mg/day
C. Probenecid 250 mg twice daily
D. Start febuxostat 40 mg/day

Managing the Chronic Disease

Which of the following options is best suited to treat his hyperuricemia to target:

A. Starting allopurinol 300/day
B. Colchicine 0.6 mg/day
C. Probenecid 250 mg twice daily
D. Start febuxostat 40 mg/day

Difficult to manage chronic gout

- Generally do not start 300 mg/day of allopurinol on most patients, especially with chronic kidney disease
- Mechanism of colchicine doesn’t treat hyperuricemia
- Probenecid won’t work without adequate GFR and is contraindicated in tophaceous gout anyway
- Starting very low allopurinol (50 mg or 100 mg QOD and titrating up is an option, but febuxostat is effective and safe in patients with moderate CKD
Febuxostat (FDA approved 2009)

- First treatment in 40 years for chronic gout
- NON-PURINE inhibitor of xanthine oxidase
- Theoretically safe to use in patients with allopurinol reactions
- Been studied in patients with mild renal insufficiency
- Dosed at 40-80mg/once daily

Fubuxostat is Not a Purine

Purine Metabolism

Comparison of Febuxostat to Allopurinol

- 80mg and 120 mg of febuxostat superior to allopurinol 300mg/day
  - Percent of patients achieving uric acid <6
  - Greater reduction in serum uric acid levels
- Safe in patients with mild-moderate renal insufficiency (SCr <1.5 in this study) and patients with previous allopurinol reactions
- Note: Allopurinol 300/day is probably suboptimal dose for many patients
Febuxostat: Summary

- More potent than 300 mg/day allopurinol (but many patients can tolerate higher doses of allopurinol)
- As it is not a purine: Appropriate for patients with allopurinol hypersensitivity
- Can be used safely in patients with mild renal insufficiency (unlike allopurinol)

Treating severe, refractory tophaceous gout

Lifetime of standard uric acid lowering treatment won’t eliminate these tophi

Uricase

- Enzyme that converts insoluble uric acid to more soluble metabolite allantoin
- Most of animal kingdom (& many mammals) posses uricase, but not humans have lost gene function
- Rasburicase: a drug derived from aspergillis used to treat tumor lysis syndrome in pediatric leukemia
- Rasburicase is extremely immunogenic, which limits its half life and use in chronic diseases

Pegloticase (FDA approval Sept. 2010)

- Mammalian uricase
- Pegylated
  - Increases half life
  - Reduces immunogenicity
- Administered by IV infusion every 2 weeks
Efficacy of Pegloticase

Sundy et al. A&R 2008

- Phase 2 randomized open label dose ranging study 41 patients with serum urate >8
- Intolerance or inadequate response to standard urate lowering therapy (UA>6) for at least 3 months
- Plus one of the following:
  - At least one tophus
  - At least one flare in last 6 months
  - Chronic gouty arthropathy

Visible Results

Before Treatment

After Treatment
Pegloticase: Not holy grail

- Adverse events:
  - Infusion reactions (not human, even with PEG)
  - Many patients develop antibodies to drug that increases its clearance and affects its efficacy
  - Anaphylaxis
  - 80% patients had gout flares despite prophylaxis
  - Contraindicated in G6PD deficient patients
  - May exacerbate CHF

Pegloticase: Summary

- Effective agent for acute lowering and chronic reduction in serum uric acid levels
- Serum uric acid levels are low enough in some patients to promote tophus resorption
- Medication is expensive, immunogenic, and associated with adverse events
- Refer these patients with severe tophaceous gout to rheumatologists!!

Renal excretion of uric acid

Probenecid: An old friend

- Uricosuric agent blocks tubular re-absorption of uric acid
- Useful in patients who under-excrete uric acid (90%)
- If need be, confirm under-excretion with 24 hr. uric acid <800 mg/24 hrs.
- Do not use if:
  - Tophi
  - Renal insufficiency
  - Clear overproduction syndrome

Chronic Gout: Uricosuric agents
Lesinurad

- FDA approved 2016 uricosuric for use in combination with xanthine oxidase inhibitor (allopurinol or febuxostat) to lower uric acid
- Useful add-on therapy in treat to target scenario
- Similar contraindications and limitations to probenecid in kidney disease (use with allopurinol is required)

Effectiveness of Lesinurad as add-on to Allopurinol in treat to target

Advances in Therapies for Gout: Summary

- Gout is an ancient disease for whom modern therapy is finally available
  - Should be managed effectively by internists and PCPs who use treat to target approach (not in ACP guidelines)
- New therapies are available
  - Febuxostat (allopurinol refractory, intolerant, or contraindicated)
  - Pegylated uricase: severe tophaceous disease
  - Novel uricosuric agents like lesinurad
- Rheumatology referral appropriate for difficult to manage cases
The future is bright for those with gout who do not go extinct.

Gout Therapy: The Future

Back to our Challenging Case....

- He has chronic swelling, synovitis, and deformities reminiscent of rheumatoid arthritis
- Numerous tophi scattered on arms, legs, and ears
- Serum creatinine is 1.8
- Uric Acid 10.2
- Diabetes

Managing the Acute Symptoms

In the acute setting, the best approach to managing this patient’s symptoms would be to start?:

A. Indomethacin 75 mg-100mg PO TID
B. Colchicine 0.6 mg PO q2hr until he improves
C. Prednisone 20 mg PO QD
D. Allopurinol 300 mg PO QD
Managing the Acute Symptoms

In the acute setting, the best approach to managing this patient’s symptoms would be to start:

A. Indomethacin 75 mg-100mg PO TID
B. Colchicine 0.6 mg PO q2hr until he improves
C. Prednisone 20 mg PO QD
D. Allopurinol 300 mg PO QD

A. Can’t use because of renal disease
B. Not standard of care for acute gout
C. Best choice, but not ideal given diabetes
D. Not used to treat acute inflammation

Are there any anti-inflammatory treatments on the horizon for those refractory to or intolerant of standard therapy??

Therapy for Acute Gout: A “Biologic” Future??

Target #2: The Inflammasome

Gout pathogenesis:
- Super saturated serum levels of uric acid lead to crystal formation and deposits in joints
- Crystals are engulfed by macrophages
- Macrophages release inflammatory cytokines
- Recruit more inflammatory cells and perpetuate joint inflammation

How do inert UA crystals lead to inflammation?

How does uric acid lead to inflammation??

- Innate Immune System:
  - Inflammatory cells can innately recognize common microbial features as danger signals
    - Flagella, viral RNA, etc...
  - Leads to rapid inflammation (even septic shock) that acts as “speed bump” until adaptive immune response kicks in
  - Microbial patterns bind to Toll-like receptors and lead to production of pro IL-1
IL-1 Production

• Pro-IL 1 is inactive, but capable of being rapidly metabolized to active IL-1

• Machinery that cleaves pro IL-1 to active IL-1 is called the inflammasome and is induced by a second required danger signal

• Uric Acid is capable of activating the inflammasome

Dual activation of pattern receptors PLUS a host danger signal (Uric Acid)

Is IL-1 Blockade Effective for Gout?

• IL-1 blockade via
  – IL-1 Receptor antagonist (Anakinra, commercially available for Rheumatoid Arthritis)
  – Anti IL-1 antibody (Canakinumab, commercially available to treat certain periodic fevers)
  – IL-1 decoy receptor fusion protein (Rilanocept, commercially available to treat certain periodic fevers)

• Several pilot studies suggest these all work!

• Single dose of Canakinumab superior to triamcinolone injection (has long half life)
Canakinumab (CK) vs. Triamcinolone
So et al. A&R 2010

- CK administered as one of 5 single doses
  - Previous gout flare
  - Acute gout flare <5 days
  - Inability to take other acute gout therapy

- Primary endpoint: find dose of CK equivalent to triamcinolone for reduction of pain at 72 hours

- No equivalent dose! All canakinumab doses superior to triamcinolone at 72 hours

Time to First Gout Flare
So et al. A&R 2010

Secondary endpoints:
- 8 week reduction in gout flares
- Time to 50% reduction in pain
- Reduction in serum inflammatory markers
- Patient and physician global assessments
- Use of other gout therapies

Not Quite Ready for Prime Time
FDA rejects expanded use of Regeneron drug for gout
Published July 31, 2012
Reuters
Regeneron Pharmaceuticals Inc said U.S. regulators have denied approval for it to expand use of its Arcalyst drug to prevent gout flares, asking that the company provide more clinical data.

The rejection follows a unanimous vote against the drug’s approval in early May by advisors to the U.S. Food and Drug Administration, with panel members expressing concern that the company had only done a 16-week study.

FDA Panel Votes Against Gout Drug
By THOMAS M. BURTON
WASHINGTON—The Food and Drug Administration is grappling with the novel question of whether a Novartis AG NVS +0.97% gout-pain drug should be marketed when patients receiving just one injection had a higher rate of serious infections in clinical studies.

An FDA advisory committee Tuesday voted 11-1 against approving the drug, called lixis, because of the safety concerns.
Parkinson’s Disease: Demographics

- 1.2% of people 60 years of age or older (~130-140 per 100,000)
- 2nd most common neurodegenerative disorder
- Average age of onset: 60 years old (range 20-95)
- Males are 1.5 times more likely to develop Parkinson’s disease
- Typical life expectancy: 12-20 years (range: 12-40)

Wishart et al. 2009 J Neurol Neurosurg Psych; Walker et al. 2010 Parkinsonism and Related Disorders
Jen et al. 2009 The Lancet; Moisan et al. 2015 Journal of Neurology, Neurosurgery & Psychiatry

Outline

- Parkinson’s Disease: Demographics
- Parkinson’s Disease: Motor Symptoms
- Parkinson’s Disease: Progression
- Parkinson’s Disease: Pathophysiology
- Parkinson’s Disease: Treatment: Motor Symptoms
- Parkinson’s Disease: Treatment: Non-motor Symptoms
- Parkinson’s Disease: Treatment: Supportive Care Model

Disclosures

- Consulting services for Bagatto, Inc. to guide the development of improved deep brain stimulation clinician programming systems and cognitive testing applications
- Consulting services for Putnam Associates and Gerson Lehrman Group to help identify treatment gaps for people with Parkinson’s disease
- Consulting services for Schlessinger Associates, ExpertConnect, KeyQuestHealth, Seagrove Partners, Cowen and Company, LLC to understand physician perspectives on current and future treatments for people with Parkinson’s disease
Parkinson’s disease progression:
**Motor Fluctuations**

![Graph showing L-DOPA concentrations over years of disease](image)

Stage 5: ~2 years
- Wheelchair bound or bedridden
- Can only ambulate with another person assisting

Stage 4: ~2 years
- Severe disability
- Needs an assistive device to walk or stand

Stage 3: ~2 years
- Mild to moderate bilateral involvement
- Postural instability
- Still independent

Stage 2: ~7 years
- Mild bilateral involvement

Stage 1: ~2 years
- Unilateral involvement

**Hoehn & Yahr staging**

![Illustrations of stages with descriptions](image)

Parkinson’s pathology:
**Substantia nigra pars compacta degeneration**

![Images of brain regions](image)


**Lewy body**

![Lewy body image](image)

Olanow and Brundin, 2013, Movement Disorders
Parkinson’s pathology: prion-like disease

Lewy body–like pathology in long-term embryonic nigral transplants in Parkinson’s disease

DaTSCANs detect presynaptic dopaminergic neuronal loss using SPECT imaging

- Measures Ioflupane (123I), which is a DAT ligand that binds to presynaptic dopamine transporters in the striatum

De la Fuente-Fernandez 2012, Neurology
Ba and Martin, 2015, Parkinsonism and Related Disorders

Parkinson’s pathology: DaTSCAN

The basal ganglia has 2 major pathways:

Direct and Indirect

- The direct pathway facilitates movement.
- The indirect pathway inhibits movement
- Striatal dopamine excites the direct pathway (increasing movement), and suppresses the indirect pathway (increasing movement)

Calabresi et al. 2014, Nature Neuroscience

Parkinson’s pathology: Rate model

Phase amplitude coupling

- Increased bursting of neuronal activity
- Increased synchronization in neuronal activity
- Increased oscillatory activity

De Hemptinne et al. 2013, PNAS
De Hemptinne et al. 2015, PNAS

Parkinson’s pathology: Brain arrhythmia
Parkinson’s etiology: gene-environment interaction

- Complex interplay between
  - genetics (ingredients)
  - environment (recipe)

Tanner et al. 2011, Envi Health Perspectives

Treatment for Parkinson’s Disease Motor Symptoms: Medications

### Carbidopa/Levodopa: Effects

- The most effective and generally well-tolerated medicine for PD
- Short half-life (~45 to 90 minutes), needs to be taken frequently as PD progresses
- Ideally should be taken 1 hour before or 2 hours after a protein-rich meal
- Main side effects: nausea, lightheadedness, hallucinations, and dyskinesias

### Carbidopa/Levodopa: Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinemet IR</td>
<td>Short half-life (45-90 minutes)</td>
</tr>
<tr>
<td>Parcopa</td>
<td>Orally disintegrating tablets, not sublingually absorbed, similar time to peak concentration compared to sinemet IR</td>
</tr>
<tr>
<td>Sinemet CR</td>
<td>~40 minutes increased sustained concentration compared to sinemet IR, impaired bioavailability, lower peak dose, time to peak concentration can be up to 120 minutes longer than sinemet IR</td>
</tr>
<tr>
<td>Rytary</td>
<td>~2 to 2.5 hours increased sustained concentration compared to sinemet IR</td>
</tr>
</tbody>
</table>

### Carbidopa/Levodopa Extenders: Effects

<table>
<thead>
<tr>
<th>Extender</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasagline (Azilect)</td>
<td>1 hour increased on-time, Side effects: drug interactions</td>
</tr>
<tr>
<td>Selegiline (Eldepryl)</td>
<td>1 hour increased on-time, Side effects: drug interactions, HTN, insomnia, delirium</td>
</tr>
<tr>
<td>Entacapone (Comtan)</td>
<td>1 hour increased on-time, Side effects: diarrhea, orange urine</td>
</tr>
<tr>
<td>Tolcapone (Tasmar)</td>
<td>2-3 hours increased on-time, Side effects: Liver failure</td>
</tr>
</tbody>
</table>
**Treatment for Parkinson’s Disease Motor Symptoms: Medications**

**Dopamine Agonist:**

- Compared to carbidopa/levodopa
- Lasts longer, half-life: ~6 hours
- Lower risk of causing dyskinesias
- More mild benefit

- Main side effects: sleep attacks, ICDs, sedation, confusion, hallucinations, cognitive deficits, dry mouth, lightheadedness
- Usually not prescribed to people over 70 years of age

**Levodopa sparing therapy:**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine agonists</td>
<td>Mild-moderate reduction in parkinsonism Side effects: ICD, sleep attacks, hallucinations, cognitive deficits</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Reduces tremor and dystonia Side effects: nephrolithiasis, somnolence, ataxia, confusion, cognitive deficits</td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
<td>Reduces tremor and dystonia Side effects: sedation, delirium, hallucinations, increased risk of dementia, dry mouth, constipation</td>
</tr>
</tbody>
</table>

**Levodopa sparing therapy:**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAO-B inhibitors</td>
<td>Very mild reduction in parkinsonism, if any Side effects: drug interactions, depends on whether rasagiline or selegiline are used</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Mild reduction in parkinsonism, Reduces dyskinesias Side effects: confusion, hallucinations, dry mouth, constipation</td>
</tr>
</tbody>
</table>

**CALM-PD Clinical Trial**

<table>
<thead>
<tr>
<th>Dosing strategy</th>
<th>Percentage developing dyskinesia after 2 years</th>
<th>Improvement in movement and function scale (UPDRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramipexole</td>
<td>10%</td>
<td>4.5 points</td>
</tr>
<tr>
<td>Levodopa</td>
<td>10%</td>
<td>9.2 points</td>
</tr>
</tbody>
</table>

CALM-PD-PSG Study Group, 2005, JAMA
Treatment for Parkinson’s Disease Motor Symptoms:

Medication Tips

• Prochlorperazine (Compazine)
• Promethazine (Phenergan)
• Metoclopramide (Reglan)
• Most anticholinergics (e.g., benadryl or oxybutynin)
• Most antipsychotics (only quetiapine, clozaril and pimavanserin are safe)

OUTPATIENT PHYSICAL THERAPY

• Parkinson Wellness Recovery (PWR!)
• Lee Silverman Voice Training (LSVT)
• Balance vest

REHABILITATION

HOME SAFETY EVALUATION

• skilled nursing
• physical therapy
• occupational therapy
• custodial non-skilled care

MEDICARE COVERS ‘SKILLED MAINTENANCE’

• Medicare covers rehab services to maintain or manage a patient’s current condition when no functional improvement is possible
• Therapy services to maintain a patient’s current condition or slow decline are covered

REHABILITATION
### Non-Pharmacological Treatments

- Reduce multi-tasking to reduce freezing episodes.
- During a freezing episode: come to a complete stop (to abort the malfunctioning automatic gait program causing the freezing episode).
- Then try any of the following techniques:
  - Count to 3 and take a large high step with one foot.
  - Try another movement (e.g. raise an arm, touch your head) and then restart walking.
  - Turn in a U-shape.
  - Change direction: step sideways and then go forward.
  - Weight shifting from side to side.
  - Metronome or musical cueing.
  - Stress-reduction techniques to minimize emotional triggers of freezing episodes.

### Pharmacological Treatments

- **Methylphenidate**: 1mg/kg/day divided TID was shown to reduce freezing of gait. ([Moreau et al. 2012](#))

### Use of Assistive Devices

- Cane, walking sticks, walker (U-step vs. Life walker vs. Other rolling walkers).
- Consider knee protectors for frequent fallers.
- Recommend Lifeline or MedAlert System.
- Wheelchair optimization.
### Treatment for Parkinson’s Disease Motor Symptoms: Physical activity must be challenging to have a benefit

**Aerobic Activity**  
Activity that works the heart, lungs, and muscles. Improves overall motor function and may delay Parkinson’s progression.

**Flexibility Exercises**  
Helps maintain flexibility, and helps muscles and joints stay flexible.

**Balance Exercises**  
Tai Chi and yoga are effective exercises that improve balance and may reduce falls.

**Strength Training**  
Improves muscle strength, functional ability, and may reduce falls.

---

### Parkinson’s disease progression: Motor Fluctuations

<table>
<thead>
<tr>
<th>Years of disease</th>
<th>Plasma L-DOPA concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 yrs</td>
<td></td>
</tr>
<tr>
<td>4-7 yrs</td>
<td></td>
</tr>
<tr>
<td>7-10 yrs</td>
<td></td>
</tr>
<tr>
<td>&gt;10 yrs</td>
<td></td>
</tr>
</tbody>
</table>

- Dyskinesia
- Akinesia
- Rigidity

---

### Treatment for Parkinson’s Disease Motor Symptoms: Duopa infusion therapy

**Intestinal infusion of dopamine (levodopa)**

- Reduces off-medication time and reduces dyskinesias
- Most patients are on duopa monotherapy

---

### Treatment for Parkinson’s Disease Motor Symptoms: Duopa infusion therapy

**Intestinal infusion of dopamine (levodopa)**

- **Possible side effects:**
  - Post-surgical complications
  - Tubing issues
  - Cases of severe neuropathy

---

**Nyholm et al. MDS Conference abstract. 2012.**  
**Olanow et al. 2014, The Lancet Neurology.**  
**Conci, 2014, Frontiers Neurology.**
**Ideal Candidate for DBS**

- Parkinson’s disease for at least 5 years
- Robust improvement in motor symptoms with dopaminergic therapy
- Consider as soon as motor symptoms are no longer easily managed with medications alone
- Freezing of gait and postural instability should not be the primary symptoms
- Good social support
- Ability to comply with complex life-long therapy
- Reasonable expectations for the surgery
- No medical contraindications for surgery
- No untreated severe psychiatric disease
- No dementia (PD-MCI can still be considered for unilateral, staged surgery)

**What can DBS do?**

- In general, only what levodopa can do
  - *Exceptions: tremor and peak dose dyskinesias*
- Increases the best “on-medication” state by 4-5 hours daily
- Improves motor function by 25-50%
- Raises the ceiling for off-medication times
- Reduction in medication dosing (30-50%)

**What are the limitations of DBS?**

- Less effective for midline symptoms
- Will not treat non-motor symptoms
- Can make certain symptoms worse (e.g. speech, falls, behavior and cognition)

**DBS Surgical Techniques**

- **Deep Brain Stimulation Awake Surgery**
  - physiology-guided implantation
- **Deep Brain Stimulation Asleep Surgery**
  - iMRI-guided implantation
### Treatment for Parkinson’s Disease Motor Symptoms: Deep Brain Stimulation: Timing of Surgery

<table>
<thead>
<tr>
<th>A 100%</th>
<th>B 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

Fasano & Deuschl 2012, Basal Ganglia

### Treatment for Parkinson’s Disease Non-motor Symptoms: Motor symptoms are just the tip of the iceberg

- Most motor symptoms (fluctuations and dyskinesias) can be treated with advanced surgical therapies, but freezing of gait and imbalance are usually refractory
- Most PD patients report an average of 8 non-motor symptoms
- Non-motor symptoms are often:
  - under-recognized and unseen
  - more difficult to treat
  - impair quality of life more than motor symptoms
  - have a greater impact on care-partner strain than motor symptoms

### Parkinson’s Disease Symptom Management

#### Cognitive deficits

<table>
<thead>
<tr>
<th>Non-Pharmacological Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce or withdraw offending medications</td>
</tr>
<tr>
<td>Rule out infections, dehydration and metabolic derangements</td>
</tr>
<tr>
<td>Rule out depression and anxiety</td>
</tr>
<tr>
<td>Rule out obstructive sleep apnea or chronic insomnia</td>
</tr>
<tr>
<td>Rule out B12 deficiency</td>
</tr>
<tr>
<td>Rule out illicit drug use</td>
</tr>
<tr>
<td>Cognitive leisure activities</td>
</tr>
<tr>
<td>Regular exercise</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacological Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimize dopamine medications (may need to be reduced)</td>
</tr>
<tr>
<td>Cholinesterase inhibitors (e.g. donepezil, rivastigmine, galantamine)</td>
</tr>
<tr>
<td>NMDA receptor antagonists (e.g. memantine)</td>
</tr>
</tbody>
</table>

Dubois et al., 2012, Mov Disord

#### Psychosis

<table>
<thead>
<tr>
<th>Non-Pharmacological Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rule out concurrent illness and/or metabolic derangements</td>
</tr>
<tr>
<td>Rule out medication side effects</td>
</tr>
<tr>
<td>Minimize disruptions at night time</td>
</tr>
<tr>
<td>Optimize light exposure and activities during the day</td>
</tr>
<tr>
<td>Place calendar in clear view</td>
</tr>
<tr>
<td>Minimize immobilization by reducing catheters and restraints</td>
</tr>
<tr>
<td>Glasses and hearing aids optimized to reduce sensory deprivation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacological Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider tapering off dopamine agonists, amantadine and anticholinergics</td>
</tr>
<tr>
<td>Consider reducing levodopa dose</td>
</tr>
<tr>
<td>Maximize cholinesterase inhibitors</td>
</tr>
<tr>
<td>Quetiapine, Pimavanserin, or Clozaril (black box warning with use in those with dementia)</td>
</tr>
</tbody>
</table>

Chang and Fox, 2016, Drugs
**PARKINSON’S DISEASE SYMPTOM MANAGEMENT**

**Agitation (seen in advanced PD dementia)**

**Non-Pharmacological Treatments**
- Rule out delirium due to underlying medical cause
- Rule out medication side effects
- Minimize disruptions at night time
- Optimize light exposure and activities during the day
- Glasses and hearing aids optimized to reduce sensory deprivation

**Pharmacological Treatments**
- Taper off dopamine agonists, amantadine, and anticholinergics
- Consider reducing levodopa dose
- Maximize cholinesterase inhibitors
- Consider morphine if underlying pain could be causing the agitation
- Quetiapine, Pimavanserin, or Clozaril (black box warning with use in those with dementia)

Chang and Foz, 2016, Drugs

**Fatigue**

**Non-Pharmacological Treatments**
- Taper off dopamine agonists, amantadine, and anticholinergics
- Consider reducing levodopa dose
- Maximize cholinesterase inhibitors
- Consider morphine if underlying pain could be causing the agitation
- Quetiapine, Pimavanserin, or Clozaril (black box warning with use in those with dementia)

Pharmacological Treatments
- Modafinil
- Methylphenidate
- Amantadine

Kluger B. 2017. International Review of Neurobiology

**Poor sleep onset and maintenance**

**Non-Pharmacological Treatments**
- Sleep study to rule out obstructive sleep apnea
- Encourage good sleep hygiene
  - No caffeine at least 4 hours before bedtime
  - Get regular exercise (avoid 2 hours before bedtime)
  - Keep a regular schedule for bedtime and wakeup time
  - Keep the bedroom quiet and dark during the night
  - Keep the bedroom mainly for sleep, avoid watching television, listening to the radio or eating in the bedroom
  - Get out of bed if not sleeping
  - Get sunlight and exercise in the morning

Albers and Anch, 2017, Sleep Medicine

**Pharmacological Treatments**
- Ensure adequate levodopa coverage overnight (consider Rytary)
- Melatonin (ideally taken 2 hours prior to bedtime)
- Mirtazapine (lower doses are optimal to treat insomnia, 7.5mg or 15mg at bedtime)
- Trazodone (main potential side effect is orthostatic hypotension)
- Quetiapine (particularly useful if there is sundowning or psychosis at bedtime)
- Gabapentin (particularly useful if nighttime leg cramps or RLS disrupt sleep)
- Doxepin (caution, may contribute to daytime confusion, useful if unable to add a serotoninergic medication such as mirtazapine or trazodone to improve sleep)

Albers and Anch, 2017, Sleep Medicine
### Parkinson's Disease Symptom Management

#### REM Behavior Disorder

**Non-Pharmacological Treatments**
- Maintain a safe sleep environment to prevent injuries
- Move furniture away from the bed
- Place padding on corners of furniture
- Consider placing a mattress on the floor near the bed
- Bed-partner may need to sleep in a separate bed until RBD is well controlled with pharmacological treatments

**Pharmacological Treatments**
- Melatonin (3-15mg, ideally taken 2 hours before bedtime)
- Clonazepam (start at 0.25mg at bedtime, caution - may cause daytime sedation, confusion and falls, may worsen OSA)
- Quetiapine (start at 12.5mg at bedtime, can increase by 12.5mg as needed)

Albers and Sack, 2017, Sleep Medicine

#### Constipation

**Non-pharmacological Treatments**
- Dietary adjustments:
  - Daily prunes or prune juice
  - Fruits, vegetables, whole grain breads
  - Stay hydrated (6-8 glasses of liquid daily)
  - Avoid bulk fiber supplements (e.g. psyllium)
  - Consider prebiotics and probiotics
  - Electro-acupuncture

Miyasaki, 2013; Curr Neurol Neurosci Rep

**Pharmacological Treatments**
- First line: miralax 1-4 times daily and senna daily (up to 4 tablets twice daily)
- Second line: can add a trial of oral dulcolax
- Third line: can add a trial of lubiprostone or linactolide
- If no BM in 3-5 days: dulcolax suppository +/- enema (short-term use only)
- If no BM in >7 days: magnesium citrate 150-300mg followed by 250ml of water (short-term use only)

Miyasaki, 2013; Curr Neurol Neurosci Rep

#### Dysphagia

**Non-pharmacological Treatments**
- All meals should be given when the person is alert & sitting upright at 90 degrees
- Use a chin-tuck position when swallowing
- Small bites of food, chew thoroughly (slow intake rate, "put your fork or spoon down between mouthfuls")
- "Mindful eating" (reduce distractions while eating)
- Alternate between one bite of food and one sip of liquid
- Make sure all food is cleared from the mouth before another bite or sip is taken.
- Double swallow and clear throat every 2-3 bites
- Avoid dry foods and nuts as dysphagia worsens
- Adding sauces to food can help with swallowing safely
- Upright position recommended for 30-45 minutes after a meal
- Consider brushing teeth after meals
- Eventually, mincing or pureeing food becomes necessary

Suttrup and Warnecke, 2017, Dysphagia
PARKINSON’S DISEASE SYMPTOM MANAGEMENT

Dysphagia

Speech Language Pathology Evaluation

• To assess severity of dysphagia and rule out other causes
• Recommend additional behavioral interventions
• Recommend swallowing rehab exercises (e.g. expiratory muscle strength training)
• Assess for the Provale cup, the Nosey cup, or the Safe straw
• We do not support thickening liquids (not palatable, can lead to dehydration)
• Carbonated thin liquids can reduce aspiration
• In the setting of severe dysphagia, we typically do not generally recommend a percutaneous gastrostomy (PEG) tube, since this symptom is a sign of the disease being at end-stage, with dementia, psychosis and chair/bed-bound status. A PEG in advanced dementia has not been shown to improve survival.

Pharmacological Treatments

• Rectal Levodopa and rotigotine patch can be considered in the short-term when patients are unable to swallow due to concurrent illness (e.g. delirium in the setting of sepsis). See the reference below for instructions on formulating rectal levodopa from oral levodopa. The rotigotine patch may worsen delirium and is contraindicated in those with advanced PD.
• Parcopa is a dissolvable form of carbidopa/levodopa that is indicated in the setting of dysphagia

Dysphagia

Sialorrhea

Non-pharmacological Treatments

• Sugar-free chewing gum or hard candy may remind the patient to swallow

Pharmacological Treatments

• Optimize dopaminergic medications (sialorrhea may improve when off-medication time is reduced
• Botulinum toxin (myobloc)
• Sublingual application of atropine ophthalmic solution
• Glycopyrrolate (caution, may cause urinary retention and constipation)

Srivanitchapoom et al., 2015, Parkinsonism Relat Disord

Central Pain Syndrome

Non-pharmacological and Pharmacological Treatments

• Optimize dopaminergic medications to reduce “off time”
• Mindfulness-based stress reduction
• Acupuncture

Ford, 2010, Movement Disorders
Non-Pharmacological Treatments

- Adequate fluid intake (6-8 glasses of liquid per day). Drinks like Gatorade, Powerade, coconut water and V8 have salt and sugar so they are more hydrating than plain water
- Head of bed elevated (wedge pillow, 7-10 inches)
- Sit-up and Stand-up slowly
- Exercises to activate calf muscles prior to standing up (e.g. repetitive foot raises, leg crossing)
- Abdominal compression bands (more comfortable than compression stockings)
- Avoid prolonged exposure to hot weather
- Eat small low-carbohydrate meals
- For acute symptomatic events: counsel patients tie sit down & drink 16 ounces as a bolus

Pharmacological Treatments

- Withdraw or reduce any offending medications (e.g. reduce antihypertensives)
- Liberalize salt in the diet (if there are no medical contraindications)
- Salt tablets (1 gram with each meal)
- Caffeine (1-2 cups of coffee daily, avoid in the evenings)
- Midodrine (last dose should be no later than 6pm to avoid supine hypertension overnight)
- Fludrocortisone (requires monitoring of potassium)
- Pyridostigmine (use for patients with supine hypertension)
- Droxidopa

Orthostatic hypotension

PARKINSON’S DISEASE SYMPTOM MANAGEMENT

Non-Pharmacological Treatments

- Exclude urinary tract infections
- Urology evaluation for BPH in males (appropriate treatment if identified)
- Timed voiding during the daytime “bladder training” (every 2-3 hours)
- Improve access to bathroom or bedside commode (to prevent functional incontinence)
- Physical therapy focused on pelvic floor muscles (e.g. Kegl maneuvers)
- Prior to bedtime - elevate legs for 30 minutes using a 7-10 inch wedge for 30 minutes, and then urinate before going to sleep
- Elevate head of the bed (7-10 inch wedge)
- Limit liquids after 6pm
- Condom catheter overnight may improve sleep maintenance
- If needed, recommend high absorbency pads (gel briefs are the most absorbent)

Pharmacological Treatments

- Specific anticholinergic medications (trospium, darifenacin, solifenacin)
- β-3 agonist (Mirabegron)

Invasive Treatments (referral to urology)

- Intravesicular botulinum toxin injections
- Electro-acupuncture
- Percutaneous tibial nerve stimulation
- Sacral nerve stimulation

PARKINSON’S DISEASE SYMPTOM MANAGEMENT

Overactive Bladder Symptoms

PARKINSON’S DISEASE SYMPTOM MANAGEMENT

Overactive Bladder Symptoms

PARKINSON’S DISEASE SYMPTOM MANAGEMENT

Overactive Bladder Symptoms

PARKINSON’S DISEASE SYMPTOM MANAGEMENT

Overactive Bladder Symptoms

Pharmacological Treatments

- Specific anticholinergic medications (trospium, darifenacin, solifenacin)
- β-3 agonist (Mirabegron)
PD Neuroprotection: Role of nutrition

Mediterranean Diet

ROCHEL PALLIATIVE CARE IN THE TREATMENT OF PARKINSON'S DISEASE

Palliative model of care for Parkinson's disease

OUTPATIENT INTERDISCIPLINARY PALLIATIVE CARE TEAM

Physician (Nonmotor symptom, prognosis); Nurse (Nutrition, Home care, Advance Directives); Social Work (Caregiver Support, Finances); Chaplain (Spiritual Wellness, Grief Counseling)

Palliative care principles address “Total Pain”

The suffering that encompasses all of a person’s physical, psychological, social, spiritual and practical struggles in the setting of serious illness

References


UCSF MOVEMENT DISORDER AND NEUROMODULATION CENTER (MDNC)
SFVA PARKINSON'S DISEASE RESEARCH, EDUCATION AND CLINICAL CENTER (PADRECC)

Jill L. Ostrem, M.D. – MDNC Medical Director
Philip A. Starr, M.D., Ph.D. – MDNC Surgical Director
Caroline M. Tanner, M.D., Ph.D. – PADRECC Director

Neurology
Jill L. Ostrem, M.D.
Caroline Tanner, M.D., Ph.D.
Ian Bledsoe, M.D., M.S.
Nicholas Galifianakis, M.D., M.P.H.
Marta San Luciano, M.D., M.S.
Maya Katz, M.D.
Jim Mass, M.D., Ph.D.
Amy Viehoever, M.D., Ph.D.
Nijee Luthra, M.D., Ph.D.
Cameron Dietiker, M.D.
Melanie Brandabur, M.D.

Psychiatry
Andreea Seritan, M.D.
Tobias Marton, M.D.

Occupational and Environmental Medicine
Samuel Goldman, M.D., M.P.H.

Clinical Fellows
Mitra Afshari, M.D.
Kyle Mitchell, M.D.
Ethan Brown, M.D.
Melissa Heiry, M.D.
Jennifer Cho, M.D.
Jessica Weinstein, M.D.
Rory Murphy, M.D.

Physical Therapy
Heather Bhide, P.T.

Social Work
Monica Eisenhardt, LCSW

Chaplain
Judy Long, M.S., M.A.
Carolyn Talmadge, M.Div.

Research Staff
Sarah Wang, Ph.D.
Nieves Lopez-Barrera, M.D.
Kathleen Courrier, B.S.
Sherry Ng, M.S.
C. Kevin Park, M.D.
Kristen Dodenhoff, B.S.
Jana Guenther, B.A.

Neuropsychology
Caroline A. Racine, Ph.D.
Johannes Rothlind, Ph.D.

Nursing
Monica Volz, N.P.
Susan Heath, M.S., R.N.
Annie Li Wong, N.P.
Karen Merchant, R.N.
Gina Bringas-Cinco, R.N.

Dental Director
Ruth Whelan, D.D.S.

Specialized Staff
Michael Redmond
Lauren Bucio

Medical Associates
Christian James
Sara Chacon
Jessie Mejia
Sara Miller

Administrative
Gwendolyn E. Smith

Workforce Development
Updates in Perioperative Medicine

Hugo Quinny Cheng, MD
Division of Hospital Medicine
University of California, San Francisco

New Guidelines for Perioperative Care:
- Coronary stents in surgical patients
- Bridging anticoagulation in atrial fibrillation
- Evaluating patients with sleep apnea

New Studies on Old Problems:
- Medical management of cardiac risk (statins)
- Opiates use after surgery

Surgery After Drug Eluting Stent

Your 63-y.o. patient needs a hemicolectomy for colon cancer. He had a drug-eluting stent placed 4 months ago for stable angina.

What do you recommend?
1. Wait 12 months after DES placed
2. Wait 6 months after DES placed
3. Operate now
4. Operate now only if antiplatelet drugs can be continued

Perioperative Cardiac Complications in Patients with Coronary Stents

Question: How do stent type and time until surgery affect risk of cardiac complications?

Study Design: Retrospective cohort analysis
- Over 25,000 pts who had noncardiac surgery between 6 weeks & 2 years after BMS or DES placement
- Identify risk factors for cardiac complications (all-cause mortality, MI, revascularization)

Effect of Stent Type & Time After Implantation

Time of surgery after PCI didn’t matter after first 6 months

Complications

60 120 180 240 300 360

6 months

Bare Metal

Drug Eluting


2016 ACC/AHA Guidelines for DAPT

- Avoid PCI if antiplatelet drugs will need to be held prematurely
- Delay elective surgery after elective PCI:
  - Bare metal stent: 30 days
  - Drug eluting stent: 6 months (optimal) 3 months (if harm in delay)


Management of Antiplatelet Drugs

ACC/AHA Guideline (2016):
If P2Y12 inhibitor must be stopped, then ASA should be continued if possible, and the P2Y12 inhibitor resumed postop ASAP.

Evidence?
- Small case series and one case-control study
- No data that any strategy leads to fewer MI or bleeds
- Mostly just expert opinion

Childers CP et al. JAMA. 2017; 318(2):120-1

Managing Perioperative Anticoagulation

Two patients on warfarin therapy are scheduled for elective hip arthroplasty. You’re asked whether they should receive perioperative bridging anticoagulation (with enoxaparin):
- One patient has atrial fibrillation due to hypertension
- The other patient has a St. Jude mechanical AVR
- Neither has any other relevant comorbidity

1. Bridge for AVR only
2. Bridge for AF only
3. Bridge for both
4. Bridge for neither
BRIDGE Trial

Patients:
• 1884 patients on warfarin for atrial fibr or flutter
• CHADS-2 score ≥ 1
• Excluded patients with mechanical valve or stroke within 12 weeks and cardiac & neurologic surgery

Intervention:
• Randomized to bridging with LMWH or placebo

Outcome:
• 30-day risk of arterial thromboembolism & bleeding

Douketis JD et al. NEJM, 2015; 373:823-33

<table>
<thead>
<tr>
<th>Bridged</th>
<th>No Bridge</th>
<th>Non-inferior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolic Event</td>
<td>0.3%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>3.2%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>21%</td>
<td>12%</td>
</tr>
</tbody>
</table>

BRIDGE Trial for Atrial Fibrillation

Conclusions:
• Bridging did not reduce risk of embolism
• Bridging increases bleeding risk

Caveats:
• Few patients with high CHADS-2 score (mean = 2.3)

My take-away:
• Don’t bridge majority of atrial fibrillation
• Carefully consider bridging if stroke risk is very high (CHADS-2 score 5 or 6, rheumatic atrial fibrillation)

ACC Guideline for AF (2017)

General considerations:
• Continue anticoagulation if procedure has low or negligible bleeding and patient’s bleeding risk is normal
• No bridging needed with DOACs

Bridging decision based on both clotting & bleeding risk:
• CHA2DS2-VASc: 1-4 = low risk; 5-6 = mod; 7-9 = high
• Bleeding risk: elevated if major bleed or ICH < 3 mo, platelets low or abnormal, aspirin use, supratherapeutic INR, or prior bleeding with bridging or similar surgery

Doherty et al. JACC, 2017; 69(7): 871–898
**ACC Guideline for AF (2017)**

<table>
<thead>
<tr>
<th>Thrombotic Risk</th>
<th>Normal Bleeding Risk*</th>
<th>Elevated Bleeding Risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Thrombotic Risk</td>
<td>Bridge</td>
<td>Clinical Judgment</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc = 7+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mod Thrombotic Risk</td>
<td>Clinical Judgment</td>
<td>No Bridge</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc = 5-6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Thrombotic Risk</td>
<td>No Bridge</td>
<td></td>
</tr>
<tr>
<td>CHA₂DS₂-VASc = 1-4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Bleeding risk elevated if major bleed or ICH < 3 months, platelets low or abnormal, aspirin use, supratherapeutic INR, or prior bleeding with bridging or similar surgery

**What About Mechanical Valves?**

<table>
<thead>
<tr>
<th>Thromboembolic Risk (%)</th>
<th>Without Anticoagulation</th>
<th>With Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>Mechanical Valve</td>
<td>4%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**Effect of Mechanical Valve Location & Design on Thromboembolic Risk**

**Valve Location:**
- Aortic: RR = 1.0
- Mitral: RR = 1.8

**Valve Design:**
- Caged Ball: RR = 1.0
- Tilting Disk: RR = 0.7
- Bi-leaflet: RR = 0.6


**Perioperative Anticoagulation: My Approach after BRIDGE Trial**

<table>
<thead>
<tr>
<th>CHADS₂</th>
<th>Mechanical Valve</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>Any MVR; older (caged-ball or tilting disc) AVR; recent CVA</td>
<td>Consider bridging</td>
</tr>
<tr>
<td>3-4</td>
<td>Bileaflet AVR plus other stroke risk factor(s)</td>
<td>No bridge</td>
</tr>
<tr>
<td>0-2</td>
<td>Bileaflet AVR without AF or other stroke risk factor</td>
<td>No bridge</td>
</tr>
</tbody>
</table>

Ansell J. *Chest.*, 2004;126:204S-233S.
Obstructive Sleep Apnea in Surgical Patients

A 55-y.o. morbidly obese man is scheduled to undergo knee arthroplasty. He has hypertension but no other medical history. He reports occasional fatigue and somnolence. He doesn't know if he snores or has apneic spells. Exam and recent lab tests were unremarkable.

What should be done?
1. Notify surgical team of suspected OSA
2. Notify surgical team & recommend empiric CPAP postop
3. Delay surgery for formal polysomnography

OSA and the Surgical Patient

OSA probably increases postoperative complications:
- Pulmonary complications (11 of 17 studies)
- Postop atrial fibrillation (5 of 6 studies)

Previously undiagnosed OSA may be associated with more complications than known OSA

Clinical screening tests have high PPV

Benefits of positive airway pressure (CPAP, BiPAP) for surgical patients with OSA uncertain


Society of Anesthesia and Sleep Medicine Guidelines for Preoperative Evaluation

1. Screen patients clinically for OSA risk
   - Snoring
   - Tired or sleepy
   - Observe apnea
   - Pressure (HTN)
   - BMI > 35 kg/m²
   - Age > 50 years
   - Neck > 17” (M)/16” (F)
   - Gender is male

   STOP-BANG
   - High risk for OSA if either
     - 5 or more total points
     - 2 STOP points + B, N, or G

http://www.stopbang.ca/osa/screening.php

2. Patient and care team should be informed about known or suspected OSA
3. Insufficient evidence to recommend delaying surgery to perform advanced testing (polysomnography)
   - Exception: patients with evidence of severe or uncontrolled systemic complications of OSA or impaired gas exchange (e.g., severe pulm HTN, hypoventilation, resting hypoxia)
4. Continue PAP after surgery
   - Insufficient evidence to recommend empiric PAP
You perform a preoperative evaluation on your colleague’s patient prior to a femoral-popliteal arterial bypass scheduled for next week. The patient is a smoker and has diabetes and PAD. His only medication is glyburide.

What would you do now:
1. Start aspirin
2. Start metoprolol
3. Start atorvastatin
4. Wonder what’s up with my colleague

### Preventing Postoperative Myocardial Ischemia & Infarction

<table>
<thead>
<tr>
<th>Strategies to Prevent Postoperative MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress from surgery</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Sympathetic tone</td>
</tr>
<tr>
<td>Catecholamines</td>
</tr>
<tr>
<td>Statin</td>
</tr>
<tr>
<td>Increased HR &amp; BP</td>
</tr>
<tr>
<td>Unstable plaque</td>
</tr>
<tr>
<td>Revascularization</td>
</tr>
<tr>
<td>Myocardial ischemia / infarction</td>
</tr>
</tbody>
</table>

### Rise & Fall of Beta-blockers

- Early studies showed that perioperative beta-blockers prevented postoperative MI and reduce mortality
- Subsequent studies less impressive, and some positive studies discredited for fraud
- Largest study found small benefit on MI prevention, but increased overall mortality

### 2014 ACC / AHA Guideline

- Only recommendation to use if… (1)
  - Already using β-blocker to treat angina, HTN, arrhythmia
- Not unreasonable to consider initiation if… (2b)
  - High clinical risk (e.g., RCRI score ≥ 3)
  - Ischemia seen on preoperative stress test
- Avoid initiation… (3)
  - On day of surgery

POISE 2 Trial: Aspirin & Clonidine

- POISE 2: Large 2 x 2 RCT comparing perioperative treatment with aspirin, clonidine, both, or neither
- Aspirin did not prevent death or MI, but increased bleeding complications
- Clonidine did not prevent death or MI, but increased clinically significant hypotension & bradycardia

2014 ACC / AHA Guidelines

- Aspirin (for patients without stent) & Clonidine
  - Initiation of ASA does not benefit patients undergoing elective noncardiac surgery
  - Alpha-2 agonists for prevention of cardiac events are not recommended in patients who are undergoing noncardiac surgery

Preoperative Coronary Revascularization

- CARP trial randomized patients with coronary disease to revascularization (PCI or CABG) or medical management alone before major vascular surgery
- Revascularized patients had higher preoperative complications
- No reduction in postoperative mortality or MI

2014 ACC / AHA Guidelines

- Preoperative Coronary Revascularization
  - Recommended for independent guideline-concordant indications only
  - Not recommended exclusively to reduce perioperative cardiac events

Trial of Statins in Vascular Surgery

- 497 statin naive patients a/f vascular surgery
- Randomized to Fluvastatin XL or placebo 1 month before OR

Reduced nonfatal MI

No difference in rates of LFT or CPK elevation

Schouten et al. NEJM, 2009; 361:980-9

Statins & Noncardiac Surgery

Study Design:
- Observational cohort study of 180,478 VA patients having noncardiac surgery
- 96,486 patients included in propensity-matched cohort
- Measured association between “early treatment” with statin (day of surgery or POD 1) with postoperative mortality and complications

London et al. JAMA Intern Med. doi:10.1001/jamainternmed.2016.8005 Published online

Statins & Noncardiac Surgery

Early statin use (POD 0 or 1) associated with:
- Lower all-cause 30-day mortality [RR 0.82; NNT 224]
- Fewer cardiac complications [RR 0.73; NNT 335]
- Reduced total complications [RR 0.82; NNT 67] (Respiratory, infection, renal but not stroke, thrombosis)

Dose effect detected:
- Moderate-high intensity statin dose associated with better outcomes than low intensity dose

Caveat:
- Retrospective, potential for confounders


2014 ACC / AHA Guideline (Statins)

Definitely continue if…  (Class I)
- Patient is already taking statins chronically

Reasonable to initiate if…  (Class 2a)
- Patient is having vascular surgery

Not unreasonable to initiate if…  (Class 2b)
- Patient has elevated clinical risk and is undergoing a moderate or high risk operation

Chronic Opiate Use after Surgery

Background:
- Growing concern about overuse of opiates, especially for chronic, non-cancer pain
- Less concern about opiate use for acute pain
- Little attention to opiate use to treat postoperative pain
- ~100 million operations per year (inpatient & ambulatory) means a large risk pool

Question: What is the risk of new persistent opiate use after surgery?

Study design:
- 36,177 surgical patients having one of 13 common operations (80% minor surgery, no ortho/spine cases)
- Only studied opiate naïve patients (no opiate rx for 12 months prior to perioperative period)
- Determine incidence and risk factors for persistent opiate use more than 90 days after surgery

Findings:
Overall 6% incidence of new persistent opiate use
- Similar for major & minor surgery
Risk factors for developing chronic use:
- Alcohol, tobacco, drug use
- Higher baseline comorbidity
- Anxiety & mood disorder
- Other pain (back, neck, arthritis)

Conclusions
- If DAPT must be stopped, delay elective surgery for 6 mo after DES implantation (3 months if surgery is time-sensitive)
- Bridging anticoagulation not indicated for most patients with atrial fibrillation (and probably mechanical valves)
- Screen patients for OSA, but not necessary to delay surgery
- Consider starting statin in patients with increased cardiac risk before surgery
- Prescribe opiates after surgery with caution, especially in presence of substance abuse and chronic pain
Thank You

quinny.cheng@ucsf.edu
Case 1

- A 65 year-old right handed woman with a history of HTN and DM presented to the ED after the sudden onset of right sided weakness.
- Exam shows mild expressive aphasia, R face and arm weakness as well as L gaze deviation.
- She was last seen normal at 1 p.m., and it is now 2:45 pm

The 2017 Acute Stroke Timeline

- Time of onset= last time seen normal
  - 0-4.5 Hours IV-tPA
  - 0-6* Hours Mechanical Embolectomy
  - Greater than 6* hours Anticoagulants or Antiplatelets

*=Basilar occlusions to 12 hours
The 2015 Endovascular Revolution

- Five major positive trials of endovascular therapy all published in 2015 in NEJM
- Trial design somewhat differed, but common to each:
  - 1. Used newer-generation devices
  - 2. Selected patients who were eligible via CTA (less commonly perfusion)
  - 3. IV t-PA in those who were eligible followed by embolectomy
  - 4. At least 6 hour time window

What do we do given this data?

- 1. All patients eligible for IV t-PA should receive it (quickly)
- 2. Patients within 6* hours (for now) should receive a CTA to look for a large vessel occlusion (LVO)
- 3. If LVO present, endovascular therapy should occur, even following IV t-PA
- Fundamental shift in hospital protocols including transfer protocols

What’s coming: 2017-2018

- DAWN and DEFUSE3 Trials
- Select patients with LVO treated up to 24 hours based on complex perfusion selection
  - Automated CT software
- Will lead to reexamination of triage and ED/hospital protocols once again

Case 2

- A 76 year-old man with a history of smoking presents with 3 days of R hand weakness
- Examination shows a R pronator drift and slowed movements of the R hand
- The patient takes aspirin 81mg daily as well as lisinopril
Which of the following is not part of the standard stroke workup?

A. Echocardiogram
B. Extended cardiac telemetry
C. Lipid panel
D. B12, TSH, RPR, ESR
E. Carotid evaluation

Standard Large-Vessel Stroke Workup

- Cardioembolic: afib, clot in heart, paradoxical embolus
  - 1. Telemetry
  - 2. TEE with bubble study
- Aortic Arch
  - 2. TEE with bubble study
- Carotids
  - 3. Carotid Imaging (CTA, US, MRA, angio)
- Intracranial Vessels
  - 4. Intracranial Imaging (CTA, MRA, angio)

And evaluate stroke risk factors

TEE vs. TTE

- 231 consecutive TIA and stroke patients of unknown etiology underwent TTE and TEE
- 127 found to have a cardiac cause of emboli, 90 of which (71 percent) only seen on TEE
- TEE superior to TTE for: LA appendage, R to L shunt, examination of aortic arch
- Recent study: TEE found additional findings in 52% and changed management in 10%


Atrial Fibrillation Detection

- EKG
- 48 Hours of Telemetry
- Long-term cardiac event monitor (>21d)
  - 15-20% of patients with cryptogenic stroke otherwise unexplained had afib detected
  - Clearly changes management
  - Probably cost effective

Approach to Stroke Treatment

Acute Stroke Therapy?
- No

Anticoagulants?
- No

Antiplatelets

Shrinking Indications for Anticoagulation in Stroke

1. Atrial Fibrillation
2. Some other cardioembolic sources
   - Thrombus seen in heart
   - ?EF<35
   - ?PFO with associated Atrial Septal Aneurysm
3. Vertebral or Carotid dissection
4. Rare hypercoagulable states: APLS

The Mess of PFOs in Stroke

- Around 20% of all patients have PFO
- PFO alone not necessarily associated with higher risk of recurrent stroke
  - High risk: Large, associated atrial septal aneurysm
- Three previous negative trials of closure devices
  - Cardiologists still performing these procedures widely
- New data coming in 2017: select closures

The Excitement Over the Demise of Warfarin

- Oral direct thrombin and Xa inhibitors will hopefully lead to more patients with afib being anticoagulated
- Stroke-specific concerns
  - Little acute data for secondary prevention
  - Contraindications to tPA
  - Reversal
Case 3

- A 70 year-old man with a history of DM, smoking presents 10 hours after the onset of slurred speech and right arm and leg weakness.
- The patient is on ASA 81mg daily

Stroke workup is unrevealing.

Your Treatment?

A. Increase ASA to 325mg daily
B. Add Plavix to ASA
C. Stop ASA, start Plavix
D. Stop ASA, start Aggrenox
E. Anticoagulate

Approach to Stroke Treatment

Acute Stroke Therapy?

\[ \text{No} \]

Anticoagulants?

\[ \text{No} \]

Antiplatelets

Antiplatelet Options

- 1. ASA
  - 50mg to 1.5g equal efficacy long-term
- 2. Aggrenox
  - 25mg ASA/200mg ER Dipyridamole
- 3. Clopidogrel (Plavix)
  - Multiple secondary prevention studies (CHARISMA, SPS3) show no benefit in combination with ASA
**PRoFESS Trial**

- Randomized, double-blind trial of Aggrenox versus Plavix in over 20,000 patients with ischemic stroke
- Recurrent 4-year event rates basically identical between the two medications
  - HR for Aggrenox 1.01 (95% CI, 0.92-1.11)
  - Composite of stroke, MI, vascular death: 13.1% in each
  - Major hemorrhagic events higher in Aggrenox group


**Antiplatelet Options**

- If on no antiplatelet medication
  - Plavix vs. Aggrenox (or ASA)
- If already on ASA
  - Switch to Plavix vs. Aggrenox
- If already on Plavix or Aggrenox
  - ???

**Clopidogrel + ASA: Ever A Winning Combination?**

- CHANCE trial
  - 5170 TIA or Minor Stroke patients assigned to daily ASA + Placebo versus daily ASA + Clopidogrel following 300mg load
  - Primary outcome was stroke at 90 days
    - NNT=29 to prevent 1 stroke
    - Similar safety endpoints
- Generalizability?
  - Await POINT trial results
- 2016: Not all pts benefit
  - CYP2C19 loss of function


**Other Acute Stroke Management**

- Statins for (almost) all
  - SPARCL (NEJM 8/06), 80mg atorvastatin in stroke and TIA if LDL>100
- Tight Glucose and Fever control
- Enoxaparin for DVT prophylaxis
  - PREVAIL trial (Lancet 2007)
  - CLOTS trial 1 (Lancet 2009): Compression Stockings
Permissive Hypertension

- National Guidelines
  - To at least 220/120
  - After IV tPA: less than 185 systolic for 24 hours
- We typically stop all meds except half-dose β-blockers

Permissive Hypertension

- When to stop remains controversial
- Situations where more important
  - Large Vessel Occlusion
  - Fluctuating Symptoms
- We begin a medicine before discharge (~72h) and aim for normotension over a matter of weeks
  - Choose thiazides and ACEI first

Case 4

- A 73 year-old woman with HTN comes to the ED after a 5 minute episode of right arm weakness that has since resolved.
- Exam is normal except blood pressure is elevated at 176/97

Other than TIA, what is the most common neurologic diagnosis here?

A. Conversion disorder
B. Migraine
C. Focal Seizure
D. UTI
E. Cervical spine lesion
Differential for Transient Focal Neurologic Deficit
- The Big Three
  - 1. Stroke/TIA
  - 2. Seizure
  - 3. Complicated Migraine

TIA versus Stroke
- Up to 30-50% of TIA have infarct on MRI
- Conceptually the same disorder
  - Same workup, same treatment
- Pendulum swing
  - Pre-2001: Much more aggressive with stroke
  - 2002-2007: TIA and stroke equally aggressive
  - 2008-present: A more aggressive approach with TIA outside of the acute treatment window

Risk of Future Stroke with TIA:
ABCD² Score
- 7-day risk overall 8.6-10.5 percent
- Age
  - ≥60 = 1 point
- Blood Pressure
  - SBP>140 or DBP>90 = 1 point
- Clinical Features
  - Unilateral weakness = 2 points
  - Speech disturbance without weakness = 1 point
- Duration
  - ≥60 minutes = 2 points
  - 10-59 minutes = 1 point
- Diabetes = 1 point

Aggressive Therapy for TIA
- 1. SOS-TIA trial
  - 1085 patients with TIA admitted to a 24-hour center
  - All treated with standard therapy
    - 74 percent discharged on same day, stroke risk reduced 80 percent from ABCD² prediction
- 2. EXPRESS study
  - 80 percent reduction in risk with urgent TIA clinic visit versus usual primary care visit in 1278 patients

When to Fix the Carotid?

- NASCET in early 1990s
  - Benefit of endarterectomy in patients with symptoms ipsilateral to 70-99% stenosis
  - Comparison: best medical management at the time
  - 50-69% symptomatic stenosis revascularization has limited benefit, especially in women
- In stroke management don’t miss carotid disease or atrial fibrillation

How to Fix the Carotid?

- Stenting vs. CEA: CREST Trial
- 4-year study of 1321 symptomatic and 1181 asymptomatic patients randomized to CEA vs. carotid stenting
- Combined endpoint of stroke, MI, death not significantly different
  - More strokes in first 90 days in stenting group, more MIs in surgical group
  - After 90 days, similar endpoints


Case 5

- A 54 year-old man with a history of HTN comes to your office concerned as his mother just died after an ischemic stroke. He wants to know what primary preventative interventions can reduce his chances of having a similar event.
Primary Prevention Guidelines

- Risk estimation schemes
- Treat vascular risk factors and encourage physical activity
- Anticoagulants for afib
  - CHA2DS2-VASc score
    - $\geq 2$= anticoagulate
    - $1$= consider anticoagulation


Asymptomatic Carotid Stenosis

- Some benefit for endarterectomy in asymptomatic stenosis
  - $>60\%$ or $>80\%$ cut-offs
  - Must have a very low perioperative risk of stroke and death to realize benefit (3%)
- Data much less convincing than symptomatic trials (CREST2 underway)
- Do not screen low risk patients (and probably shouldn’t screen anyone)

Antiplatelets to prevent stroke?

- Consider low-dose ASA in specific populations based on risk stratification schemes
  - 1. 10-year risk $> 10\%$
  - 2. Women (esp with DM)
  - 3. Chronic kidney disease (but not stage 4 or 5)
- In all cases, since data marginal, balance risk of hemorrhage
Dermatology in Primary Care:
Recognition and treatment of common disorders of the skin

Kanade Shinkai, MD PhD
Associate Professor of Clinical Dermatology
University of California, San Francisco

Disclosures

I have no conflicts of interest to disclose.

I may discuss off-label use of treatments for cutaneous disease.

A preview

• Fictional patient
• Series of dermatology visits
• Numerous concerns
  • Common skin infections
  • Acne
  • Drug eruptions
  • Skin cancer

Classic skin infections
Chronic atopic dermatitis with acute flare

Best first test to be performed in clinic:
1. Bacterial culture
2. Fungal culture
3. Viral direct fluorescence antibody (DFA)
4. Skin biopsy
5. KOH test

Eczema herpeticum

Best first test to be performed in clinic:
1. Bacterial culture
2. Fungal culture
3. Viral direct fluorescence antibody (DFA)
4. Skin biopsy
5. KOH test
Eczema herpeticum

Itchy rash, not improving with topical steroids

Rash not responding to topical steroids

Best first test to be performed in clinic:

1. Bacterial culture
2. Viral culture
3. Viral direct fluorescence antibody (DFA)
4. Skin biopsy
5. KOH test
Best first test to be performed in clinic:

1. Bacterial culture
2. Viral culture
3. Viral direct fluorescence antibody (DFA)
4. Skin biopsy
5. KOH test

Tinea corporis

- *Trichophyton rubrum*
- *Trichophyton mentagrophytes*
- *Microsporum canis* (inflammatory)
- *Microsporum audouinii*

Diagnosis:

- KOH Morphology on mold cultures (low yield)
- Lactophenol plates (higher yield)
- Skin biopsy (PAS-D)
Most common cause of “football” shaped vesiculopustules:
1. Herpes simplex virus
2. Erythema multiforme
3. Coxsackie A16
4. Varicella zoster virus
5. Chilblains lupus

Most common cause of “football” shaped vesiculopustules:
1. Herpes simplex virus
2. Erythema multiforme
3. Coxsackie A16 – Hand, foot, mouth disease
4. Varicella zoster virus
5. Chilblains lupus

Itchy rash: is my eczema flaring?
Scabies: Distribution of involvement

Suggested scabies treatment (for non-crusted)

- Permethrin 5% cream: from neck down for 8-14 hour
  - 95% effective after one dose
  - Repeat weekly x 2 weeks

- Pregnant patients: precipitate 6% sulfur in vaseline
  - Repeat daily for 3 days

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Week 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permethrin</td>
<td>Permethrin</td>
</tr>
</tbody>
</table>

Powdery sand stuck on skin by egg white” = crusted scabies

Crusted Scabies

Who:
- Immunosuppression, AIDS, Down’s
- Neurologic disease + immunosuppression
- May be non-pruritic
- Highly Contagious!!!
Suggested crusted scabies treatment

• Permethrin 5% cream: from neck down for 8-14 hour
  – 95% effective after one dose
  – Repeat weekly x 3 weeks (may need BIW or TIW)

• Ivermectin
  – 200 µg/kg orally x 2 doses, two weeks apart
  – 70% effective after one dose
  – 95% effective when used in two doses

<table>
<thead>
<tr>
<th>Permethrin</th>
<th>Permethrin</th>
<th>Permethrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivermectin</td>
<td>Ivermectin</td>
<td></td>
</tr>
</tbody>
</table>

Week 1 | Week 2 | Week 3

Next clinic visit:
The red leg

D/dx of the red leg?

• erysipelas
• cellulitis
• DVT
• vasculitis
• pyomyositis
• necrotizing fasciitis
• asthrotic dermatitis
• venous stasis dermatitis
• contact dermatitis

Red Leg: Speed rounds
No fever, no leukocytosis, bilateral itchy red legs

Stasis dermatitis
Key features:
- bilateral erythema, edema (L>R)
- varicose veins
- brawny (golden) hyperpigmentation
- no WBC, LAD, lymphangitis

Rx: compression, topical steroids

Fever, leukocytosis, red leg

Cellulitis
- Unilateral
- GAS, Staph aureus
- Rapid spread
- Toxic-appearing patient
- WBC up, LAD, streaking
Fever, leukocytosis, red leg

Erysipelas

- Superficial cellulitis (leg, face)
- Strep (GAS > GBS)
- F>M
- Involves lymphatics
- Clue: raised, shiny plaques

Fever, leukocytosis, minimally “red” leg not responding to antibiotics
Pyomyositis

- bacterial infection of muscle
  - S. aureus (77%), strep (12%)
- risk factors:
  - trauma
  - travel (tropics)
  - immunocompromised
- Dx: MRI
- Rx: surgical drainage

Necrotizing fasciitis

- Strep/staph infection of fascia
- post-surgical
- 20% mortality
- pain out of proportion to exam
- rapid spread (minutes to hours)
- Dx: MRI
- Rx: surgical debridement
  IV antibiotics

No fever, no leukocytosis, but a red leg
history of topical neomycin for “rash”
Contact dermatitis

- clue: red, angry, weeping, itch>pain
- patient looks well
- history is key
- neomycin is top contact allergen
- also: poison oak (rhus)
  topical diphenhydramine

Red leg: Pearls

- Not all red legs are cellulitis
- Bilateral cellulitis is rare. Reconsider diagnosis
- Many treatments for the “red leg” are exclusive

Common skin disorders & Drug eruptions

Acne “emergency”
**Acne pearls for adult female patients**

- Many adult females fail standard acne therapy
  - 82% fail multiple systemic antibiotics
  - 1/3 fail systemic isotretinoin
  - consider OCP (any) + spironolactone (50-200mg)
  - no K+ monitoring required for healthy patient

- Systemic antibiotics (short-term use only)
  - indicated for nodulocystic acne, truncal acne
  - may require 3 months for truncal lesions
  - works faster than hormonal therapy (2-3 weeks)

**10 days later, your acne patient develops an itchy generalized maculopapular rash**

- medications: vitamins, doxycycline (for acne)
- no recent travel, food exposures, sick contacts
- vaccinations up to date
- ROS: no URI, GI symptoms

**Morbilliform drug eruption**

- common
- erythematous macules, papules (can be confluent)
- pruritus
- no systemic symptoms
- begins in 1st or 2nd week
- treatment:
  - D/C med if severe
  - symptomatic treatment: hydroxyzine, topical steroids
When do the symptoms subside?
Up to 1 week

Drug eruptions:
when to worry

<table>
<thead>
<tr>
<th>Minimal systemic symptoms</th>
<th>Systemic involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbilliform drug eruption</td>
<td>Simple</td>
</tr>
<tr>
<td>DRESS</td>
<td></td>
</tr>
<tr>
<td>AGEP</td>
<td></td>
</tr>
<tr>
<td>Stevens-Johnson (SJS)</td>
<td></td>
</tr>
<tr>
<td>Toxic epidermal necrolysis (TEN)</td>
<td></td>
</tr>
</tbody>
</table>

Drug eruptions:
timing of onset can be helpful

<table>
<thead>
<tr>
<th>Minimal systemic symptoms</th>
<th>Systemic involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbilliform drug eruption</td>
<td>Simple</td>
</tr>
<tr>
<td>DRESS</td>
<td></td>
</tr>
<tr>
<td>AGEP</td>
<td></td>
</tr>
<tr>
<td>Stevens-Johnson (SJS)</td>
<td></td>
</tr>
<tr>
<td>Toxic epidermal necrolysis (TEN)</td>
<td></td>
</tr>
</tbody>
</table>

Signs of a serious drug eruption:

- Mucosal involvement (i.e., oral ulcerations)
- Erythroderma
- Skin pain
- Target lesions
- Bullous lesions
- Denudation (skin falling off in sheets)
- Pustules
- Facial swelling, anasarca
- Fever
- Internal organ involvement: liver, kidney > lung, cardiac

Potentially life threatening
Require systemic immunosuppression
Target lesions: Stevens Johnson Syndrome (SJS)

Mucosal involvement: SJS/ TEN

Bullous lesions, denudation, pain: TEN

Facial swelling: drug-induced hypersensitivity syndrome or DRESS
Also: eosinophilia, transaminitis, renal failure
Widespread pustules: acute generalized exanthematous pustulosis (AGEP)
Also: eosinophilia, renal failure

Drug eruption pearls
Look for cutaneous signs of a potentially-fatal drug eruption
Consider ordering labs if you are not sure

<table>
<thead>
<tr>
<th>Lab order</th>
<th>What you are looking for</th>
<th>Drug eruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential</td>
<td>Eosinophilia</td>
<td>Any drug hypersensitivity (may be slightly increased in simple drug eruption)</td>
</tr>
<tr>
<td>ALT, AST</td>
<td>Transaminits</td>
<td>Drug-induced hypersensitivity syndrome</td>
</tr>
<tr>
<td>BUN, Cr</td>
<td>Acute renal failure</td>
<td>Drug-induced hypersensitivity syndrome, AGEP</td>
</tr>
</tbody>
</table>

“Spots,” skin cancers, melanoma

Patient returns with a changing mole
Melanoma

A = asymmetry
B = irregular border
C = color
D = diameter >6mm
E = evolution

Melanoma: initial evaluation

• Prognosis is DEPENDENT on the depth of lesion (Breslow’s depth)
  – < 1mm thickness is low risk
  – > 1mm consider sentinel lymph node biopsy

• If melanoma is on the differential, complete excision or full thickness incisional biopsy is indicated

D/dx of a pigmented lesion?

Mole/ nevus
Seborrheic keratoses
- benign keratinocytic papules
- trunk, extremities > face
- do not progress to malignancy
- stuck-on tan, ovoid papule/plaque
- sometimes symptomatic

Solar lentigo/lentigines
- Pigmented, flat, even color
- Irregular borders
- Sun exposed areas

Cherry angioma (d/dx: Spitz nevus, melanoma)
- Multiple, 1-2 mm in size
- Age 30+
Actinic purpura, actinic keratoses

Non-melanoma skin cancer

What about this new skin lesion?

Basal cell carcinoma

- pearly papule or plaque
  - central ulceration
  - telangiectasia

- slow growing

- invade locally

- Rx: surgical excision
curettage
superficial -> topical
BCC can be pigmented

Squamous cell carcinoma
- scaly erythematous plaque to nodule
- sun exposed area
- potential to metastasize
- Rx: surgical excision IL 5-FU, MTX in situ -> topical

SCC on sun-damaged skin

Keratoacanthoma: self-resolving SCC

Sun-damaged skin = worry
What is the recommended frequency of skin cancer screening?

- USPTF: 2015 update
  - recommended only for patients with known history of melanoma, NMSC
  - no routine screening (including self-exams)
  - biopsy in 4.4% screened patients
  - 1 in 28 biopsies = melanoma

- SCREEN study (Germany):
  - 48% reduction in melanoma-related death
  - NNT: 100,000 screening to prevent 1 death

Prevention?
Let’s talk about photoprotection

Ultraviolet radiation

UVA: 320-400nm
Photoaging, melanoma
Not blocked by glass, clouds, ozone

UVB: 290-320nm
Sunburn, skin cancer, melanoma
Blocked by clouds, ozone
Sunscreen and the UV spectrum

- Octinoxate
- Octocrylene
- Octisalate
- Oxybenzone
- Titanium Dioxide (Ti)
- Zinc Oxide (Zn)
- Avobenzone

(μm) 220 240 260 280 300 320 340 360 380 400

- UVC
- UVB
- UVA 1
- UVA 2

Sunscreen versus sunblock
- SPF
- Broad-spectrum
- Nano-technology
- Vitamin D

Photoprotection

Pearls for approach to the skin

- Using skin morphology to make the diagnosis
- Keep differential broad: infection & non-infectious causes
- If it scales, scrape it (part I): tinea corporis
- If it scales, scrape it (part II): scabies
- Differential diagnosis of the red leg
- Important differential of drug eruption, changing skin lesions

Kanade Shinkai (kanade.shinkai@ucsf.edu)
NEW DRUGS FOR DIABETES
Which Ones, For Which Patients?

Robert B. Baron MD MS
Professor and Associate Dean
UCSF School of Medicine
baron@medicine.ucsf.edu

Presentation Outline

- Updates in prevention of complications (other than glycemic control)
- Controversies in glycemic control
- Updates/controversies with diabetes medications

Screening for Diabetes 2017

- BMI ≥25 (or ≥23 in Asian Americans) plus other risk factors
  - Inactivity
  - First degree relative
  - High-risk ethnicity
  - Gestational DM
  - Low HDL or high TG
  - PCOS
  - Acanthosis nigricans
  - Hx CVD
  - HTN
- Age 45
- Repeat Q3 years

Disclosure

No relevant financial relationships
USPSTF Screening for Diabetes 2015

- Screen as part of cardiovascular risk assessment in adults 40-70 who are overweight or obese

Diagnosis of Diabetes 2017

- A1C ≥ 6.5%
- FPG ≥ 126 mg/dl (7.0 mmol/L)
- 2-h plasma glucose ≥ 200 during OGTT
- Symptoms and random plasma glucose ≥200 mg/dl (11.1 mmol/L)
- Need two separate measurements

Diagnosis of Pre-Diabetes 2017

- A1C 5.7 – 6.4%
- FPG 100 - 125 mg/dl (5.6mmol/L - 6.9 mmol/L)
- 2-h plasma glucose 140 mg/dl – 199 mg/dl during OGTT (7.8mmol/L – 11.0 mmol/L)

2017 Practice Guidelines: ASA

- Use in all patients with DM and CVD
- ASA: For primary prevention - only use in those at increased CV risk (10 year risk >10%).
  - Typically men over 50, women over 60 with other risk factors.
2017 Practice Guidelines: HTN and Tobacco

- BP: Goal < 140 and <90
  - But not <130 (no evidence) and not <70 (higher mortality)
  - Still prefer ACEI or ARB

- Don’t forget tobacco.
  - Recommend against e-cigarettes

2017 Practice Guidelines: Lipids

- Mostly consistent with ACC/AHA
  - CVD: High intensity statin
  - 40-75: moderate or high intensity statin

- Differences with ACC/AHA
  - <40 with other risks: consider statin
  - >75: consider statin

2017 Practice Guidelines: Bariatric Surgery

- Bariatric (Metabolic) Surgery should be recommended for adults with BMI > 35 and type 2 DM, especially if diabetes and comorbidities are difficult to control with lifestyle and meds

- Bariatric (Metabolic) Surgery should be considered for adults with BMI < 35 and type 2 DM, especially if diabetes and comorbidities are difficult to control with lifestyle and meds

Case 1

74 year old woman with type 2 diabetes, hypertension, coronary heart disease (s/p MI in 2010), GERD, and osteoarthritis.

Meds: Metformin, glipizide, aspirin, lisinopril, metoprolol, atorvastatin, omeprazole, tylenol, topical diclofenac

Exam: BP 132/80, BMI 29 kg/m²
  - Normal exam
Case 1
Her glycemic goal should be:

1. HbA1c <6.5%
2. HbA1c <7.0%
3. HbA1c <7.5%
4. HbA1c <8.0%
5. HbA1c <9.0%

Glycemic Control Update

- 3 important newer trials
  - ADVANCE
  - ACCORD
  - VA Diabetes Trial

ACCORD Trial

- NIH RCT in DM 2, 10,251 patients, known CVD or risk factors, mean A1c 8.1%
  - Intensive vs. standard BP (120 v. 140)
  - Lipid control (statins v. statins + fibrates)
  - Normalization v. standard BS control (A1c 6 v. 7-7.9)
  - Outcomes: CV events. Also microvascular events, quality of life, others

ACCORD Trial

<table>
<thead>
<tr>
<th></th>
<th>Intensive n=5,128</th>
<th>Standard n=5,123</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c achieved</td>
<td>6.5%</td>
<td>7.5%</td>
<td>-</td>
</tr>
<tr>
<td>1* outcome</td>
<td>352</td>
<td>371</td>
<td>0.90 (0.78-1.04)</td>
</tr>
<tr>
<td>Total mortality</td>
<td>5.0%</td>
<td>3.1%</td>
<td>1.22 (1.01-1.46)</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>2.6%</td>
<td>1.8%</td>
<td>1.35 (1.04-1.76)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>10.5%</td>
<td>3.5%</td>
<td>-</td>
</tr>
<tr>
<td>Wt. gain&gt;10 kg</td>
<td>27.8%</td>
<td>14.1%</td>
<td>-</td>
</tr>
</tbody>
</table>
**ACCORD Trial**

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>203</td>
<td>257</td>
</tr>
<tr>
<td>11/1000/y</td>
<td>11/1000/y</td>
<td>14/1000/y</td>
</tr>
<tr>
<td>Number Needed to Harm:</td>
<td>333</td>
<td></td>
</tr>
</tbody>
</table>

February 2008 (after 3.5 years): NIH stops this arm of study

**Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>↓</td>
<td>←</td>
<td>↓</td>
</tr>
<tr>
<td>DCCT / EDIC*</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>ACCORD</td>
<td>↓</td>
<td>←</td>
<td>↑</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>VADT</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
</tbody>
</table>

*Initial Trial*  
*Long Term Follow-up*  
*in T1DM*

**Glycemic Control Summary**

- No consistent evidence that tight glycemic control reduces risk of CVD in DM 2
- Possible subgroups with benefit: 
  - shorter diabetes duration, no CVD
- Strong evidence of decrease in microvascular disease outcomes with more intensive glucose control
- More hypoglycemia and weight gain with more intensive regimens

**2017 ADA Practice Guidelines: Glucose Control**

- Goal A1C ≤7 for most
- Goal A1C ≤6.5 for some: short duration, long life expectancy, and no CVD
- Goal less stringent (<8) for history of hypoglycemia, limited life expectancy, advanced micro or macrovascular complications, extensive comorbid conditions, and longstanding DM in whom the goal is difficult to achieve.
Glycemic Control in Older Adults

- For majority of adults older than 65, the harms of HgA1c <7.5 or >9 are likely to outweigh the benefits.

- Optimal targets depend on patient factors, meds, life expectancy, and patient preferences.

- For example: if only need metformin, lower target may be preferred; if need insulin or finger sticks a higher target may be preferred.

2016 AACE Practice Guidelines: Glucose Control

- A1C ≤6.5 is optimal if it can be achieved in a safe and affordable manner.

- Higher targets (>6.5) may be appropriate for certain individuals (patients with concurrent serious illness and risk of hypoglycemia) and may change over time

Case 1

Her glycemic goal should be:

1. HbA1c <6.5%
2. HbA1c <7.0%
3. HbA1c <7.5%
4. HbA1c <8.0%
5. HbA1c <9.0%
Case 2: 48 yo woman with DM, BMI 33, on diet and exercise and max dose metformin. HbA1C is now 8.5. Your next best step is:

1. **Continue current therapy**

2. Begin a sulfonylurea

3. Begin pioglitizone

4. Begin NPH insulin or long-acting insulin analogue

5. Begin exenatide (Byetta™), liraglutide (Victoza™), sitagliptin (Januvia™), saxagliptin (Onglyza™)

6. Begin canagliflozin (Invokana™), dapagliflozin (Farxiga™), empagliflozin (Jardiance™)

---

**Metformin**

- Lowers A1C 1.5-2%
- Weight loss (0-2 kg)
- Lowers triglyceride and LDL; increases HDL
- No hypoglycemia
- No self monitoring
- Inexpensive
- Disadvantages: GI side effects, decreased B12 absorption, (very low) risk of lactic acidosis

**Thiazolidinediones (TZD)**

- Lowers A1C 0.4-1.5%
- No hypoglycemia when used alone
- Other risks: osteoporosis, bladder cancer with pioglitazone, weight gain edema
- FDA lifted restrictions on rosiglitazone in November 2013
- No hypoglycemia
- No self monitoring
- Preference for pioglitazone
Oral Agent “Failure”
Why does this occur?

- Changing HbA1c goals
- Compliance, side effects
- Wrong diagnosis (LADA—latent autoimmune diabetes in adults 10%)
- Stress, diabetogenic medications
- Postprandial hyperglycemia
- Natural progression of the disease

Natural History of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Years of Diabetes</th>
<th>Glucose (mg/dL)</th>
<th>Relative Function (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>150</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>200</td>
<td>150</td>
</tr>
<tr>
<td>20</td>
<td>250</td>
<td>200</td>
</tr>
<tr>
<td>25</td>
<td>300</td>
<td>250</td>
</tr>
<tr>
<td>30</td>
<td>350</td>
<td>300</td>
</tr>
</tbody>
</table>

*IFG = impaired fasting glucose

Insulin

Introduction of insulin
- Bedtime
- Intermediate/Long-acting insulins
  - NPH, glargine, levemir
  - 10 units
- Self-monitoring of blood glucose
  (hypoglycemia education)
When to go to > 1 shot per day
- HgA1c >7
- Glucose in AM at goal but glucose before dinner >140

Options
- Add premeal lispro/aspart
- Add bid premixed insulin – 70/30, 75/25

Questions
- Continue metformin
- ? Sulfonylurea, ? Thiazolidinedione (mostly not)

Function of Insulin in Regimens
- Basal insulin
- Meal coverage (carbohydrates)
- Correction of high blood sugar

INCRETINS
Gut factors that promote insulin secretion in response to nutrients
Major incretins: GLP-1, CCK, GIP

Oral Glucose Promotes More Insulin Release than IV Glucose - Indicating a Role for Incretins
Incretin Drugs

**GLP Agonists**
- Exenatide (2005/2012)
- Liraglutide (2010)
- Dulaglutide (2014)
- Albiglutide (2014)
- Taspoglutide
- Lixisenatide
- Semaglutide

**DPP IV Inhibitors**
- Sitagliptin (2006)
- Saxagliptin (2009)
- Alogliptin (2013)
- Linagliptin (2011)
- Vildagliptin
- Dutosipiitin
- Metgliptin
- Gemigliptin

A1C (%) Effect (change from baseline)

<table>
<thead>
<tr>
<th></th>
<th>Placebo BID</th>
<th>5 mcg exenatide BID</th>
<th>10 mcg exenatide BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET</td>
<td>0.1</td>
<td>-0.4</td>
<td>-0.8</td>
</tr>
<tr>
<td>SFU</td>
<td>0.1</td>
<td>-0.5</td>
<td>-0.9</td>
</tr>
<tr>
<td>MET+SFU</td>
<td>0.2</td>
<td>-0.6</td>
<td>-0.8</td>
</tr>
</tbody>
</table>

Changes in A1C from baseline vs placebo statistically significant

Weight (change from baseline) & Hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>Placebo BID</th>
<th>5 mcg exenatide BID</th>
<th>10 mcg exenatide BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>-1.4</td>
<td>-3.1</td>
<td>-4.2</td>
</tr>
<tr>
<td>Hypoglycemia (%)</td>
<td>5.3</td>
<td>4.5</td>
<td>5.3</td>
</tr>
<tr>
<td>SFU</td>
<td>3.3</td>
<td>14.4</td>
<td>35.7</td>
</tr>
<tr>
<td>MET + SFU</td>
<td>1.26</td>
<td>19.2</td>
<td>27.8</td>
</tr>
</tbody>
</table>

Open-label extension study to 90 weeks: persistence in weight loss and ↓A1C
**Side Effects**

GI
- Nausea (44% vs 18% with placebo); incidence lessens over time; 3% dropout rate due to nausea
- Vomiting (13% vs 4%)
- Diarrhea (13% vs 6%)

Headache (9% vs 6%)

Hypoglycemia (see previous slide)

---

**Improvements in HbA1C With Initial Co-administration of Sitagliptin and Metformin**

![Graph showing improvements in HbA1C](image)

Mean Baseline HbA1C = 8.8%

N=1091

- Placebo
- Sitagliptin 100 mg QD
- Metformin 500 mg BID
- Metformin 1000 mg BID
- Sitagliptin 50 mg BID + Metformin 500 mg BID
- Sitagliptin 50 mg BID + Metformin 1000 mg BID

*Placebo-subtracted LS mean change from baseline at Week 24. Metformin: Microalbuminuria.

---

**Sitagliptin – Adverse Reactions**

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
<th>Sitagliptin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy n = 443</td>
<td>n = 443</td>
<td>n = 363</td>
</tr>
<tr>
<td>Nasopharyngitis 23 (5.2)</td>
<td>12 (3.3)</td>
<td></td>
</tr>
<tr>
<td>+ pioglitazone n = 175</td>
<td>n = 175</td>
<td></td>
</tr>
<tr>
<td>Upper resp. infection 11 (6.3)</td>
<td>6 (3.4)</td>
<td></td>
</tr>
</tbody>
</table>

Small increase in neutrophil count

No nausea or vomiting

No weight loss

---

**Two Newer Studies of DPP-4 Meds**

- Saxagliptin not inferior (nor superior) to placebo for CV outcomes.
  - But statistically significant increase in CHF admissions
  - A1C 0.2% lower

- Sitagliptin not inferior (nor superior) to placebo for CV outcomes.
  - No increase in CHF
  - A1C 0.3% lower
CV outcomes with Liraglutide
- RCT, 9340 patients, high CV risk, 3.8 years
  - A1C 0.2% lower
- Fewer events with liraglutide: 13.0% vs. 14.9%
- Few deaths with liraglutide: 8.2% vs. 9.6%

SGLT2 Inhibitors
Sodium-glucose cotransporter 2 Inhibitors
- Inhibit glucose reabsorption in renal proximal tubule (Canagliflozin, Dapagliflozin, Empagliflozin)
- Potential advantages
  - Weight loss (2.5-4kg), low risk of hypoglycemia, reduced BP, lowers A1C about 1%
- Potential disadvantages
  - Polyuria, electrolyte disorders, UTI, fungal genital infections, syncope, increased Cr, expensive

Empagliflozin, CV Outcomes, and Mortality
- RCT 7020 patients, high risk CV disease, 3.1 years
- Minimal changes in A1C (0.24% lower)
- Reduced combined CV outcome (10.5% vs. 12.1%) and reduced CV (3.7% vs. 5.9%) and all cause mortality (5.7% vs. 8.3%)
  - No difference in stroke or MI
  - No difference when secondary outcomes (unstable angina) included
  - Increased genital infections

Natural History of Type 2 Diabetes
Pharmacological Therapy for Type 2 Diabetes

- Metformin is the preferred agent

- In patients with new DM2, marked symptoms, or marked BS or A1C, consider initiating insulin (with or without other agents).

- If monotherapy not to goal, add second oral agent, GLP-1 agonist, or basal insulin

---

### A1C and Cost/month

<table>
<thead>
<tr>
<th>Drug</th>
<th>A1C</th>
<th>Cost/month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1-2%</td>
<td>$4</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>1-2%</td>
<td>$5</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>0.5-1.5%</td>
<td>$20</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>0.5-0.8%</td>
<td>$320</td>
</tr>
<tr>
<td>Exenatide</td>
<td>0.5-1.5%</td>
<td>$450</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>0.5-1.5%</td>
<td>$330</td>
</tr>
<tr>
<td>Acarbose</td>
<td>0.5-0.8%</td>
<td>$30</td>
</tr>
<tr>
<td>Test strips</td>
<td>0.4% (?)</td>
<td>$20-$60</td>
</tr>
<tr>
<td>Glargine 45 U</td>
<td></td>
<td>$150</td>
</tr>
<tr>
<td>YMCA</td>
<td></td>
<td>$65</td>
</tr>
</tbody>
</table>
Case 2: 48 yo woman with DM, BMI 33, on diet and exercise and max dose metformin. HbA1C is now 8.5. Your next best step is:

1. **Continue current therapy**
2. Begin a sulfonylurea
3. Begin pioglitizone
4. Begin NPH insulin or long-acting insulin analogue
5. Begin exenatide (Byetta™), liraglutide (Victoza™), sitagliptin (Januvia™), saxagliptin (Onglyza™)
6. Begin canagliflozin (Invokana™), dapagliflozin (Farxiga™), empagliflozin (Jardiance™)

**Conclusions**

- Tight glycemic control not effective in lowering total mortality or CV mortality (but is effective at preventing microvascular complications)
- Many newer diabetes agents available, all with some side effects and higher costs...few with hard outcome data. (But hard outcome data coming...)

**Conclusions**

- Glucose control may be more important early in diabetes
- Good BP, lipid control, smoking cessation, and aspirin use is important throughout the course of diabetes

**Conclusions**

The best way to treat DM in the long term...

...is to not develop it in the first place.
Current and Emerging Strategies for Osteoporosis

Douglas C. Bauer, MD
Professor of Medicine and Epidemiology & Biostatistics
University of California, San Francisco

What's New in Osteoporosis

- The Big Picture: a looming “crisis”?
- Risk identification and stratification
- Under recognition and poor compliance
- New potential concerns about treatments
- When to start and stop drug therapy


A Clear Example of a Therapeutic Gap: Post Hip Fractures Treatment

- Study of post hip fracture treatments in the US
Under Recognition and Inadequate Treatment of Osteoporosis

- Among women with fracture or BMD<-2.5 about a third are evaluated and treated!
- Ask about fracture history, note vertebral fractures, use chart reminders for DXA
- Priority: identify all hip fractures in your practice and treat if appropriate!


A Quick Review: Risk Factors for Fracture

- The Big Three: older age, postmenopausal female, and Caucasian/Asian
- Other important risk factors
  - Family history of fracture (hip)
  - Low body weight (<127 in women)
  - Smoker, 3 or more drinks/d
  - Certain drugs (steroids, AIs) and diseases (RA, sprue)
  - Previous fracture (especially hip or spine)
- Bone mineral density (BMD) strongly predicts fracture: 2-3 fold increase per SD

A Quick Review: Interpretation of DXA Bone Mineral Density

- Absolute mineral (calcium) content using x-rays
- Relative to a healthy reference population
- T-score is the number of standard deviations above or below average 30 year old female
  - T greater than -1.0 = “normal”
  - T between -1.0 and -2.5 = “low bone mass” (previously “osteopenia”)
  - T less than -2.5 = “osteoporosis”
- Z-score is number of SDs above or below others of the same age (use in those <50)

BMD and Risk Factors

Cummings et al., NEJM 332(12):767-773, 1995
Calculating Absolute Fracture Risk: FRAX
http://www.shef.ac.uk/FRAX/tool.jsp

Who Should Be Tested and Treated?

- **NOF and ACP Practice Guidelines**
  - Preventive measures for everyone: adequate calcium/vitamin D, exercise, avoid bad habits
  - Hip BMD: women >65 (or >50 with risk factors), men >70, anyone >50 after fracture
  - Consider vertebral fracture assessment >70. Use DXA?
  - US pharmacologic treatment thresholds:
    - Anyone with hip or spine fracture
    - T-score (any site) < -2.5
    - "Low bone mass" and FRAX 10 year hip fracture risk >3% or OP-related fracture risk >20%*

*Not specified in 2017 ACP Treatment Guidelines

Repeat Screening: Risk at Age 65 of Developing Osteoporosis Over Next 15 Years

<table>
<thead>
<tr>
<th>BMD Result Femoral Neck</th>
<th>15 Yr Risk for Osteoporosis</th>
<th>Time to 10% BMD &lt; -2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal &gt; -1.0</td>
<td>0.8%</td>
<td>16.8 y</td>
</tr>
<tr>
<td>T = -1.01 to -1.49</td>
<td>4.6%</td>
<td>17.3 y</td>
</tr>
<tr>
<td>T = -1.50 to -1.99</td>
<td>20.9%</td>
<td>4.7 y</td>
</tr>
<tr>
<td>T = -2.00 to -2.49</td>
<td>62.3%</td>
<td>1.1 y</td>
</tr>
</tbody>
</table>

Gourlay, NEJM 2012

Implications for Follow-up Testing

- BMD results higher than –1.5 at age 65 can safely defer repeat screening until age 80
- BMD between –1.5 and –2 at age 65 merits repeat screening BMD at 5 years
- BMD results –2 to –2.5 merits rescreening at 2 years
- Caveat: applies to untreated US white women >65 at average risk

Gourlay, NEJM 2012
**Medical Work-up**

- Very little data, lots of opinions
- A reasonable start:
  - Vitamin D (25-OH, not 1,25-OH)
  - Serum calcium, Cr, TSH
- Additional tests that may be helpful:
  - Sprue serology, SPEP, UEP
- Unlikely to be helpful: PTH, urine Ca

*Jamal et al, Osteo Inter, 2005*

**What Else Can Be Done To Prevent Osteoporosis?**

**Non-pharmacologic Interventions**

- Little new data
- Smoking cessation, avoid alcohol abuse
- Physical activity: modest transient effect on BMD but reduced fracture risk
- Fall prevention: targeted PT, home eval.
- Conflicting data on hip protector pads (compliance is big issue)

**Calcium and Vitamin D**

- Chapuy, 1992
  - Elderly women in long-term care
  - 30% decrease in hip fracture
- Porthouse, 2005:
  - Women >70 with 1+ risk factor
  - No benefit on hip, nonspine (RR=1.01, CI: 0.71, 1.43)
- USPSTF meta-analysis: 11% fewer fractures (together not alone)
**Can Your Calcium Pills Kill You?**

- Meta-analysis of 15 calcium RCTs: CHD increased 30%
  - Not 1st endpoint, trials with vitamin D (WHI) excluded
- Add calcium+D trials? Results similar but only after excluding those taking personal calcium supplements in WHI. No harm if everyone included...
- Little supporting mechanistic data
  - No effect on surrogates (coronary calcium, IMT)
  - Dietary calcium not implicated
- ASBMR Task Force: “evidence is insufficient to conclude that calcium supplements cause adverse CV events...”


**How Much Is Enough? The IOM Report**

- Calcium (elemental)
  - 1200 mg/d for women >50 and men >70; no more than 2500 mg/d
  - Dietary sources preferred (estimate intake using 300 mg/d plus 300-400 per dairy serving)
- Vitamin D (non-skeletal benefits not established)
  - 600-800 IU/d (maximum 4,000/d)
  - Recommends serum levels 20-50 ng/ml

Institute of Medicine Report, 2010

**Calcium and the US Preventive Task Force? Widely Misunderstood...**

- “Insufficient evidence to assess risks/benefits for daily routine supplementation with calcium >1000 mg/d and vitamin D3 >400 IU”
- “Recommend against routine supplements with calcium 1000 mg or less and vitamin D 400 IU or less...”
  - Not applicable if inadequate intake!
- Vitamin D supplements effective for fall prevention ≥ 65 yr at high risk

Moyer VA, USPTF, Ann Intern Med 2013; 691-6

**Bisphosphonates**

- Four approved generic agents in US: alendronate, risedronate, ibandronate, and IV zoledronic acid
  - No head-to-head fracture studies
- What we know: fracture risk reduced 30-50% if
  - Existing vertebral fracture OR
  - Low hip BMD (T-score < -2.5)
- What about those with low bone mass (“osteopenia”)?
  - Multiple risk factors resulting in increased absolute risk?
Effect of Alendronate on Non-spine Fracture Depends on Baseline BMD

<table>
<thead>
<tr>
<th>Baseline hip BMD</th>
<th>Relative Hazard (± 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T -1.5 – -2.0</td>
<td>1.06 (0.77, 1.46)</td>
</tr>
<tr>
<td>T -2.0 – -2.5</td>
<td>0.97 (0.72, 1.29)</td>
</tr>
<tr>
<td>T &lt; -2.5</td>
<td>0.69 (0.53, 0.88)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.86 (0.73, 1.01)</td>
</tr>
</tbody>
</table>

Cummings, Jama, 1998

Risedronate HIP Study: Two Groups

Group 1
- 5445 age <80; hip BMD T-score < -3.0
- 39% reduction in hip fracture risk

Group 2
- 3886 age >80; risk factors for hip fx, no BMD
- No significant effect on hip fracture risk

McClung, NEJM, 2001

More Bad News: Compliance with Oral Osteoporosis Medications is Poor

- 50-60% persistence after one year
  - Multiple practice settings (similar to other preventive treatments)
- Reasons for non-compliance?
  - Burdensome oral administration (fasting, remain upright for 30 minutes)
  - Upset stomach and heartburn can occur
- Asking about side effects and positive re-enforcement increases compliance by 59%

Clowes, JCEM, 2004

Does Dosing Interval Matter?

- Poor quality data:
  - Daily to weekly improves compliance
  - Unclear if weekly to monthly helps
- Consider yearly dosing: zoledronic acid
  - Extremely potent IV bisphosphonate
  - Fracture reduction with 3 annual injections: hip 40%, spine 60%, non-spine 25%
  - Precautions: acute phase reaction, renal insufficiency
- Many patients are declining treatment. Why?

Black et al, NEJM, 2007
A New Side Effect of Potent Bisphosphonates

Osteonecrosis of the Jaw
- Associated with potent anti-resorptive use:
  - 94% treated with IV bisphosphonates for cancer
  - 4% of cases have OP (risk similar with oral & IV)
  - 60% caused by tooth extraction. Other risk factors unknown. Infection?
- Key points: extremely rare, >8 wks of exposed bone (not TMJ pain), early identification, conservative tx
- Dental exam recommended before high-dose Rx, but no need to stop for dental procedures

Other Things to Worry About
- Atrial fibrillation (zoledronic acid and alendronate RCTs)
  - No association in other trials
  - Likely spurious
- Esophageal cancer
  - Case series (FDA author) and two conflicting cohorts
  - Might be spurious
- Subtrochanteric fracture (with atypical features)
  - Likely real...

Woo et al; Ann Intern Med, 2006
ADA Guidelines, 2011
**Atypical Femoral Fractures (AFF)**

- Thousands of reports in long-term bisphosphonate users (and others)
- Transverse not spiral, cortical thickening, minimal trauma
- Often bilateral, prodromal pain, abn. imaging (x-ray, bone scan/MR)
- Over-suppression stress fractures?
- Other risk factors? (steroids, RA, DM, Asian...)

ASBMR Task Force, JBMR 2013

---

**Critical Unknowns About AFFs**

- Mechanism and exact relationship with BP use?
  - RR vary from 2 to over 40
  - NNTH for 3 yr of use is between 800-43,000
- Risk with shorter vs. longer use?
  - RR may increase after 5-8 years
- Risk after stopping treatment?
  - After 1 yr, AFF risk fell 70% in Sweden. Really?

Black et al NEJM, 2016 and Schilcher et al, NEJM 2011, 2014

---

**How Long to Treat with Bisphosphonates?**

- Long half-life also suggests that life-long treatment may not be necessary
- FIT Long-term Extension (FLEX) study
  - 1099 ALN-treated FIT subjects
  - Re-randomized to ALN or PBO for 5 yr.
- Horizon Extension
  - 1233 zoledronic acid-treated women
  - Re-randomized to ZOL or PBO for 3 yr.

Black et al, Jama 2006
Black et al, JBMR 2012

---

**FLEX Change in Femoral Neck BMD:**

% Change from FIT Baseline

![Graph showing change in femoral neck BMD over years (FIT and FLEX)]

- Start of FLEX
- Mean Percent Change
- Placebo = ALN (Pooled 5 mg and 10 mg groups)
P<0.001 ALN vs PBO
## Cumulative Incidence of Fractures During FLEX

<table>
<thead>
<tr>
<th></th>
<th>PBO (N = 437)</th>
<th>ALN (N = 662)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-spine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-vertebral</td>
<td>20%</td>
<td>19%</td>
<td>1.0 (0.8, 1.4)</td>
</tr>
<tr>
<td>Hip</td>
<td>3%</td>
<td>3%</td>
<td>1.1 (0.5, 2.3)</td>
</tr>
<tr>
<td>Vertebral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphometric</td>
<td>11%</td>
<td>10%</td>
<td>0.9 (0.6, 1.2)</td>
</tr>
<tr>
<td>Clinical</td>
<td>5%</td>
<td>2%</td>
<td>0.5 (0.2, 0.8)</td>
</tr>
</tbody>
</table>

### 2017 Update: Who Should Be Treated and When to Stop?

- US treatment guidelines:
  - Existing hip or vertebral fracture? Yes!
  - T-score < -2.5? Yes!
  - “Low bone mass” + FRAX score that exceeds absolute threshold? Oral BPs may not work
- Drug holiday after 3-5 yr of bisphosphonate? Maybe
  - No hip/vertebral fracture; no fracture on therapy
  - BMD T-score > -2.5 before stopping
  - How long? Monitor? Risk stratify after 3-5 yr

### Other Anti-resorptive Agents

- Some clearly less effective than bisphosphonates
  - Calcitonin (poor quality studies)
  - Raloxifene ( restricts vertebral fractures only; use for breast cancer?)
- Denosumab ( antibody to RANKL)
  - SQ q 6 mo, not cleared by kidneys, rapid off-set
  - Effective but expensive, less long-term data
  - Both ONJ and AFF reported
The Future: Anabolic Agents

- Anti-resorptives inhibit bone resorption > formation
- Anabolic agents (intermittent PTH, abaloparatide) stimulate formation > resorption
- Daily SQ PTH (1-34) or abaloparatide for 18 mo. reduces vertebral and non-spine fracture. No hip fracture data
- After anabolic use bisphosphonate
- Expensive, self-administered injections, benefit over anti-resorptives (particularly zolendronic acid) uncertain...
  - Use with severe OP, when other agents have failed?

Conclusions

- After decades of progress, fracture rates no longer declining and rates of treatment are dropping rapidly...
- Screening and appropriate treatment = fewer fractures
  - Identify those who have already have the disease!
- Bisphosphonates: treatment of choice
  - Use when spine/hip fracture or T<-2.5; >-2.5 less clear
  - Adherence counseling. Consider yearly dosing
  - Duration of therapy: 3-5 years then off for many
- Denosumab and anabolics effective but less clear when to use, and others (eg sclerostin antibody) on the way...

Thanks for Listening
Questions or Comments?
Psychiatric Dilemmas in the Primary Care Setting

Erick K. Hung, MD
Associate Professor of Clinical Psychiatry
University of California, San Francisco

No Disclosures

Objectives

- Describe approaches to the difficult patient in the primary care setting.
- Discuss common pitfalls in initiating antidepressants.
- Discuss strategies for effectively managing a patient who expresses suicide ideation.

The Difficult Patient
Difficult Patient Factors

Provider Factors

Patient Factors

Structural Factors

Contributing Factors

<table>
<thead>
<tr>
<th>Patient Factor</th>
<th>Difficulty</th>
</tr>
</thead>
</table>
| Psychiatric diagnosis | Anxiety, depression, psychosis, etc. shape patient behavior
| Personality disorders | Cluster A: eccentric, peculiar or withdrawn
| Cluster B: emotional, dramatic or inconsistent
| Cluster C: anxious or fearful |
| Somatization |
| Substance use disorders | Barrier to engaging in patient care
| May affect patient behavior |
| Nonadherence | Barrier to optimal health outcomes and care goals |
| Social support | Family may not agree with care plan |
| Communication | Language and ability can be barriers to effective patient interactions |
| Structural Factors | Culture, housing status, race, socioeconomic status, healthcare navigation, transportation, etc. |

4 Difficult Behaviors

The “Clingers”

The “Demanders”

“The Hateful Patient”

- James Groves (1978)

The “Help-Rejecters”

The “Deniers”

The “Clingers”

- Personality Traits: Dependent
- Clinician Reaction: Aversion
- Practical Strategy: Set limits

Groves (1978)
The “Demanders”

- Personality Traits: Narcissistic
- Clinician Reaction: Counter-attack
- Practical Strategy: Acknowledge demands and reframe

The “Help-Rejecters”

- Personality Traits: Histrionic
- Clinician Reaction: Despair
- Practical Strategy: Lower expectations and share doubts

The “Deniers”

- Personality Traits: Mixed
- Clinician Reaction: Despair
- Practical Strategy: Lower expectations and let things go

Common Antidepressant Pitfalls

Groves (1978)
Start at a low dose!

- Sometimes you only get one chance to make a good impression
- Consider starting an antidepressant at half the starting dose
  - sertraline 25 mg
  - fluoxetine 10 mg
  - citalopram 10 mg
  - escitalopram 2.5 mg
  - bupropion XL 150 mg

Wait for at least 8 weeks

**Likelihood to Remission**

The likelihood for full remission of a major depressive episode with treatment at four treatment levels

- Level 1: 33%
- Level 2: 50%
- Level 3: 60%
- Level 4: 70%
Clinicians and patients need to be patient for treatment response (i.e. 8-12 weeks) before trying another treatment strategy.

Patients with treatment-resistant depression can get well after multiple treatment strategies.

The odds of beating depression diminish with every additional treatment strategy needed.

Treat to remission (i.e. PHQ-9 score < 4) to minimize risk of episode relapse.

STAR-D Take Home Points

Can We Intervene?
Medical Setting within 6 Weeks of Suicide Attempt

Can We Intervene?
Medical Setting within 1 Week of Suicide Attempt

Suicide
Definitions

Suicide
Self-inflicted death with evidence that the person intended to die.

Shea (2002)
Definitions

Suicide Attempt
Self-injurious behavior with a non-fatal outcome accompanied by evidence that the person intended to die.

Aborted Suicide Attempt
Potentially self-injurious behavior with a non-fatal outcome accompanied by evidence that the person intended to die but stopped before physical damage occurred.

Suicide
Suicide Attempt
Aborted Suicide Attempt
Suicidal Ideation
Deliberate Self-Harm
Definitions

Suicidal Ideation

Thoughts of serving as the agent of one's own death. The seriousness may vary depending on the specificity of the plans and the degree of intent.

Deliberate Self-Harm

Willful self-inflicting of painful, destructive, or injurious acts without the intent to die.

Suicide Statistics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fatal</th>
<th></th>
<th>Nonfatal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All Self-Harm</td>
<td>30,622</td>
<td>100.0</td>
<td>322,991</td>
<td>100.0</td>
</tr>
<tr>
<td>Cut/Pierce</td>
<td>458</td>
<td>1.5</td>
<td>62,817</td>
<td>19.4</td>
</tr>
<tr>
<td>Fall</td>
<td>651</td>
<td>2.1</td>
<td>1,434</td>
<td>0.4</td>
</tr>
<tr>
<td>Gouged</td>
<td>-</td>
<td>-</td>
<td>3,020</td>
<td>0.9</td>
</tr>
<tr>
<td>Firearms</td>
<td>16,869</td>
<td>55.1</td>
<td>2,980</td>
<td>0.9</td>
</tr>
<tr>
<td>BB/pellet gun</td>
<td>-</td>
<td>-</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Poisoning/Overdose</td>
<td>5,191</td>
<td>17.0</td>
<td>215,814</td>
<td>66.8</td>
</tr>
<tr>
<td>Suffocation</td>
<td>6,198</td>
<td>20.2</td>
<td>2,761</td>
<td>0.9</td>
</tr>
<tr>
<td>Other, specified</td>
<td>1,109</td>
<td>3.6</td>
<td>35,099</td>
<td>10.0</td>
</tr>
<tr>
<td>Other, unspecified</td>
<td>146</td>
<td>0.5</td>
<td>2,097</td>
<td>0.6</td>
</tr>
</tbody>
</table>

National Center for Injury and Prevention and Control, U.S. 2001 Data
### Suicide Statistics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fatal No.</th>
<th>Fatal %</th>
<th>Nonfatal No.</th>
<th>Nonfatal %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Self-Harm</td>
<td>30,622</td>
<td>100.0</td>
<td>322,991</td>
<td>100.0</td>
</tr>
<tr>
<td>Cut/Pierce</td>
<td>458</td>
<td>1.5</td>
<td>62,817</td>
<td>19.4</td>
</tr>
<tr>
<td>Fall</td>
<td>651</td>
<td>2.1</td>
<td>1,434</td>
<td>0.4</td>
</tr>
<tr>
<td>Gunshot</td>
<td>-</td>
<td>-</td>
<td>3,020</td>
<td>0.9</td>
</tr>
<tr>
<td>Firearm</td>
<td>16,869</td>
<td>55.1</td>
<td>2,980</td>
<td>0.9</td>
</tr>
<tr>
<td>BB/pellet gun</td>
<td>-</td>
<td>-</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Poisoning/Overdose</td>
<td>5,191</td>
<td>17.0</td>
<td>273,814</td>
<td>86.8</td>
</tr>
<tr>
<td>Suffocation</td>
<td>6,198</td>
<td>20.2</td>
<td>2,761</td>
<td>0.9</td>
</tr>
<tr>
<td>Other, specified</td>
<td>1,109</td>
<td>3.6</td>
<td>35,059</td>
<td>10.0</td>
</tr>
<tr>
<td>Other, unspecified</td>
<td>146</td>
<td>0.5</td>
<td>2,097</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*National Center for Injury and Prevention and Control, U.S. 2001 Data*

### Estimating Risk

Estimating risk is more than just “SI”
Suicide Statistics

Annual Incidence per 100,000

<table>
<thead>
<tr>
<th>Category</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicide Completion</td>
<td>10.7</td>
</tr>
<tr>
<td>Suicide Attempts</td>
<td>260</td>
</tr>
<tr>
<td>Suicidal Ideation</td>
<td>4,000</td>
</tr>
</tbody>
</table>

National Center for Injury and Prevention and Control, U.S. 2001 Data

“The rarity of the suicidal event makes it impossible to predict behavior.”

“Although an understanding of risk factors allows the clinician to recognize individuals at relatively increased risk, it does not allow for prediction.”

Risk Factors

Past
- Previous suicide attempts
- Previous self harm
- Sexual or physical abuse
- Neglect
- Medical History
- Family history
- Psychotic history
- Substance use History

Present
- Psychiatric conditions
- Substance use
- Suicidal ideation (plans, intent, and behavior)
- Acute psychosocial stressors (family discord, interpersonal losses, financial difficulties)
- Hopelessness
- Impulsivity
- Employment status
- Living situation

Future
- Reasons for living
- Plans for the future
- Cultural and religious views about suicide
- Presence of external support
- Likelihood of exposure to ongoing stressors
- Quality of therapeutic relationship
- Quality of problem solving skills
- Access to weapons such as firearms
- Resilience traits
- Risk engages to some extent
- Capacity for reality testing
Framework #1

Risk Factors
- Past
- Present
- Future

Protective Factors

Shea (2002)

Framework #2

Risk Factors
- Static
- Modifiable

Protective Factors

Shea (2002)

The Method

Risk Factors
- Past attempt
- SI/intent/plan
- Intoxication
- Active symptoms
- Access to weapons
- Future-orientation

Estimated Risk
- Low
- Moderate
- High

Shea (2002)

The Method

Estimated Risk
- Low
- Moderate
- High

Intervention
- Low
- Moderate
- High

Shea (2002)
Acute vs. Chronic

- Acute: 24-48 hours
- Chronic: Months to Years

Talk is Cheap

- Patient (Behavior > Words)
- Medical Records
- Health Care Providers
- Friends and Family
- Roommates

Interventions

- When in doubt, consult with your colleagues
The Next Level
Responding to +SI

Shea (2002)

Responses to SI

- “I understand that you are suffering.”
- “I will promise to help you to the best of my ability. I will not abandon you.”
- “Your suffering is temporary.”
- “You are blinded by suffering.”
- “Many people have been in your situation, have survived, and are living happily.”
- “When this crisis is over, you will be stronger.”
- “What has stopped you from killing yourself?”
- “I understand you wish to die. What do you think these thoughts represent?”

Shea (2002)
The Next Level
Moving Beyond +SI

Interview Techniques

Approach Strategies

High Risk
- “I’m suicidal”
- “I’m NOT suicidal”

Low Risk
- “No-Brainer” Patient
- “Inconsistent” Patient
- “Gamey” Patient
- “Conditional” Patient
- “Stable” Patient

Shea (2002)

“Inconsistent” Patient
“I feel fine now.”
“It was all a misunderstanding.”
“Can I go home now?”

Obtain collateral information

Behavioral Incident

Normalization

Symptom Amplification
Denial of the Specific

“Gamey” Patient

“If I really wanted to kill myself, I wouldn’t tell you!”
Clarify your role and force the issue

“Conditional” Patient
“If you don’t admit me (or give me pain meds, or find me housing, or...), I will kill myself!”

Separate “condition” from suicidal ideation

References

- Shea SC. The Practical Art of Suicide Assessment 2002.
Sexually Transmitted Diseases: What’s New in the Guidelines and Beyond?

Susan S. Philip, MD, MPH
Director, Disease Prevention and Control Branch
Population Health Division
San Francisco Department of Public Health
Assistant Clinical Professor of Medicine
Division of Infectious Diseases
University of California, San Francisco

Overview

- (Very!) Brief US STD Epidemiology
- Sexual History
- Select STDs: Updates in screening, prevention or treatment, focused on the Big Three: chlamydia (CT), gonorrhea (GC), and syphilis

Disclosures

The views expressed herein do not necessarily reflect the official policies of the City and County of San Francisco; nor does mention of the San Francisco Department of Public Health imply its endorsement.

S. Philip has received research support to City Clinic from Roche Diagnostics, Melinta Therapeutics, and GlaxoSmithKline
Why Diagnose and Treat STDs?

- Estimated > 19 million STDs in US annually
- Cost: $16.4 billion (2008 dollars)
- Health consequences
  - Pelvic Inflammatory Disease
  - Ectopic pregnancy
  - Infertility
  - Neonatal infection
  - Increase risk of HIV
- Screening as a quality indicator
  - HEDIS/CT screening in young women
  - HIV Primary Care
  - UGDSB Grade A or B recommendations
    - Intensive Behavioral Counseling for prevent STDs
    - Chlamydia and Gonorrhea in non-pregnant women (≥15 yr) (≥45 yr at risk)
    - HIV, syphilis, Hep B in at-risk women (≥20 yr, ≥45 yr at risk)
    - HIV, syphilis, Hep B in at-risk MSM (≥15 yr, ≥45 yr at risk)
    - HIV RNA test in all patients ≥35 yr
    - Syphilis in non-pregnant adults and adolescents

<table>
<thead>
<tr>
<th>Recommendation Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>Men who have sex with men, HIV-positive persons</td>
</tr>
</tbody>
</table>

STD Health Disparities

- Nationally there are populations who bear a disproportionate share of STDs
  - Men who have sex with men (MSM)
  - Adolescents
  - African Americans
  - Transgender persons
- Studies demonstrate that individual behaviors alone do not account for the increased rates

High rates of syphilis and HIV in US MSM

<table>
<thead>
<tr>
<th></th>
<th>Rates per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis</td>
<td>91</td>
</tr>
<tr>
<td>HIV</td>
<td>522</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MSM</th>
<th>MSW</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis</td>
<td>91</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>HIV</td>
<td>522</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

Sexual History in Primary Care?

- Felt Adequately Trained
- Sexual History at routine visit Components of Sexual History

Sexual History: Keep it Simple

- Neutral language:
  - “Do you have sex with men, women, or both?” (Single best question to ask with every patient at least once)
  - “What are you doing to prevent unwanted pregnancies or STDs” rather than “You use condoms 100%, right?”
- Consider adding questions to self-registration materials
- Find referral resources for complex trauma or sexual dysfunction
Practical Provider Tools for Sexual History

Fenway Institute and National Association of Community Health Centers
- Scripts
- Downloadable presentation
- Coding Guides
- EMR implementation

So, What Should We be Screening for?

STD/HIV: Recommended Asymptomatic Screening for All

- One HIV test for all persons age 13-64 (opt out)
- HCV Ab test for all persons born 1945-1965 (Baby Boomers)

STD Asymptomatic Screening for Women

Sexually Active women up to age 25
- Routine annual chlamydia and gonorrhea screening
- Other STD/HIV based on risk - including prior STDs, concurrent partners

Women over 25 years of age
- STD/HIV testing based on risk – including prior STDs, concurrent partners
- Pregnant women
  - Chlamydia
  - Gonorrhea (<25 years of age or risk)
  - HIV
  - Syphilis serology
  - HepB sAg
  - Hep C (if high risk)
STD Asymptomatic Screening for MSM

Screen at least annually, or every 3-6 mos if high risk regardless of reported condom use*
- HIV
- Syphilis
- Urethral GC and CT
- Rectal GC and CT (if receptive anal sex)
- Pharyngeal GC (if receptive oral sex)

Also screen for:
- Hepatitis B surface Ag (frequency not specified)
- Hepatitis C if born 1945-65, IDU, transfusion before 1992, long term HD, intranasal drug use*

*: High risk: multiple and/or anonymous partners, drug use, or these risks in patient’s partners

CDC 2015 STD Tx Guidelines www.cdc.gov/std/treatment

STD Asymptomatic Screening for HIV+ MSM

Same as HIV uninfected MSM plus:

Anal Cancer in HIV+ MSM: Annual digital rectal exam may be useful, some centers perform anal Pap and HRA for ASC-US or worse.

HCV: “HCV antibody tests should be serially monitored, at least yearly and more frequently depending on local circumstances (HCV prevalence, incidence, resources, and other factors), to detect conversion from HCV-antibody-negative to positive.”

CDC 2015 STD Tx Guidelines www.cdc.gov/std/treatment

Case 1

A 17 year old girl comes in for a sports physical. She has no complaints and is hoping to get in and out of the office quickly. You see she lists oral contraceptives on her med history and think about chlamydia screening

Would you:
1. Ask her if she is willing to have a pelvic exam today, and collect an endocervical swab for CT NAAT
2. Make a note in her chart to do CT screening at her next visit
3. Ask her to give a urine sample for CT NAAT
4. Ask her to perform a self collected vaginal swab for CT NAAT

Summary:
- Use Nucleic Acid Amplification Tests (NAATs) for symptomatic AND asymptomatic patients
- Optimal Specimens:
  - Women –vaginal swabs (may be self collected)
  - Men – first catch urine
- Extragenital (oropharyngeal, rectal) NAAT not FDA-cleared, but recommended – need lab validation

MMWR

Recommendations for the Laboratory-Based Detection of Chlamydia trachomatis and Neisseria gonorrhoeae — 2014

Centers for Disease Control and Prevention
Morbidity and Mortality Weekly Report

March 14, 2014
Chlamydia Treatment
Adolescents and Adults

**Recommended regimens (non-pregnant):**
- Azithromycin 1 g orally in a single dose
- Doxycycline 100 mg orally twice daily for 7 days

**Recommended regimens (pregnant):**
- Azithromycin 1 g orally in a single dose

CT Treatment – Changes to 2015 Guidelines

**Additional Alternative Regimens (non-pregnant):**
- Doxycycline (delayed release) 200 mg po QD x 7 d
  - Equally efficacious to BID doxy, less GI side effects
  - More $$$$

**Move to Alternative Regimen (PREGNANCY):**
- Amoxicillin 500 mg po TID x 7 days
  - CT persistence documented in vitro after treatment prompted removal from recommended to alternate

Expedited Partner Therapy (EPT)*, where allowed by law, is recommended to reduce repeat infection in the index patient

Case 2
At a new patient's initial visit, you learn he is a gay man who has had 3 sex partners in the last year. He feels fine and says all STD tests were negative a year ago. In addition to an HIV test, what else would you order?

1. No additional tests – he is asymptomatic
2. Urine gonorrhea and chlamydia
3. Syphilis serology
4. Pharyngeal GC, rectal GC and CT, syphilis serology
5. I need to know more before deciding
STD Asymptomatic Screening for MSM

Screen at least annually, or every 3-6 mos if high risk regardless of reported condom use*

- HIV
- Syphilis
- Urethral GC and CT
- Rectal GC and CT (if receptive anal sex)
- Pharyngeal GC (if receptive oral sex)

Also screen for:

- Hepatitis B surface Ag (frequency not specified)
- Hepatitis C if born 1945-65, IDU, transfusion before 1992, long term HD, intranasal drug use*

* High risk: multiple and/or anonymous partners, drug use, or these risks in patient or partners

CDC 2015 STD Tx Guidelines www.cdc.gov/std/treatment

Anatomic Site-Specific GC/CT Screening is Critical in MSM Patients

Rectal Infections

Chlamydia n=308

Gonorrhea N=237

Urethral Infections

Chlamydia n=234

Gonorrhea n=244

Case 2, continued

Patient reports receptive anal sex (intermittent condom use) and oral sex. The GC/CT NAATs come back positive for rectal gonorrhea. All others neg. Treatment? Oh, and by the way, patient has documented anaphylaxis to cephalosporins

1. Azithromycin 2 g PO x 1
2. Levofloxacin 250 mg PO x 1
3. Cefixime 400 mg PO x1 PLUS azithromycin 1 PO x1
4. Gentamicin 240 mg IM + azithromycin 2 g PO
5. Gemifloxacin 320 mg PO + azithromycin 2 g PO
6. 1, 4 or 5
7. 4 or 5

Cannot Rely on a Negative Urine Test Alone!

This Strategy will Miss the Majority of GC/CT Cases

MISSE 77%

MISSE 95%

Morsut et al. STD Oct 2011, 36: 322-4  Slide-Courtesy: J. Park MD, MS
Gonorrhea Treatment is one of CDC's key strategies to reducing risk of resistant Neisseria gonorrhoeae

Antibiotic Resistance Threats in the United States, CDC 2013

Current Recommended Gonorrhea Treatment – any anatomic site

Ceftriaxone 250mg IM x 1 + Azithromycin 1g PO x 1

This is Dual treatment for GC – add the azithromycin regardless of CT result

Example: If patient is treated empirically with azithromycin for urethritis and the NAAT is GC+ 3 days later, but patient returns on day 6, must repeat azithro in combination with ceftriaxone to meet treatment recommendations

CDC 2015 STD Tx Guidelines www.cdc.gov/std/treatment

When do you have to re-dose?

• May not always need to re-dose if azithro taken first
  • Most experts state due to long half life of azithromycin, probably OK to administer ceftriaxone within 5 days
• But, if Ceftriaxone administered first and delay in taking azithro (e.g. delay in picking up azithro at pharmacy) MUST re-administer both simultaneously

CDC 2015 STD Tx Guidelines www.cdc.gov/std/treatment

Gonorrhea Treatment and Test of Cure

• Doxycycline no longer recommended (leave only Ceftriaxone + Azithromycin as recommended tx)
• High level resistance has been documented to Azithromycin, with clinical failures – Avoid using as monotherapy
• For cephalosporin allergic, 2 options:
  • Gentamicin 240 mg IM (or 5mg/kg IM) with azithromycin 2g orally OR
  • Gemifloxacin 320 mg orally with azithromycin 2g orally

• Who needs a test of cure?
  • Pregnant patients
  • Patients with pharyngeal GC treated with an alternative regimen
  • Cases of suspected treatment failure (culture AND simultaneous NAAT)
  • Consider if using non-recommended or monotherapy

• Obtain test of cure 14 days after treatment, using either culture or NAAT
• In addition, all patients should have a repeat test 3 months after treatment

CDC 2015 STD Tx Guidelines www.cdc.gov/std/treatment Slides courtesy I. Park MD, MS
Take Home Messages: Practical Implementation of STD screening in Primary Care?

- Sexual history documented at least once for each patient
- Consider standing orders for screening at recommended intervals
- Use self-collected vaginal swabs (FDA-cleared) – can separate screening from pelvic exams and simpler than urine (no need to aliquot!)
- Some sites have moved to self-collected rectal, pharyngeal swabs in consultation with lab
- Provide prescriptions for your patient to take to their partner, if allowable by law where you practice

Case 3

48 year old woman, new to your practice, previously injected drugs but none in the past 10 years. HIV and HCV screen negative and he is asymptomatic. The lab calls to tell you that the patient’s syphilis results are:

RPR 1:128, TPPA Reactive

Best next step?

1. Treat with benzathine PCN 2.4 mu IM x 1
2. Treat with benzathine PCN 2.4 mu IM x 3
3. Need more information before proceeding
4. Do nothing as this is unlikely to be syphilis
5. Perform an LP to rule out neurosyphilis

Non-treponemal tests (e.g., RPR, VDRL)
- NON-SPECIFIC ANTIBODY TO LIPOIDAL ANTIGENS
- QUANTITATIVE
- REACTIVITY DECLINES WITH TIME

Treponemal tests (e.g., TPPA, FTA-Abs)
- SPECIFIC TO TP
- QUALITATIVE
- REACTIVITY PERSISTS OVER LIFETIME

Syphilis Diagnostic Strategies are Evolving

Syphilis Natural History

Neurosyphilis can occur at any stage
Syphilis Treatment – no change in 2015 Guidelines

Primary, Secondary & Early Latent:  
• Benzathine penicillin G 2.4 million units IM in a single dose

Late Latent and Unknown Duration:  
• Benzathine Penicillin G 7.2 million units total, given as 3 doses of 2.4 million units each at 1 week intervals

Neurosyphilis:  
• Aqueous Crystalline Penicillin G 16-24 million units IV daily administered as 4-6 million IV q 4 hr for 10-14 d

No enhanced efficacy of additional doses of penicillin, amoxicillin or other antibiotics even if HIV infected!

In pregnancy, benzathine penicillin is the only recommended therapy. No alternatives

Additional Screening after an STD infection

• Women with CT, GC or trichomonas should be rescreened for all at 3 months after treatment.
• Men with CT or GC should be rescreened at 3 months after treatment.
• Patients diagnosed with syphilis should undergo follow up serologic serology per current recommendations as well as be screened for other STDs and HIV.
• HIV testing should also be considered in all patients with a prior STD history

Should also perform pregnancy testing in women diagnosed with an STD!
**Additional Points on Preventing Congenital Syphilis**

- Congenital cases are sentinel events for clinical delivery systems AND public health
- Public health prioritizes female partners of male syphilis cases – please prepare patients and encourage them to work with us to ensure partners are treated
- Remember that penicillin is the only acceptable treatment for pregnant women with syphilis – must desensitize if serious true allergy
- Must adhere to strict 7-day interval for weekly benzathine penicillin in pregnant patients with late latent syphilis. If longer, must restart series.

**Clinicians should be on the Alert for Ocular Syphilis**

- Ask patients with syphilis about vision changes or delays in diagnosis have been associated with visual loss*
- Refer patients with positive syphilis tests and visual complaints for immediate ophthalmologic evaluation
- Report cases of syphilis to the health department within 1 day
- Treat with Aqueous crystalline penicillin G 18-24 million units IV daily administered as 3-4 million units IV q 4 hr for 10-14 days (regardless of CSF result)

---

**Thank You!**

Ina Park  
California STD/HIV Prevention Training Center  
Stephanie Cohen

2015 CDC STD Treatment Guidelines:  

Contact information:  
Susan.Philip@sfdph.org  
www.sfcityclinic.org

*Moradi Am J Ophthal 2015; CDC 2015 STD Treatment Guidelines  
Kirkcaldy CID 2014
MANAGEMENT OF HYPERLIPIDEMIA AND CARDIOVASCULAR RISK: Balancing Benefits and Harms

Robert B. Baron, MD MS
Professor and Associate Dean
UCSF School of Medicine
baron@medicine.ucsf.edu

EXPLAINING THE DECREASE IN DEATHS FROM CVD

1980 to 2000: death rate fell by approximately 50% in both men and women

2000 to 2010: Death still falling: down 31%

• About 1/2 from acute treatments, 1/2 from risk factor modification:
  • Predominantly cholesterol (1/4), BP, smoking

Disclosure

No relevant financial relationships

Placebo-Controlled Statin Trials

Reductions in Major Coronary Events Relative to Placebo

simv 20-40 mg prava 40 mg prava 40 mg simv 40 mg prava 40 mg lov 50-80 mg
The benefit from any given intervention is a function of:
1) The relative risk reduction conferred by the intervention, and
2) The native risk of the patient

ACC/AHA Guidelines

- 4 groups of patients who benefit from statins
- Identifies high and moderate intensity statins
- No LDL treatment targets
- Non-statin therapies do not provide acceptable risk reduction
- Estimate 10-year ASCVD risk with new equation

Heart Protection Study: Vascular Events by Baseline LDL-C

<table>
<thead>
<tr>
<th>Baseline LDL-C</th>
<th>Statin No. Events (10,269)</th>
<th>Placebo No. Events (10,207)</th>
<th>Risk Ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>285</td>
<td>360</td>
<td>Statin better</td>
</tr>
<tr>
<td>100-130</td>
<td>670</td>
<td>881</td>
<td>Statin better</td>
</tr>
<tr>
<td>≥130</td>
<td>1087</td>
<td>1365</td>
<td>Statin worse</td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2042 (19.9%)</td>
<td>2606 (25.4%)</td>
<td>24% reduction (p&lt;0.00001)</td>
</tr>
</tbody>
</table>

ACC/AHA Guidelines

Four Groups of Patients Who Benefit From Statins

- Individuals with clinical ASCVD
- Individuals with primary elevations of LDL ≥190
- Individuals age 40-75 with diabetes and LDL ≥70
- Individuals without ASCVD or diabetes, age 40-75, with LDL ≥70, and 10 year risk 7.5% or higher
**ACC/AHA Guidelines**

Importance of Lifestyle Recommendations

- Heart healthy diet
- Regular aerobic exercise
- Desirable body weight
- Avoidance of tobacco

**Heart Healthy Diet 2017**

- Two dietary factors increase LDL:
  - Saturated fat
  - Total Calories
- Restriction of dietary cholesterol is no longer recommended (Dietary Guidelines 2015)

**Saturated Fat 2017**

- Some newer observational studies: no association between sat fat and CVD
- But: RCTs that replace sat fat with unsat fat reduce total and LDL cholesterol and CVD events and mortality
- And: replacing sat fat with carb reduces total and LDL cholesterol but increases triglycerides and HDL and does not lower CVD events

**ACC/AHA Guidelines**

What Statin for Each Group?

- **Individuals with clinical ASCVD:**
  - Treat with: high intensity statin, or moderate intensity statin if > age 75

- **Individuals with primary elevations of LDL ≥190:**
  - Treat with: high intensity statin
ACC/AHA Guidelines
What Statin for Each Group?

- Individuals 40-75 with diabetes and LDL ≥ 70:
  - Treat with: moderate intensity statin, or high intensity statin if risk over 7.5%
- Individuals without ASCVD or diabetes, 40-75, with LDL ≥ 70, and 10 year risk 7.5% or higher:
  - Treat with: moderate-to-high intensity statin

ACC/AHA Guidelines
High Intensity vs. Moderate Intensity Statin

- High Intensity: lowers LDL by >50%
  - Atorvastatin 40 - 80
  - Rosuvastatin 20 - 40
- Moderate Intensity: lowers LDL by 30-50%
  - Atorvastatin 10 - 20
  - Rosuvastatin 5 – 10
  - Simvastatin 20 - 40
  - Pravastatin 40 – 80
  - Lovastatin 40

How Best To Calculate 10 Year Risk?

Pooled Cohort Risk Assessment Equations: hard CHD events and stroke

- http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/PreventionGuidelines_UCM_457698_SubHomePage.jsp

Pooled Cohort Risk Assessment Equations

- Age
- Gender
- Race (White/African American)
- Total cholesterol (170 mg/dl)
- HDL cholesterol (50 mg/dl)
- Systolic BP (110 mmHg)
- Yes/no meds for BP
- Yes/no DM
- Yes/no cigs
- Outcome: 10-year risk of total CVD (fatal and non-fatal MI and stroke)
How Best To Calculate 10 Year Risk? Baron Approach 2017

- Use both CHD (hard end points) calculator and new CV risk calculator
- Include both in shared decision-making discussion

Percent of U.S. Adults Who Would Be Eligible for Statin Therapy for Primary Prevention, According to Set of Guidelines and Age Group.

How Best To Calculate 10 Year Risk? Mayo Clinic Statin Choice Decision Aid:

- http://statindecisionaid.mayoclinic.org/index.php/statin/index?PHPSESSID=0khk8nm14h9vubjm3423e6h6b2
63 yo woman; s/p MI

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>115</td>
</tr>
<tr>
<td>HDL</td>
<td>45</td>
</tr>
<tr>
<td>TG</td>
<td>160</td>
</tr>
</tbody>
</table>

The best next step in lipid management is:

1. Atorvastatin 40 mg
2. Rosuvastatin 10 mg
3. Pravastatin 40 mg
4. Simvastatin 40 mg
5. Lovastatin 40 mg
6. Whatever works to get her LDL below 70 mg/dl

2013 ACC/AHA Guidelines
What Statin for Each Group?

- Individuals with clinical ASCVD:
  - Treat with: high intensity statin, or moderate intensity statin if > age 75

The best next step in lipid management is:

1. Atorvastatin 40 mg
2. Rosuvastatin 10 mg
3. Pravastatin 40 mg
4. Simvastatin 40 mg
5. Lovastatin 40 mg
6. Whatever works to get her LDL below 70 mg/dl
63 yo woman; s/p MI. On atorvastatin 80.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>95</td>
</tr>
<tr>
<td>HDL</td>
<td>40</td>
</tr>
<tr>
<td>TG</td>
<td>200</td>
</tr>
</tbody>
</table>

The best next step in lipid management is:

1. Continue current therapy
2. Switch to rosuvastatin 40 mg
3. Add fenofibrate
4. Add fish oil
5. Add niacin
6. Add ezetimibe

Summary Lipid-Lowering Drugs

- Statins are treatment of choice based on RCT to decrease risk
- No evidence to support adding niacin or fibrates to statins
- If completely statin-intolerant, niacin may reduce CVD risk (weak evidence)
- Fibrates appear to lower MI risk, but no other CVD endpoints

Summary Lipid-Lowering Drugs

- Ezetimibe study: (IMPROVE-IT)
  - 18,000 ACS patients (40% from North America)
  - RCT: Simvastatin vs simvastatin + ezetimibe. Took 7 years. Death, MI, Stroke
  - Simvastatin: 34.7% vs Simva/ezetimibe 32.7% (270 fewer events over 7 years)
PCSK9 Inhibitors
- Evolocumab (Repatha) and alirocumab (Praluent)—monoclonal antibodies that reduce liver LDL-receptor degradation
- Reduce LDL by 50%. Injectable Q2 – 4 weeks
- Approved for FH or patients with CVD “who need additional LDL lowering.”

FOURIER TRIAL
- 27,564 patients, CV disease, on statin, LDL >70, 2.2 years
- Evolocumab vs placebo (SQ injections)
- Primary composite CV endpoint: death, MI, stroke, ACS revascularization
- Secondary endpoint: CV death, MI, stroke

FOURIER TRIAL
- LDL reduced 59% (92 mmol/L to 30)
- Primary composite endpoint:
  - 1344 (9.8%) vs 1563 (11.3%)
  - 15% reduction
- Secondary endpoint: CV death, MI, stroke
  - 816 (5.9%) vs 1013 (7.4%)
  - 20% reduction

FOURIER TRIAL
- NNT 66 over 2 years
- No reduction in death
- No obvious safety concerns
- Reflections:
  - Evolocumab reduces risk
  - Risk reduction less than hoped/thought
  - $14,000 per year
The best next step in lipid management is:

1. Continue current therapy
2. Switch to rosuvastatin 40 mg (Also potentially correct, but medication still on patent)
3. Add fenofibrate
4. Add fish oil
5. Add niacin
6. Add ezetimibe

63 yo woman, no traditional risk factors

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>155</td>
</tr>
<tr>
<td>HDL</td>
<td>55</td>
</tr>
<tr>
<td>TG</td>
<td>160</td>
</tr>
<tr>
<td>SBP</td>
<td>120</td>
</tr>
</tbody>
</table>

No BP meds
No DM
Nonsmoker

The best next step in lipid management is to calculate 10 year risk and:

1. Continue current therapy (no meds)
2. Begin atorvastatin 40
3. Begin atorvastatin 10
4. Begin simvastatin 20
5. Begin sustained release niacin
6. Begin red yeast rice

63 yo woman, no risks

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>155, HDL</td>
<td>55, TG</td>
</tr>
<tr>
<td>SBP</td>
<td>120, No BP meds</td>
<td>Non smoker, No DM</td>
</tr>
</tbody>
</table>

10 yr CHD risk (old calculator): 2%
10 yr CV risk (new calculator): 4.5%

Therefore no medication recommended
63 yo man, no traditional risk factors

- LDL: 155
- HDL: 55
- TG: 160
- SBP: 120
- No BP meds
- No DM
- Nonsmoker

The best next step in lipid management is to calculate 10 year risk and:

1. Continue current therapy (no meds)
2. Begin atorvastatin 40
3. Begin atorvastatin 10
4. Begin simvastatin 20
5. Begin sustained release niacin
6. Begin red yeast rice

63 yo man, no risks

- LDL: 155, HDL: 55, TG: 160
- SBP: 120, No BP meds
- Nonsmoker, No DM

10 yr CHD risk (old calculator): 10%
10 yr CV risk (new calculator): 10.8%

“Toss-up.” Shared decision making. If start statin (per new guidelines), can start with moderate intensity statin.
The best next step in lipid management is to calculate 10 year risk and:

1. Continue current therapy (no meds)- old (but toss-up)
2. Begin atorvastatin 40-new (but still close call)
3. Begin atorvastatin 10-new (but still close call)
4. Begin simvastatin 20-new (but still close call)
5. Begin sustained release niacin
6. Begin red yeast rice

Key is shared decision-making

Other Factors That Could Affect Treatment Decisions

- LDL £ 160 mg/dl or evidence of genetic disorder
- Family history of premature ASCVD (<55 in first degree male relative, <65 in first degree woman)
- hs-CRP £2mg/dl
- CAC score £ 300 (or £75% for age, sex, ethnicity
- Ankle brachial index <0.9
- Elevated lifetime risk of ASCVD

The Good and The Controversial of the ACC/AHA Cholesterol Guidelines

- Focus on healthy lifestyle is good
- Focus to use statins (and not other agents) is good
- Focus to treat patients at high risk is good
- Focus to treat all patients with LDL <190 mg/dl and treat patients with DM/existing CV disease is good
- Not having target LDL is controversial
- Adults with no DM or heart disease and 10-year calculated risk >7.5% (using new risk calculator) to be treated – controversial

Statin Use for Primary Prevention of CVD: USPSTF

- Age 40 – 75, no CVD, 1 or more CVD risk factor* and calculated risk of and 10% or greater
- USPSTF B: Prescribe if no contraindications
- Treat with low to moderate dose statin

*Risk : dyslipidemia, diabetes, HTN, smoking

USPSTF 2016
**Statin Use for Primary Prevention of CVD: USPSTF**

- Age 40 – 75, no CVD, 1 or more CVD risk factor and calculated risk of and 7.5 – 10%

USPSTF C: Individualized decision

- Age 76 and older: USPSTF I

**USPSTF vs. ACA/AHA**

- Recommendations modeled in NHANES primary prevention population.

- 3416 adults, 40-75. 21.5% already on statins.

- USPSTF: 15.8% additional
- ACA/AHA: 24.3% additional

- 55% of extra ACC/AHA group 40-59 years old.

**NSAIDS and CVD**

- Danish national study, 97,698 patients with prior MI. 44% received NSAIDS.

- NSAIDS associated with 42% increase in CV death (CI 1.36 – 1.49)

- Diclofenac 96% and rofecoxib 66% increase

- Ibuprofen 34% and naproxen 27% increase

**Competing Risks**

- Example: women with 10-year risk 10%

- Reduce risk by 30% with statins. Risk now 7%.

- Add NSAID. Increase risk by 50%

- Total risk now back to 10%.
Aspirin and CVD

- Aspirin reduces nonfatal MI by about 20%; no benefit on non-fatal stroke.
- Also reduces incidence of colorectal cancer.
- Has definable off-setting harms: GI bleed, hemorrhagic stroke.

Aspirin and CVD

- Age 50 – 59 and 10% 10-yr risk: USPSTF B (Prescribe if no contraindications)
- Age 60 – 69 and 10% 10-yr risk: USPSTF C (Individualized decision)
- Less than age 50, over age 70: USPSTF I (Insufficient evidence)

USPSTF 2016

Conclusions I

- Statins are effective and cost effective in selected groups of patients
- Optimal screening age not known.
  - ACC/AHA age 21 (to identify those > LDL 190)
  - USPSTF age 35 men and 45 women for most, age 20 if increased risk.
- Use statins in patients with ASCVD, LDL ≥190 and diabetes

Conclusions II

- For those without ASCVD and diabetes, calculate 10 year risk, and treat those with risk greater than 7.5% (or 10% or maybe even 15%). Use shared decision making.
- Use appropriate intensity statin (high and moderate)
- Monitor adherence, but do not treat to specific LDL goal
Conclusions III

- Do not treat those over age 75 (unless ASCVD),

- Do not treat with other lipid-modifying drugs in addition to statins (but may need if truly statin intolerant)

- Avoid other factors that raise risk (i.e. NSAIDS) and use those that lower it (i.e. aspirin)
Update on COPD & Asthma

Michael C. Peters, M.D. MAS
Division of Pulmonary & Critical Care Medicine
Cardiovascular Research Institute
University of California San Francisco
UCSF Primary Care Medicine
San Francisco, CA
October 13, 2017

Disclosures

- No Pharma Disclosures
- NHLBI - Asthma Clinical Research Network
- NHLBI - Severe Asthma Research Program

Update on the Management of COPD

What is COPD

- Disease state characterized by airflow limitation that is not fully reversible*
  - Post-Bronchodilator FEV1/FVC <0.7
- Generally caused by cigarette smoke
  - Biomass fuels (developing world)
  - α1-antitrypsin deficiency
  - Pollution, chronic infection
- Bronchiectasis, cystic fibrosis are not included in the definition
Rate of Deaths per 100,000 in the USA 2005-2011

Cancer Death by Site

MEN
- Lung 85,920 (27%)
- Prostate 26,120 (8%)
- Colorectal 26,020 (8%)
- Pancreas 21,450 (7%)
- Liver 18,280 (6%)

WOMEN
- Lung 72,120 (26%)
- Breast 40,450 (14%)
- Colorectal 23,170 (8%)
- Pancreas 20,330 (7%)
- Ovary 14,240 (5%)

American Cancer Society 2016

• CHRONIC Obstructive Pulmonary Disease
  • NEED SPIROMETRY: FEV1/FVC < 0.70

Simel and Rennie
Evidence-based Clinical Diagnosis
Observational study 2734 current and former smokers and controls who never smoked

Examined whether current or former smokers with preserved lung function had symptoms or suffered COPD exacerbations

Prevalence of Symptoms and Risk of Respiratory Exacerbations

- No benefit of screening adults with no symptoms
- No evidence that treating asymptomatic individuals prevents future symptoms, or reduces the subsequent decline in lung function.

Anthonisen et al JAMA 272:1497-505, 1994
USPTF JAMA 2016
**GOLD Criteria**

When assessing risk, choose the highest risk according to GOLD grade or exacerbation history.

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Characteristics</th>
<th>Spirometric Classification</th>
<th>Exacerbations per year</th>
<th>mMRC</th>
<th>CAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low Risk, Less Symptoms</td>
<td>GOLD 1-2</td>
<td>≥2</td>
<td>0-1</td>
<td>≤10</td>
</tr>
<tr>
<td>B</td>
<td>Low Risk, More Symptoms</td>
<td>GOLD 1-2</td>
<td>≥1</td>
<td>1-2</td>
<td>≥10</td>
</tr>
<tr>
<td>C</td>
<td>High Risk, Less Symptoms</td>
<td>GOLD 3-4</td>
<td>≥12</td>
<td>2-3</td>
<td>≥10</td>
</tr>
<tr>
<td>D</td>
<td>High Risk, More Symptoms</td>
<td>GOLD 3-4</td>
<td>≥20</td>
<td>2-3</td>
<td>≥10</td>
</tr>
</tbody>
</table>

**GOLD Guidelines 2017**

≥1 leading to hospital admission (no hospital admission)

- **Take HOME**
  - Treat the patient
    - Symptoms
    - Exacerbations
  - Spirometry assists with diagnosis
  - Lung Cancer Screening

- **Treat The Patient!!!**
  - Prevention of Acute Exacerbations
  - Prevent Progressive Loss of Lung Function
  - Improve Symptoms
What treatment is the most effective for preventing COPD exacerbations?

A) Roflumilast  
B) Pulmonary Rehab  
C) Duel LAMA + LABA  
D) Azithromycin

Treat The Patient!!!

- Prevention of Acute Exacerbations
- Prevent Progressive Loss of Lung Function
- Improve Symptoms

Hospitalized Severe AECOPD and Mortality: Severity of AECOPD

Predictors of Acute Exacerbations of COPD

<table>
<thead>
<tr>
<th>Predictor</th>
<th>≥2 vs. 0 (Odds Ratio (95% CI))</th>
<th>1 vs. 0 (Odds Ratio (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbation in Prior Year</td>
<td>5.7 (4.5-7.3)</td>
<td>2.2 (1.8-2.8)</td>
</tr>
<tr>
<td>FEV1 per 100ml decrease</td>
<td>1.1 (1.08-1.1)</td>
<td>1.1 (1.0-1.1)</td>
</tr>
<tr>
<td>SGRC (symptom score) per 4 points</td>
<td>1.1 (1.0-1.1)</td>
<td>1.1 (1.0 – 1.1)</td>
</tr>
<tr>
<td>GERD</td>
<td>2.1 (1.6-2.7)</td>
<td>1.6 (1.2-2.1)</td>
</tr>
<tr>
<td>WBC Count</td>
<td>1.1 (1-1.1)</td>
<td>1.1 (1.0-1.1)</td>
</tr>
</tbody>
</table>
Prevention of AECOPD

American College of Chest Physicians & Canadian Thoracic Society Guideline

- PICO (population, intervention, comparator, outcome)
- Literature Search
- Quality Assessment (AGREE II, DART)
- Grading Evidence (GRADEpro)
- Recommendations (CHEST)

Criner et al. CHEST 147:894-942, 2015

Prevention of AECOPD Recommendations

Non-Pharmacologic Treatments/Vaccinations:

- Influenza Vaccine (Grade 1B)
- Pulmonary Rehab (Grade 1C)
- Smoking Cessation (Grade 2C)
- Pneumococcal Vaccine (Grade 2C) *Mod-severe-very severe; recent AECOPD<4 weeks*

Criner et al. CHEST 147:894-942, 2015

Figure 1. Forest plot of comparison: I Rehabilitation versus control, outcome: I.1 Hospital admission (to end of follow-up).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Forest Odds Ratio</th>
<th>M-H Random Effects LL/UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enanti 2019</td>
<td>3</td>
<td>1</td>
<td>13</td>
<td>0.30 (0.15-0.61)</td>
<td></td>
</tr>
<tr>
<td>Han 2004</td>
<td>2</td>
<td>1</td>
<td>13</td>
<td>0.30 (0.16-0.59)</td>
<td></td>
</tr>
<tr>
<td>Murphy 2001</td>
<td>2</td>
<td>3</td>
<td>15</td>
<td>0.36 (0.16-0.83)</td>
<td></td>
</tr>
<tr>
<td>Enanti 2013</td>
<td>3</td>
<td>1</td>
<td>14</td>
<td>0.30 (0.14-0.66)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>10</td>
<td>20</td>
<td>0.30 (0.15-0.61)</td>
<td>0.22 (0.08-0.58)</td>
</tr>
</tbody>
</table>

Puhan Cochrane Database 2011

Pulmonary Rehab

Table 1. Forest plot of comparison: I Rehabilitation versus control, outcome: I.1 Hospital admission (to end of follow-up).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Forest Odds Ratio</th>
<th>M-H Random Effects LL/UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enanti 2019</td>
<td>3</td>
<td>1</td>
<td>13</td>
<td>0.30 (0.15-0.61)</td>
<td></td>
</tr>
<tr>
<td>Han 2004</td>
<td>2</td>
<td>1</td>
<td>13</td>
<td>0.30 (0.16-0.59)</td>
<td></td>
</tr>
<tr>
<td>Murphy 2001</td>
<td>2</td>
<td>3</td>
<td>15</td>
<td>0.36 (0.16-0.83)</td>
<td></td>
</tr>
<tr>
<td>Enanti 2013</td>
<td>3</td>
<td>1</td>
<td>14</td>
<td>0.30 (0.14-0.66)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>10</td>
<td>20</td>
<td>0.30 (0.15-0.61)</td>
<td>0.22 (0.08-0.58)</td>
</tr>
</tbody>
</table>

Puhan Cochrane Database 2011
Pulmonary Rehab

Figure 1. Forest plot of comparison: Rehabilitation versus control, outcome: Hospital admission (to end of follow-up).

<table>
<thead>
<tr>
<th>Study</th>
<th>Event Difference</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>3 12 15</td>
<td>8 17 15</td>
<td>0.22</td>
<td>(0.08-0.58)</td>
<td>0.005</td>
</tr>
<tr>
<td>2012</td>
<td>2 18 15</td>
<td>5 11 15</td>
<td>0.23</td>
<td>(0.06-0.74)</td>
<td>0.05</td>
</tr>
<tr>
<td>2015</td>
<td>2 15 15</td>
<td>5 15 15</td>
<td>0.36</td>
<td>(0.13-0.92)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Total events: 50

Number Needed to Treat = 4

CI 3-8

Puhan Cochrane Database 2011

Prevention of AECOPD
Recommendations

Maintenance Inhaled Therapy:

- LAMA vs PBO (Grade 1A)
- LABA vs PBO (Grade 1B)
- LAMA vs LABA (Grade 1C)
- COMBO Therapy vs MonoTherapy (Grade 1B, C)

Criner et al. CHEST 147:894-942, 2015

FLAME TRIAL

- LAMA + ICS = Good
- LABA + ICS = Good

ICS risk of Pneumonia?
FLAME TRIAL

- LAMA + ICS = Good
- LABA + ICS = Good
- LABA + LAMA = ?

ICS risk of Pneumonia?

LABA (indacaterol) + LAMA (glycopyrronium) QDay
VS.
LABA (salmeterol) + ICS (fluticasone) BID

NNT = 9
Prevention of AECOPD

Recommendations

Oral Therapy:

- **Macrolide (Grade 2A)**
  (Frequent AECOPD despite Tx)
- **Systemic Corticosteroids (Grade 2B)**
  (For AECOPD - prevent next 30 days)
- **Roflumilast (Grade 2A)**
  (Chr Bronchitis, ≥ 1 AECOPD in year)
- Do not use statins for AECOPD (Grade 1B)

---

**The MACRO Study**
(Azithromycin 250mg/day x 1 year)

- NHLBI - COPD Clinical Research Network
- N = 1130
- Moderately-severe COPD
  FEV1/FVC < 70%, FEV1 < 80%
- “Exacerbation Prone”
- Primary Outcome: Time to first AECOPD
Rates of Acute Exacerbations of Chronic Obstructive Pulmonary Disease per Person-Year, According to Study Group.

Albert RK et al. NEJM 2011

Macrolides Decrease AECOPD

NNT=15


Macrolides May Increase risk of Cardiovascular Death

Ray WA et al. NEJM 2012

Macrolide Antibiotics and the Risk of Cardiac Arrhythmias

Macrolide Antibiotics and the Risk of Cardiac Arrhythmias

Macrolide Antibiotics and the Risk of Cardiac Arrhythmias

Richard K. Albert1,2 and Joseph L. Schuller1,3; for the COPD Clinical Research Network

1Denver Health, Denver, Colorado; and University of Colorado Denver, Aurora, Colorado

Am J Respir Crit Care Med 2014; 189:1173-1180

- Macrolides can prolong QT and QTc leading to arrhythmias, including torsades de pointes
- Most arrhythmias with macrolides occur in patients with underlying risk factors
- Incidence of arrhythmias in absence of additional risk factors is very low, perhaps 1 in 100,000.

Mosholder, NEJM 2013

"Macrolide-associated arrhythmias can be reduced by not prescribing to patients with comorbidities of concern...the majority of which can be discovered by:

- History
- ECG before initiating therapy
- ECG a short time after initiating therapy"
Roflumilast

- Oral Tablet
- 500 ug Once Daily
- Phosphodiesterase-4 Inhibitor

- 1 year trial
- 40 years old, >20 pack years, +COPD
- FEV1% predicted<50%
- Symptoms of chronic bronchitis, +cough and sputum
- "Exacerbation Prone"
- ICS + LABA

Martinez et al. Lancet 2015

Effect of Corticosteroids on Treatment Failure Rates after AE COPD

- 2 week = Solumedrol 125mg q6hr x 3d, Prednisone 60mg qd x 4d, 40mg qd x 4d, 20mg qd x 4d
- 8 week = additional 10mg qd x 5 week, then 5 mg qd x 1 week

Niewoehner et al., NEJM 340:1941, 1999

<table>
<thead>
<tr>
<th>Treatment Failure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>14</td>
</tr>
<tr>
<td>16</td>
</tr>
<tr>
<td>18</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>22</td>
</tr>
<tr>
<td>24</td>
</tr>
<tr>
<td>26</td>
</tr>
<tr>
<td>28</td>
</tr>
<tr>
<td>30</td>
</tr>
<tr>
<td>32</td>
</tr>
<tr>
<td>34</td>
</tr>
<tr>
<td>36</td>
</tr>
<tr>
<td>38</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>42</td>
</tr>
<tr>
<td>44</td>
</tr>
<tr>
<td>46</td>
</tr>
<tr>
<td>48</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>52</td>
</tr>
<tr>
<td>54</td>
</tr>
<tr>
<td>56</td>
</tr>
<tr>
<td>58</td>
</tr>
<tr>
<td>60</td>
</tr>
</tbody>
</table>

Rate of Treatment Failure (%)

Table 3: Adverse events occurring in at least 3-5% of patients in either treatment group


Martinez et al. Lancet 2015
Summary

• Pulmonary Rehab (NNT=4)
• Duel Long Acting Bronchodilator Medications over ICS + LABA (NNT=9)
• Azithromycin prevents COPD Exacerbations (NNT=15)
  – Potential Risk of Cardiac Arrhythmias
• Roflumilast offers some benefit in bronchitis patients (NNT=25), (NNH=16)
• 5 days of corticosteroids is the appropriate time frame
**Tiotropium Reduces Lung Decline**

- Benefits all levels of disease severity
- Reduces respiratory symptoms
- Reduces anxiety and depression
- Reduces medical and hospital usage
- Improves exercise performance
- Improves quality of life
- Is typically provided as outpatient
- Can be initiated as an inpatient until functional ability has improved

---

**Definition of Asthma (Clinical)**

- Epidemiological: Questionnaires
  - Diagnosed with asthma by a physician and wheeze in past 12 months
  - Diagnosed with asthma by a physician and currently taking asthma medications

- Clinical:
  - Intermittent Airflow Obstruction + Symptoms
    - + Bronchodilator Response (200ml +12%)
    - + Methacholine Challenge test (PC 20 vs. Resistance)
**Definition of Asthma (Biological)**

- Chronic inflammatory disorder; many different cells; BHR; variable/reversible symptoms and obstruction; phenotypes? [GINA, 2011]

- Heterogeneous; Chronic airway inflammation; variable/reversible symptoms and obstruction; Different phenotypes or clusters [GINA, 2014]

**Epidemiology**

- 250-300 million people have asthma globally

- Asthma rates have been increasing in low/middle income countries (caught up)

- Most of the morbidity/mortality from asthma stems from the 5-10% with severe disease

**Causes of Asthma**

- **Hygiene Hypothesis** (Stein, NEJM 2016)

- **Exposure to Antibiotics**
  - Microbiome (Fujimura, Nature 2016)

- **Genetics** (Moffatt, NEJM 2010)

- **Obesity** (Sutherland AJRCCM 2007)

- **Environmental Influences**
  - Dogs/Cats
  - Medications

**Asthma Prevalence in USA 2001-10**

- Graph showing asthma prevalence from 2001 to 2010 with a steady increase.
ICS Formulations

- **MDI: Metered Dose Inhalers**
  - Aerosol
  - Theoretically achieves more distal distribution (small airways), ciclesonide
  - Flovent

- **DPI: Dry Powder Inhalers**
  - No propellant
  - Easier to use
  - Less systemic absorption

ICS Toxicity

(figures showing comparisons of different ICS formulations and toxicity profiles)
ICS Toxicity

### Table 4. Estimated Cortisol Suppressive Doses

<table>
<thead>
<tr>
<th>Labeled dose</th>
<th>C15α*</th>
<th>C15β*</th>
<th>C15α</th>
<th>C15β*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FU-IFC</td>
<td>9.97</td>
<td>15.58</td>
<td>10.73</td>
<td>15.58</td>
</tr>
<tr>
<td>T4A-IFC</td>
<td>7.87</td>
<td>13.79</td>
<td>8.46</td>
<td>13.79</td>
</tr>
<tr>
<td>BDP-IFC</td>
<td>6.80</td>
<td>11.14</td>
<td>7.28</td>
<td>11.14</td>
</tr>
<tr>
<td>IN-IFC</td>
<td>5.81</td>
<td>9.19</td>
<td>6.40</td>
<td>9.19</td>
</tr>
<tr>
<td>BLD-DP</td>
<td>5.03</td>
<td>8.39</td>
<td>5.64</td>
<td>8.39</td>
</tr>
<tr>
<td>IN-DP</td>
<td>4.17</td>
<td>6.80</td>
<td>4.77</td>
<td>6.80</td>
</tr>
<tr>
<td>MSI</td>
<td>3.75</td>
<td>6.27</td>
<td>4.35</td>
<td>6.27</td>
</tr>
</tbody>
</table>

Martin AJRCCM 2002

---

**Research**

Reevaluation of Diagnosis in Adults With Physician-Diagnosed Asthma

Shawn D. Jarid, MD, Katherine L. Kravchenko, MS, J. Mark Tierney, MD, Martha Arneja, MD, Simon Gatto, MD, Catherine Lemaire, MD, Stephanie V. Fial, MD, R. Andrew McCarroll, MD, Paul Hernandez, MD, Irvin Meyer, MD, Santo Mavromatis, MD, Fernando J. Alvarez, MD, Santo Pollock, MD, Ranjeeta Mallick, PhD, Louis-Philippe Boudreault, MD for the Canadian Respiratory Research Network

JAMA 2017
Called patients "Do you have asthma"?

Spirometry Pre/Post BD
Positive
Asthma Confirmed

Methacholine
Positive
Asthma Confirmed

Stop All Meds
Methacholine
Positive
Asthma Confirmed
Called patients "Do you have asthma?"

- Spirometry Pre/Post BD
  - Positive → Asthma Confirmed

- Methacholine
  - Stop All Meds
  - Positive → Asthma Confirmed

- Methacholine Or worse symptoms
  - 12 Month Follow up
  - Positive → Asthma Confirmed

What percentage of patients had no asthma?
A) 0-10%
B) 10-20%
C) 30-40%
D) 40-50%
E) >50%

Black Box Warning

- Data from a large placebo-controlled U.S. study that compared the safety of salmeterol or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks) versus those on placebo (3 of 13,179)*.

Original Article

Serious Asthma Events with Fluticasone plus Salmeterol versus Fluticasone Alone

Adolescent and adult patients >12 years with persistent asthma were randomized to ICS (fluticasone) vs ICS + LABA (salmeterol) for 26 weeks

All patients had a history of a severe asthma exacerbation in the past year

NEJM 2016
Primary Safety End Point (Intention-to-Treat Population).

![Graph showing probability of freedom from end point over time for Fluticasone-salmeterol and Fluticasone alone.]


Summary of Safety End Points.

<table>
<thead>
<tr>
<th>Safety End Point</th>
<th>Fluticasone-salmeterol (N=5834)</th>
<th>Fluticasone Alone (N=5845)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite safety end point — no. (%)</td>
<td>34 (1-3)</td>
<td>33 (1-1)</td>
</tr>
<tr>
<td>Asthma-related death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asthma-related intubation</td>
<td>0</td>
<td>2 (1-1)</td>
</tr>
<tr>
<td>Asthma-related hospitalization</td>
<td>34 (1-1)</td>
<td>33 (1-1)</td>
</tr>
<tr>
<td>Total no. of asthma-related hospitaliza-</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>tions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause — no. (%)†</td>
<td>3 (1-1)</td>
<td>6 (1-1)</td>
</tr>
</tbody>
</table>

*The analysis was performed in the intention-to-treat population.†Details regarding all-cause mortality are provided in Section 4 in the Supplementary Appendix.*


Asthma Phenotypes

![Diagram illustrating asthma phenotypes with core abnormalities, disease modifiers, asthma endotypes, and treatment options.]

Holder AJRCCM 2009

Fathy, NRI, 2015
Not all asthma is the same!!

(Heterogeneity)

(Phenotypes)

A Large Subgroup of Mild-to-Moderate Asthma Is Persistently Noneosinophilic (NON Allergic)

- Asthma is a heterogeneous disease
- ~50% of asthmatics - poor response to steroids
- Eosinophilic airway inflammation not ubiquitous

Sputum Eosinophil Percentage (No ICS)

McGrath et al (ACRN)
Am J Respir Crit Care Med 185:612–619, 2012
TH2 Genes Overexpressed in Asthma

Th2 Status Predicts Corticosteroid Response

The NEW ENGLAND JOURNAL of MEDICINE

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

- N=135, prednisone ≥ 6 months, eosinophils >300
Type-2 Inhibitors for Severe Asthma

- Anti IL-5 Agents
  - Mepolizumab (NUCALA)*
  - Resilizumab (CINQAIR)*
- Anti IL-13 Agents
  - Lebrikizumab
- Anti IL-4/IL-13
  - Dupilumab
- Anti TSLP
  - AMG 157

* FDA Approved

A Large Subgroup of Mild-to-Moderate Asthma Is Persistently Noneosinophilic (NON Allergic)

- Asthma is a heterogeneous disease
- ~50% of asthmatics - poor response to steroids
- Eosinophilic airway inflammation not ubiquitous

Sputum Eosinophil Percentage (No ICS)

McGrath et al (ACRN)
Am J Respir Crit Care Med 185:612–619, 2012
Alternative Treatment?

Tiotropium Step-Up for Uncontrolled Asthma

Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

Peters et al.

Recommendations:

- In adults with severe asthma – use sputum eos in experienced centers

- In severe allergic asthma – therapeutic trial of omalizumab: Mepolizumab?

- Do not use methotrexate for asthma

- Do not use azithromycin for asthma

Peters et al.
Eur Respir J 43:343-73, 2014

International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

Eur Respir J 43:343-73, 2014
NAEPP GUIDELINES

“If there is a clear and positive response for at least 3 months, a careful step down in therapy should be attempted to identify the lowest dose required to maintain control. (Evidence D)”

Evidence D = Panel Consensus Judgment

Is There Really A Difference Between Asthma And COPD?

GINA GUIDELINES

“Controller treatment may be stopped if the patient’s asthma remains controlled on the lowest dose of controller and no recurrence of symptoms occurs for 1 year (Evidence D)”

Evidence D = Panel Consensus Judgment

Global strategy for asthma management and prevention: GINA executive summary.
Eur Respir J. 2008 Jan;31(1):143-78.

International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

Recommendations:
• Use anti-fungals for ABPA
• Do not use anti-fungals without ABPA
• Consider bronchial thermoplasty only as part of a study

Eur Respir J. 43:343-73, 2014
Pathophysiology in COPD versus Asthma

**COPD**
- Loss of elastic recoil
- Changes in small airways
- “Inflammation”
- Fixed airway obstruction

**Asthma**
- Inflammation
- Bronchial hyperresponsiveness
- Varying airway obstruction

Inflammation in COPD versus Asthma

<table>
<thead>
<tr>
<th>COPD</th>
<th>Predominant Cells</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophages</td>
<td>Eosinophils</td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Activated Mast Cells</td>
<td></td>
</tr>
<tr>
<td>CD-8 T-Lymphocytes</td>
<td>CD-4 T Lymphocytes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Predominant Cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin 8</td>
</tr>
<tr>
<td>Leukotriene B4</td>
</tr>
<tr>
<td>Tumor Necrosis Factor alpha</td>
</tr>
<tr>
<td>Interleukin 4</td>
</tr>
<tr>
<td>Interleukin 5</td>
</tr>
<tr>
<td>Interleukin 13</td>
</tr>
</tbody>
</table>

Calverley, Barnes. AJRCCM 2000; 161:341-344

Asthma Summary

- The “Cause” of asthma remains unknown, but is unlikely to be fully explained by genetics
- Many patients with asthma diagnosis may not have asthma
- LABA are safe to use in asthma patients
- Patients respond differently to medications based upon underlying “endotype/phenotype”
- “Th2-High” or Allergic Asthma responds to corticosteroids
- New Medications are on the way for Severe Allergic Asthma

Calverley, Barnes. AJRCCM 2000; 161:341-344
The Opioid Public Health Problem...

- Pain as the “Fifth Vital Sign”
- US consumes 80% of the world’s opiates
- Pharm companies spent $880 million between 2006 and 2015 to influence federal and state opioid policies
- Abuse deterrent formulations don’t prevent patients from taking higher doses than prescribed; not “abuse-proof”
- Prevalence of heroin use/use disorder increasing

Rates of Prescription Medication Abuse – Ages 12+

<table>
<thead>
<tr>
<th></th>
<th>Ever Use</th>
<th>Use in Last Year (2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Medical Use of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotherapeutics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain Medications</td>
<td>20.5%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Sedatives</td>
<td>13.6%</td>
<td>3.9%</td>
</tr>
<tr>
<td></td>
<td>3%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Opiate Non-Medical Use

- Non-Medical Use = Use without a prescription or for the feeling the drug caused
- Associated with increased mortality (HR 1.60)
- 1960’s: 80% reported first opioid was heroin
- 2000’s: 75% reported first opioid was prescription opioids

Outline

- Substance Use Disorders
  - Definitions
  - Screening
- Pharmacology of Opiates
- Opiate Substance Use Disorder Pharmacotherapy
- Treatment of Non-Cancer Pain
  - Balance risks/benefits of opiate therapy
DSM5 - Substance Use Disorder

- No longer need to differentiate between substance abuse and substance dependence
- Each substance can be categorized as a disorder
  - Ex: Alcohol use disorder, stimulant use disorder, etc
- Grade Severity: Mild, Moderate, Severe

DSM5 - Substance Use Disorder

- “Maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by 2 (or more) of the following, occurring within a 12-month period:"

Criteria for Substance Use Disorder (contd)

- Failure to fulfill role obligations
- Recurrent substance use in situations that are physically hazardous
- Persistent use despite social/interpersonal problems
- Tolerance
- Withdrawal
- Using more than originally intended
- Persistent desire or unsuccessful efforts to cut-down
- Time spent obtaining/using substance or recovering from side effects
- Reduction of social/occupational activities
- Use despite physical/psychological problems
- Craving

DSM5 - Substance Use Disorder

- Of the 11 items:
  - Need 2 criteria for SUD
  - 2-3 criteria =mild SUD
  - 4-5 = moderate SUD
  - ≥6 = severe SUD
Opiate Use - How to Screen?

- Ask permission: “Would it be ok to spend the next few minutes talking about drug use?”
- Single Drug Use Screen Question:
  - How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?
- Positive Screen=1 or more

Smith PC, et al. J Gen Intern Med 2009;24(7); NIAAA Guidelines 2005

A Positive Screen…

- What to do next? Assess…
  - Ask which drugs the patient has been using
  - Determine frequency/amounts
  - Ask about negative impacts

The follow-up questions assess impact and determine whether he/she has a substance use disorder diagnosis.

Determining “At Risk” vs. “Substance Use Disorder”

- Pts with positive screen should get a brief intervention
- Patients who meet substance use disorder criteria abuse should get a
  - Brief intervention
  - A referral to specialty care (if they are willing)
  - Be considered for pharmacotherapy

What is a Brief Intervention?

- Short motivational interviews that encourage patients to create a plan of action that is based on their willingness to change their behavior
- Non-judgmental, direct, honest feedback
- If not ready to change→harm reduction
- Plan for follow-up
- Mixed data for at-risk drug use
**Brief Intervention**

- “You are drinking more than is medically safe”
- “I strongly recommend that you cut down or quit and I’m willing to help”
- “Are you willing to consider making changes in your drinking?”

**Motivational Interviewing**

- Express empathy, develop discrepancy, support self-efficacy
- Tools:
  - Listen for “change talk”
  - Readiness to change ruler
  - Importance/confidence ruler

---

**Background - Types of Opioids**

<table>
<thead>
<tr>
<th>Type</th>
<th>Source</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural Opiates</td>
<td>From the poppy</td>
<td>Morphine, Thebaine, Codeine, Opium</td>
</tr>
<tr>
<td>Semi-Synthetic</td>
<td>From the poppy but processed</td>
<td>Heroin, Oxycodone</td>
</tr>
<tr>
<td>Synthetic</td>
<td>Designed in lab</td>
<td>Methadone, Fentanyl, etc</td>
</tr>
</tbody>
</table>

**Background - Opioid Receptors**

- Found peripherally and centrally
  - Central (brain, spinal cord) most important for controlling pain
- Also bind endogenous opioid peptides (endorphins)
- Several types of opioid receptors, but analgesia largely from action on **mu receptors**
Background - Opioid Receptors

- **Receptor affinity** = strength with which a drug physically binds to receptor
  - Buprenorphine, naloxone, naltrexone have strong affinity
    - Will displace heroin, methadone from mu receptor
- **Receptor dissociation** = the speed of uncoupling of a drug from the receptor
  - Dissociation of buprenorphine and naltrexone is slow

- **Function at receptors** = does drug activate receptor?
  - **Full agonist binding**: highly reinforcing is most misused (ex: heroin)
  - **Antagonist binding**: occupies receptor without activating (ex: naloxone)
  - **Partial agonist binding**: activates receptor at low levels but less reinforcing (so less misused) = buprenorphine

Pharmacotherapies for Opiate Dependence

- Methadone
- Buprenorphine
- Naltrexone

Opioid Dependence Maintenance Therapy: Methadone

- Can only be prescribed through a registered “narcotic treatment program”
- Long acting mu agonist (24-36h)
- Peak levels 4 hours; average half-life 24 hours
- 30-40 mg will block withdrawal, but not craving
- 80-100 mg is more effective at reducing opioid use than lower doses (e.g.: 40-50 mg/d)

Strain EC, et al. JAMA, 1999
### Opioid Dependence Maintenance Therapy: Methadone

- Variable and complex pharmacodynamics so caution with titration
- Many drug interactions
- Side effects
  - Constipation, weight gain, lowered libido
  - Interacts with LOTS of medications
  - QT prolongation (approx 2%)
    - EKG at start, 1 month, every 3-6 months
    - Discontinue if QTc > 490 ms

Strain EC, et al.  JAMA, 1999

### Opioid Dependence Maintenance Therapy: Buprenorphine

- Mu Opioid receptor, high affinity, partial agonist
- Binds opioid receptors; slow to dissociate
- If recent opioids, may withdraw
- OD can’t be reversed with standard dosing of naloxone
- Active metabolite: nor-buprenorphine
- Poor oral bioavailability so given SL, buccal or subdermal
- Half-life > 24 hours

McNicholas, 2004

### Opioid Dependence Maintenance Therapy: Buprenorphine

- Relieves withdrawal symptoms in patients already in withdrawal, less physical dependence capacity
- Can precipitate withdrawal in patients on other opiates
- Little effect on respiration or cardiovascular responses at high doses

McNicholas, 2004

### Opioid Dependence Maintenance Therapy: Buprenorphine

- Dosage Forms of buprenorphine/Naloxone
  - Sublingual
  - Buccal
  - Implant Probuphine (approved 5/26/16)*
- Implant will give steady low-level amount of medication for six months
  - Studied in patients on stable oral dose (8mg or less) for >90 days
  - *Use only in patients “who are already stable on low-to-moderate doses of other forms of buprenorphine, as part of a complete treatment program”
Opioid Dependence Maintenance Therapy: Buprenorphine

- To reduce diversion, combined with naloxone in 4:1 ratio
- Cheaper price than buprenorphine alone!
- Occas increase in LFTs
- SE: N/V (if due to withdrawal), minimal sedation
- Equivalent to lower dose of methadone in reducing illicit opioid use (though 80mg methadone better)
- Buprenorphine DEA certification required to prescribe for opiate use disorder (8 hrs of training)

Opioid Dependence Therapy: Antagonist Treatment (Naltrexone)

- Prevent impulsive use of drug
- Relapse rates high (90%) following detoxification with no medication treatment
- Requires full withdrawal before initiation or severe withdrawal will be precipitated
  - 3-6 days off short-acting
  - 7-10 days off long acting

Opioid Dependence Therapy: Antagonist Treatment (Naltrexone)

- Dose (oral): 50 mg daily, 100 mg every 2 days, 150 mg every third day
- Dose (IM): 380mg IM q month
- Side effects
  - Nausea, headache, dizziness
  - Blocks effect of opioid analgesics
  - Hepatotoxicity, monitor liver function tests every 3 months
  - Biggest issue is lack of compliance
  - Risk of overdose if medication stopped

Case

- 64 yo woman presenting with c/o chronic osteoarthritis in both knees. X-rays are c/w OA. She has a h/o ulcer approximately 3 years ago. She says she needs something for pain as she is not interested in knee replacement. Do you:
  - A) Start her on acetaminophen with codeine
  - B) Refer her to orthopedics anyway
  - C) Start an NSAID with clear precautions on GI side effects
  - D) Try other treatment modalities (PT, tramadol)
**Chronic Pain**

- Over 100 million in US with chronic pain
- Pain plays substantial role in initiating opioids and continuing illicit opioid use
- Almost always multifocal and is almost always accompanied by other symptoms (energy, sleep, memory, mood disturbance)

**Opioids for Non-Cancer Pain**

- Good evidence opioids help with acute pain in the short-term (<6 weeks)
- Opiates prescribed for short-term therapy associated with greater likelihood of long-term use
- No study has evaluated long-term (>1 year) outcomes for chronic non-cancer pain
- Increased risk overdose, abuse, addiction, MI, fractures, road trauma, androgen deficiency

**Opioid Dose and Risk for Overdose**

<table>
<thead>
<tr>
<th>Daily Opioid dose (MSO4 eq)</th>
<th>Hazard Ratio for OD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0.31 (0.12-0.8)</td>
</tr>
<tr>
<td>0 to &lt;20 mg</td>
<td>1</td>
</tr>
<tr>
<td>20 to &lt;50 mg</td>
<td>1.44 (0.57-3.62)</td>
</tr>
<tr>
<td>50 to &lt;100 mg</td>
<td>3.73 (1.47-9.5)</td>
</tr>
<tr>
<td>100+</td>
<td>8.87 (3.90-19.72)</td>
</tr>
<tr>
<td>Any dose</td>
<td>5.16 (2.14-12.48)</td>
</tr>
</tbody>
</table>

Dunn et al. 2010 Annals

**What is a High Dose of an Opioid?**

- Cut-off is not exact
- MSO4 50 mg is about the same as….
  - Codeine 60 mg q4h
  - Hydrocodone/APAP 10/300 5 times a day
  - Methadone 5 mg tid
  - Hydromorphone 4 mg tid
  - Oxycodone/APAP 10 mg/300 tid
  - Oxymorphone ER 7.5 mg bid
  - Fentanyl 25 mcg/hr patch

Opioidcalculator.practicalpainmanagement.com
### Long vs. Short-Acting Opiates and Risk of Overdose

<table>
<thead>
<tr>
<th>Duration of Use</th>
<th>Event Rates/10,000 person years LONG-ACTING</th>
<th>Event Rates/10,000 person years SHORT-ACTING</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>35</td>
<td>15</td>
<td>2.33</td>
</tr>
<tr>
<td>&lt;14 days</td>
<td>143</td>
<td>25</td>
<td>5.25</td>
</tr>
<tr>
<td>15-60 days</td>
<td>36</td>
<td>16</td>
<td>2.30</td>
</tr>
</tbody>
</table>


### Chronic Non-Cancer Pain

- Complete hx and PE to evaluate pain
- Agree on pain control goal and function goal
- Consider non-medication options
  - Lifestyle changes
  - Exercise*/PT
  - Cognitive Behavioral Therapy*, biofeedback
  - Alternative medicine: mindfulness, massage, acupuncture, alternate movement therapies, etc


### Opioids for Non-Cancer Pain – CDC Guidelines

- Non-opioid therapy preferred for treatment of chronic pain
- Only use opioids when benefits > risks
  - Re-evaluate this every 3 months
- Establish treatment goals
- Prescribe the lowest effective doses
- Avoid other risky medications (benzos, other opiates)
- Monitor use and discuss safety


### Treatment Non-Cancer Pain

- Consider non-opiate meds first
  - Tylenol, topical NSAIDS, NSAIDS – best for peripheral nociceptive pain
  - Neuropathic pain: gabapentin, TCAs (nortriptyline), pregabalin, lidocaine patch
  - SNRIs: Duloxetine, milnacipran
  - Diabetic neuropathy: carbamazapine
  - Muscle relaxants
  - Tramadol, tapentadol (weak affinity for Mu receptor)
- Injections, nerve blocks
Reducing Risk for Opioid Prescribing
- Addiction to opiates = interaction between the person at risk and the properties of the drug
- Risk assessment of the patient
- Increased risk doesn’t necessarily rule out opiate therapy but should dictate monitoring of therapy

Opioid Misuse Risk Stratification
- Opioid Risk Tool, Current Opioid Misuse Measure and others
- Stratify to low (not “no”), moderate and high risk
- Some patients may be too risky for opioid analgesics
- Agree on level of monitoring
- Explain risks/benefits of opioid therapy to patients

How To Balance Treating Pain with Risk*
- ID factors for abuse (accuracy limited)
- Pain Agreement to discuss risks of opioids
- Monitor for benefit and risk
  - Regular face-to-face visits
  - Get permission to talk to one family/friend who is NOT on opiates
- Monitor for adherence, addiction, diversion
  - Toxicology screening, get old records
  - Pill counts, PDMP

Building a Patient-Provider Agreement

*For all patients
Establish Treatment Goals - “PEG”
Tracks Benefits of Pain Treatments
Primary goal: not elimination of pain but improvement of function. Document pain score and function at each visit:

On a scale of 0-10, over the last week:

What has your average pain been? (0-10)

How much has your pain interfered with your enjoyment of life? (0-10)

How much has your pain interfered with your general activity? (0-10)

Krebs, 2009

Opiates for Non-Cancer Pain
- Avoid concomitant benzos/sedative-hypnotics
- Initiate with short-acting low dose
  - Don’t increase more frequently than q2 weeks
  - If long-acting, use one with predictable pharmacokinetics (avoid methadone, fent patch)
  - Avoid combining short-and long-acting
  - Avoid escalating doses above 90 mg/d morphine equivalent doses

How To Balance Treating Pain with Opioid Risk?
- Compliance monitoring
  - Pill counts, Utox, Prescription Drug Monitoring Program
- Watch for aberrant behaviors
  - Unsanctioned use, drug seeking behaviors, rx losses, etc
- Re-assess function and goals at each visit
- Check last dosing (for Utox)

Urine Drug Testing
- Test everyone, with frequency standardized according to risk.
  - Morphine equiv 200 mg+ or recent aberrancy: monthly
  - 50-199 mg: quarterly
  - 20-49 mg: annually

### Urine Toxicology Results

- If concern for tampering, order urine creatinine (should be >20)
- Check what type of screening is the best/cheapest in your area
- ALWAYS cause opiate screen to be positive?
  - Heroin, morphine, codeine
- SOMETIMES cause opiate screen to be positive?
  - Hydrocodone, hydromorphone, oxycodone, oxymorphone
- NEVER cause opiate screen to be positive?
  - Buprenorphine, fentanyl, meperidine, methadone, tramadol
  - Check fentanyl immunoassay or methadone screen

Adapted from UCSF Outpatient Handbook, 2014

### When to Taper Prescription Opioids (Non-Cancer Pain)?

- When risks > benefits
- Aberrant behaviors
- If multiple agents, convert to morphine equivalents to calculate total dose
- http://opioidcalculator.practicalpainmanagement.com/
- Reduce long-acting agents first vs. convert to short-acting and taper

Steiger S, Drug Testing FAQ
When to Taper Prescription Opioids (Non-Cancer Pain)?

- **Slow Taper:** reduce dose by 10%/month
  - Minimizes withdrawal sx
- **Rapid Taper**
  - Remove 10-15%/week
  - Indications: substance abuse, loss of control over pill use
  - Consider referral for substance abuse counseling/treatment
- **Immediate Cessation**
  - Overdose, suicide attempt, rx forgery, diversion, other threats

Reducing Risk for All Patients

Which of the following interventions has been demonstrated to reduce rates of overdose in patients prescribed opioids for chronic non-cancer pain?

a) Implementing pill count visits  
b) Random urine toxicology testing  
c) Tapering them to lower doses  
d) Prescription of naloxone

Reducing risk for all patients

- 1985 adults receiving long-term opioid therapy for pain  
- 6 safety-net clinics in SF; 2 year study  
- 38.2% were prescribed naloxone  
  - 47% fewer opioid-related ED visits in the 6 months after prescription  
  - 63% fewer visits after 1 year

- [http://prescribetoprevent.org/prescribers/palliative/](http://prescribetoprevent.org/prescribers/palliative/)

Opioid safety and how to use naloxone

Pain Control in Patients Treated for Opiate Use Disorder

- Patients dependent on methadone/buprenorphine must be maintained on daily equivalence before any analgesic effect is realized with opioids to treat acute pain.
- Opioid analgesic requirements are often higher:
  - Increased pain sensitivity
  - Tolerance

Take Home Points

- Three medications FDA-approved for the maintenance treatment of alcoholism
- Prescription opioids high abuse/misuse potential
- Consider non-opioid treatments for chronic non-cancer pain
- Ongoing monitoring required for opioid prescribing

Thank You!

- Special thanks to Scott Steiger, MD, UCSF
- Resources
  - Local mutual help groups
    - www.ncadi.samhsa.gov (resources)
    - www.aa.org
  - Substance Abuse Facility Treatment Locator Website
    - http://findtreatment.samhsa.gov/
    - https://www.niaaa.nih.gov
Becker WC and Fiellin DA. Abuse deterrent opioid formulations—putting the potential benefits into perspective. NEJM, 2017;376 (22): 2013-2105.


Schneiderhan J, Clauw D and Schwenk TL. Primary care of patients with chronic pain. JAMA, 2017;317(23):2367-2368.


Interventional Cardiology for the Non-Cardiologist: New Innovations and New Guidelines

Krishan Soni, MD, MBA, FACC
Assistant Professor of Medicine
Division of Cardiology

Disclosures

No Conflicts of Interest

Krishan.soni@ucsf.edu
Interventional Cardiology for the Non-Cardiologist

TOPICS

- Anti Platelet Therapy
- Updates on Bioresorbable Scaffolds
- Updates on TAVR
  (Transcatheter Aortic Valve Replacement)

Interventional Cardiology for the Non-Cardiologist

- Major Society Guideline updates 2016-2017
- Clinical Trials Published 2016-2017
- Regulatory News and Events
**Strength of Guideline Recommendations**

<table>
<thead>
<tr>
<th>CLASS I (STRONG)</th>
<th>Benefit &gt;&gt; Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td></td>
</tr>
<tr>
<td>- Is recommended</td>
<td></td>
</tr>
<tr>
<td>- Is indicated/useful/effective/beneficial</td>
<td></td>
</tr>
<tr>
<td>- Should be performed/administered/other</td>
<td></td>
</tr>
<tr>
<td>- Comparative-Effectiveness Phrases:</td>
<td></td>
</tr>
<tr>
<td>- Treatment/strategy A is recommended/indicated in preference to treatment B</td>
<td></td>
</tr>
<tr>
<td>- Treatment A should be chosen over treatment B</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLASS IIa (MODERATE)</th>
<th>Benefit &gt;&gt; Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td></td>
</tr>
<tr>
<td>- Is reasonable</td>
<td></td>
</tr>
<tr>
<td>- Can be useful/effective/beneficial</td>
<td></td>
</tr>
<tr>
<td>- Comparative-Effectiveness Phrases:</td>
<td></td>
</tr>
<tr>
<td>- Treatment/strategy A is probably recommended/indicated in preference to treatment B</td>
<td></td>
</tr>
<tr>
<td>- It is reasonable to choose treatment A over treatment B</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLASS IIb (WEAK)</th>
<th>Benefit &gt; Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td></td>
</tr>
<tr>
<td>- May/might be reasonable</td>
<td></td>
</tr>
<tr>
<td>- May/might be considered</td>
<td></td>
</tr>
<tr>
<td>- Usefulness/effectiveness is unknown/unclear/uncertain or not well established</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLASS III: No Benefit (MODERATE)</th>
<th>Benefit &gt; Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td></td>
</tr>
<tr>
<td>- Is not recommended</td>
<td></td>
</tr>
<tr>
<td>- Is not indicated/useful/effective/beneficial</td>
<td></td>
</tr>
<tr>
<td>- Should not be performed/administered/other</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLASS III: Harm (STRONG)</th>
<th>Risk &gt; Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td></td>
</tr>
<tr>
<td>- Potentially harmful</td>
<td></td>
</tr>
<tr>
<td>- Causes harm</td>
<td></td>
</tr>
<tr>
<td>- Associated with excess morbidity/mortality</td>
<td></td>
</tr>
<tr>
<td>- Should not be performed/administered/other</td>
<td></td>
</tr>
</tbody>
</table>

---

**Acronyms**

- **ACS**: Acute Coronary Syndrome
- **BMS**: Bare Metal Stent
- **CAD**: Coronary Artery Disease
- **CABG**: Coronary Artery Bypass Graft Surgery
- **DAPT**: Dual Antiplatelet Therapy
- **DES**: Drug Eluting Stent
- **PCI**: Percutaneous Coronary Intervention
- **PPI**: Proton Pump Inhibitor
- **SIHD**: Stable Ischemic Heart Disease
- **TAVR**: Transcatheter Aortic Valve Replacement
Interventional Cardiology for the Non-Cardiologist

TOPICS
- Anti Platelet Therapy
- Updates on Bioresorbable Scaffolds
- Updates on TAVR
  (Transcatheter Aortic Valve Replacement)

Antiplatelet Agents

<table>
<thead>
<tr>
<th></th>
<th>Aspirin</th>
<th>Clopidogrel (Plavix)</th>
<th>Prasugrel (Effient)</th>
<th>Ticagrelor (Brilinta)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>ACS Post PCI Stroke PVD</td>
<td>ACS Post PCI Stroke PVD</td>
<td>Post PCI</td>
<td>ACS Post PCI</td>
</tr>
<tr>
<td><strong>Dose Load Maintenance</strong></td>
<td>325 mg 81 mg DAILY</td>
<td>300-600 mg 75 mg DAILY</td>
<td>60 mg 10 mg DAILY</td>
<td>180 mg 90 mg BID</td>
</tr>
<tr>
<td><strong>Class</strong></td>
<td>NSAID</td>
<td>2nd gen thienopyridine (PRODRUG)</td>
<td>2nd gen thienopyridine (PRODRUG)</td>
<td>CTPT</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>IRREVERSIBLE COX 1</td>
<td>IRREVERSIBLE P2Y12</td>
<td>IRREVERSIBLE P2Y12</td>
<td>REVERSIBLE P2Y12</td>
</tr>
<tr>
<td><strong>Peak Effect</strong></td>
<td>1-3 hours</td>
<td>6 hours</td>
<td>4 hours</td>
<td>2 hours</td>
</tr>
<tr>
<td><strong>CYP Metab</strong></td>
<td>NA</td>
<td>2C19</td>
<td>3A4</td>
<td>3A4/5</td>
</tr>
</tbody>
</table>
Aspirin Dosing in Patients with Coronary Artery Disease (CAD)

Aspirin Dosing in Patients Treated With DAPT

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.</td>
</tr>
</tbody>
</table>

- Higher doses of aspirin are associated with bleeding and no increased anti-ischemic benefit
- When used with ticagrelor (Brilinta), aspirin doses of >100 mg are contraindicated
According to US Guidelines, how long should patients be on Dual Antiplatelet Therapy (DAPT) after PCI with a Drug Eluting Stent?

A. 3 months  
B. 6 months  
C. 12 months  
D. It depends on the indication for PCI  
E. Call a cardiology consult

Duration of Dual Antiplatelet Therapy (DAPT)

- Duration of DAPT depends on:
  - Underlying condition  
  - Treatment provided

Stable Ischemic Heart Disease (SIHD)  
Acute Coronary Syndromes (ACS)
**Duration of Dual Antiplatelet Therapy (DAPT) in Patients with ACS**

1. **Recent ACS (NSTEMI or STEMI)**
   - CABG
   - Medical Therapy
   - Lytic (STEMI)
   - PCI (BMS or DES)

2. **Stabilization**
   - After CABG, restart DAPT, consider to complete 1 year of DAPT.
   - After PCI with BMS, restart DAPT, consider completion.

3. **Stabilization**
   - After PCI with DES, restart DAPT, consider completion.

### Stopping early
- At 6 months
- At 3 months
- At 1 month
- At 0 months

**Class I**
- No high risk of bleeding and no significant event bleeding on DAPT.
- >12 mo may be reasonable.

**Class IIIa**
- Desirability of shortening duration if 6 mo may be reasonable.

**Class IIIb**
- Desirability of further continuation may be reasonable.

---

**Duration of Dual Antiplatelet Therapy (DAPT) in Patients with SIHD**

1. **Stable Ischemic Heart Disease (SIHD)**
   - PCI with Bare Metal Stent (BMS)
   - PCI with Drug Eluting Stent (DES)

2. **Stopping early**
   - At 3 months

**Class I**
- At least 12 mo (stentless)
- >12 mo (stentless)

**Class IIa**
- At least 6 mo and up to 10 mo (stentless)

**Class III**
- At least 12 mo (stentless)
- Completion of DAPT.

**Class IIIa**
- At least 12 mo (stentless)
- >12 mo (stentless)

**Class IIIb**
- Desirability of further continuation may be reasonable.

**Class IIIc**
- High bleeding risk or significant event bleeding.

---
When should DAPT therapy be continued for LONGER Duration?

**Risk of Ischemia**
- Increased risk of stent thrombosis
- ACS presentation
- Diabetes mellitus
- Left ventricular ejection fraction <40%
- First-generation drug-eluting stent
- Stent undersizing
- Stent underdeployment
- Small stent diameter
- Greater stent length
- Bifurcation stents
- In-stent restenosis

**Risk of Bleeding**
- Increased Bleeding Risk (may favor shorter-duration DAPT)
  - History of prior bleeding
  - Oral anticoagulant therapy
  - Female sex
  - Advanced age
  - Low body weight
  - CKD
  - Diabetes mellitus
  - Anemia
  - Chronic steroid or NSAID therapy

The DAPT Score can guide risk / benefit of longer therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥75 y</td>
<td>-2</td>
</tr>
<tr>
<td>Age 65 to &lt;75 y</td>
<td>-1</td>
</tr>
<tr>
<td>Age &lt;65 y</td>
<td>0</td>
</tr>
<tr>
<td>Current cigarette smoker</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>MI at presentation</td>
<td>1</td>
</tr>
<tr>
<td>Prior PCI or prior MI</td>
<td>1</td>
</tr>
<tr>
<td>Stent diameter &lt;3 mm</td>
<td>1</td>
</tr>
<tr>
<td>Paclitaxel-eluting stent</td>
<td>1</td>
</tr>
<tr>
<td>CHF or LVEF &lt;30%</td>
<td>2</td>
</tr>
<tr>
<td>Saphenous vein graft PCI</td>
<td>2</td>
</tr>
</tbody>
</table>

**Score ≥2**
Favorable benefit/risk
For prolonged DAPT

**Score <2** NOT
Favorable benefit/risk
For prolonged DAPT
Which P2Y12 Agent should I recommend?

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>B-8</td>
<td>In patients with ACS (NSTEMI or STEMI) treated with DAPT after coronary stent implantation and in patients with NSTEMI treated with medical therapy alone (without revascularization), it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y12 inhibitor therapy (53,71,72).</td>
</tr>
<tr>
<td>Ia</td>
<td>B-8</td>
<td>In patients with ACS (NSTEMI or STEMI) treated with DAPT after coronary stent implantation who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel for maintenance P2Y12 inhibitor therapy (54,55).</td>
</tr>
<tr>
<td>IIb</td>
<td>B-8</td>
<td>Prasugrel should not be administered to patients with a prior history of stroke or TIA (54).</td>
</tr>
</tbody>
</table>

For Medically Managed ACS

- Ticagrelor *(Brilinta)* Recommended over Clopidogrel *(Plavix)*

For ACS with PCI

- Ticagrelor *(Brilinta)*
- Prasugrel *(Effient)*

Recommended over Clopidogrel *(Plavix)*

What’s the update on triple therapy?

**TABLE 6** Summary and Synthesis of Guideline, Expert Consensus Documents, and Comprehensive Review Article Recommendations on the Management of Patients Treated With Triple Therapy (14,68,91-93)

- Assess ischemic and bleeding risks using validated risk predictors (e.g., CHA2DS2-VASc, HAS-BLED)
- Keep triple therapy duration as short as possible; dual therapy only (oral anticoagulant and clopidogrel) may be considered in select patients
- Consider a target INR of 2.0-3.5 when warfarin is used
- Clopidogrel is the P2Y12 inhibitor of choice
- Use low-dose (<100 mg daily) aspirin
- PPIs should be used in patients with a history of gastrointestinal bleeding and are reasonable to use in patients with increased risk of gastrointestinal bleeding

CHADS2-VASc indicates congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65-74 years, sex category; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, liable INR, elderly, drugs/ Alcohol concurrently; INR, international normalized ratio; and PPIs, proton pump inhibitors.

- **For patients who require triple therapy:**
  - Use Coumadin (keep INR at low end of range)
  - Use Clopidogrel
  - Use low dose aspirin
  - Consider PPI
65 yo man underwent PCI with a drug eluting stent to the LAD 2 months ago for stable angina. He now has severe knee osteoarthritis and is asking you when he can have surgery. How long after his stent should he wait?

A. 1 month  
B. 3 months  
C. 6 months  
D. 12 months  
E. He should be managed medically indefinitely

Perioperative Management and Timing of Non Cardiac Surgery

Wait at least 3 months and preferably 6 months after PCI with DES

Wait 30 days after PCI with BMS
Perioperative Management and Timing of Non Cardiac Surgery

**How long before surgery should DAPT be stopped?**
- **CONTINUE ASPIRIN** if possible!
- **STOP Clopidogrel**: 5 days prior to surgery
- **STOP Ticagrelor**: 5 days prior to surgery
- **STOP Prasugrel**: 7 days prior to surgery

Class IIb (Level C)
Extrapolated from 2013 ACC/AHA STEMI Guidelines
Key Points Regarding DAPT (1/3)

- Dose of Aspirin for all patients is **81 mg daily**
- Duration of DAPT:
  - ACS Patients: **1 YEAR for ALL** (with/without stent)
  - SIHD (Stable Ischemic Heart Disease) Patients:
    - Drug Eluting Stent (DES): **6 MONTHS**
    - Bare Metal Stent (BMS): **1 MONTH**
- Stopping Early:
  - DAPT could be stopped **3 months** after DES (drug eluting stent) for high bleeding risk patients
- Longer Therapy:
  - Risk benefit between bleeding and ischemia
  - DAPT score can be helpful

Key Points Regarding DAPT (2/3)

- Choice of Agents:
  - Medical Management of **ACS**: Ticagrelor > Plavix
  - PCI in ACS: Ticagrelor or Prasugrel > Plavix
  - Do NOT USE Prasugrel if history of **stroke or TIA**
- Triple Therapy:
  - Short Duration
  - Use clopidogrel/coumadin
  - Target INR 2-2.5
  - Use PPI (Proton Pump Inhibitor)
**Key Points Regarding DAPT (3/3)**

- **Timing of Non-Cardiac Surgery:**
  - Ideally > 1 month after BMS, 6 months after DES
  - **Continue Aspirin** if possible
  - **Hold:**
    - Clopidogrel **5 days** prior to surgery
    - Ticagrelor **5 days** prior to surgery
    - Prasugrel **7 days** prior to surgery

---

**Interventional Cardiology for the Non-Cardiologist**

**TOPICS**

- Anti Platelet Therapy
- **Updates on Bioresorbable Scaffolds**
- **Updates on TAVR**
  (Transcatheter Aortic Valve Replacement)
Limitations of current Metallic Stents

- The standard of care for PCI for the last decade has been metallic stents
  - Bare Metal or Drug Eluting

- Metallic stents have **disadvantages**:
  - Rigid metallic cages hamper vasomotion
  - Development of neoatherosclerosis
    - Risk of stent thrombosis 0.1-0.2%/yr
    - Risk of repeat revascularization 2-3%/yr
  - Delayed stent endothelialization
  - Permanent implant cannot be removed

Bioresorbable Vascular Scaffold (BVS): ABSORB

- NO Permanent Implant!
  - Allows for restoration of vessel function (theoretical benefit)
  - Maintain option for future surgery (CABG)
  - Fewer permanent layers of metal in patients requiring treatment for stent restenosis (ISR)

**ABSORB GT1 (Abbott Vascular)**

Absorbable polymer, poly (L-lactide) (PLLA) with **everolimus** drug coating
A 52 yo M has ongoing CCS Class III stable angina despite maximal medical therapy. Coronary angiography demonstrates a 90% focal RCA lesion. He is considering PCI and requests your opinion regarding a bioresorbable stent. What do you tell him?

A. “It’s the latest and greatest, go for it”
B. “The risks and benefits appear to be similar to current metallic stents.”
C. “Steer Clear, at least for now!”

---

ABSORB III Trial: BVS comparable to DES

2008 patients with stable or unstable angina randomly assigned in a 2:1 ratio to receive Absorb or an everolimus-eluting cobalt–chromium (Xience) stent

- Primary end point: target-lesion failure (cardiac death, target-vessel myocardial infarction, or ischemia-driven target-lesion revascularization) at 1 year
**ABSORB III Results**

- Target lesion failure non-inferior for ABSORB
- No difference in cardiac death at 1 (0.6% vs 0.1% p=0.29)
- Signal for increase in stent thrombosis at 1 year (1.5% vs 0.7%, p=0.13)

**Follow up data shows higher Stent Thrombosis (March 2017)**

- AIDA trial showed significantly higher stent thrombosis
  - 27 events vs 5!
The fate of ABSORB

Results from 2 year follow up of ABSORB shown at American College of Cardiology Meeting (3/2017):

- Target Lesion Failure: 11.0% vs 7.9% (significant)
- Target Vessel Myocardial Infarction: 7.3% vs 4.9% (p=0.04)
- Stent Thrombosis: 1.9 vs 0.8%

The fate of ABSORB

Sales Halted September 2017
Key Points Regarding BVS

- Data through 2 years demonstrate a significantly higher risk of stent thrombosis with ABSORB bioresorbable vascular scaffold (BVS)
- FDA warning letter issued MARCH 2017
- ABSORB withdrawn from sale SEPTEMBER 2017

Bioresorbable Vascular Scaffolds May Not be Ready for Primetime

Interventional Cardiology for the Non-Cardiologist

TOPICS
- Anti Platelet Therapy
- Updates on Bioresorbable Scaffolds
- Updates on TAVR (Transcatheter Aortic Valve Replacement)
An 82 yo lady presents to your office with severe shortness of breath while walking from her bed to the bathroom. She appears frail. On exam, you hear a 3/6 mid systolic murmur. She has 1+ LE edema at the shins. Echo shows severe aortic stenosis with LVEF 35%. What do you recommend?

A. Surgical Aortic Valve Replacement
B. Transcatheter Aortic Valve Replacement
C. Medical Therapy
D. Hospice
E. Ask my local cardiologist

Aortic Stenosis

◆ Degree of Aortic Stenosis is determined by Echocardiography
◆ Symptoms are key!

<table>
<thead>
<tr>
<th>AHA Guidelines for Severity of Aortic Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve Area (cm²)</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td>Critical</td>
</tr>
</tbody>
</table>
### 2014 ACC/AHA Valvular Heart Disease (VHD) Guidelines

#### Concept of Valve Disease Stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At risk</td>
<td>Patients with risk factors for the development of VHD</td>
</tr>
<tr>
<td>B</td>
<td>Progressive</td>
<td>Patients with progressive VHD (mild-to-moderate severity and asymptomatic)</td>
</tr>
<tr>
<td>C</td>
<td>Asymptomatic severe</td>
<td>Asymptomatic patients who have reached the criteria for severe VHD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C1: Asymptomatic patients with severe VHD in whom the left or right ventricle remains compensated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C2: Asymptomatic patients who have severe VHD, with decompensation of the left or right ventricle</td>
</tr>
<tr>
<td>D</td>
<td>Symptomatic severe</td>
<td>Patients who have developed symptoms as a result of VHD</td>
</tr>
</tbody>
</table>

Valve replacement indicated for Stage C2 and D

---

#### Aortic Stenosis – Progression of Disease

![Image showing progression of aortic stenosis]

*Intervening on patients with severe symptomatic AS improves survival*
5 year survival of breast cancer, lung cancer, prostate cancer, ovarian cancer and severe inoperable aortic stenosis

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>5-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>23</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>4</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>12</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>30</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>28</td>
</tr>
<tr>
<td>Severe Inoperable AS*</td>
<td>9</td>
</tr>
</tbody>
</table>

*Using constant hazard ratio. Data on file, Edwards Lifesciences LLC. Analysis courtesy of Murat Tucuo, MD, Cleveland Clinic

High Risk Patients Previously Untreated

2. Iung B et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. European Heart Journal 2003;24:1231-1243 (*includes both Aortic Stenosis and Mitral Regurgitation patients)
TAVR Approved by FDA in US in 2011

Multiple TAVR Valve Platforms have been developed

Two valves commercially available in US

**Edwards Sapien S3**
- Transfemoral, transpical, transaortic delivery
- Balloon expandable system

**Medtronic CoreValve**
- Transfemoral or subclavian delivery
- Repositionable, self-expanding system
Inoperable PARTNER Cohort
Primary Endpoint: All-Cause Mortality

Delta at 1 yr = 20.0%
NNT = 5.0 pts
50.7%
30.7%

Leon et al, NEJM 2010; 363:1597-1607

Numbers at Risk

<table>
<thead>
<tr>
<th></th>
<th>TAVR</th>
<th>Standard Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>348</td>
<td>298</td>
</tr>
<tr>
<td>6</td>
<td>298</td>
<td>260</td>
</tr>
<tr>
<td>12</td>
<td>260</td>
<td>147</td>
</tr>
<tr>
<td>18</td>
<td>260</td>
<td>67</td>
</tr>
<tr>
<td>24</td>
<td>260</td>
<td>24.2</td>
</tr>
<tr>
<td>30</td>
<td>260</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>260</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>260</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>260</td>
<td></td>
</tr>
</tbody>
</table>

Primary Endpoint:
All-Cause Mortality at 1 Year

HR [95% CI] = 0.93 [0.71, 1.22]
P (log rank) = 0.62
CoreValve US Pivotal Trial High Risk Study
3-Year Outcomes (All Cause Mortality)

- Lower all cause mortality for TAVR group

CoreValve US Pivotal Trial High Risk Study
3-Year Outcomes (Stroke)

- Lower stroke for TAVR group
**TAVR for High Risk and Inoperable Patients**

**KEY POINT:**

For high risk and inoperable patients, TAVR is better than medical therapy and equivalent or better than surgery.
TAVR has been studied across the risk spectrum of patients

Two-thirds of patients are optimal surgical candidates

**Low Risk**
- STS PROM < 4%
- 30-Day Mortality < 2-4%

Surgical Aortic Valve Replacements 70-90,000 yearly

**Intermediate Risk**
- STS 4-8

**High Risk**
- STS ≥8

Approved 2011

Futility

Studied 2016

Inoperable 20-50K

Pivotal Trials for Intermediate Risk TAVR

**The NEW ENGLAND JOURNAL OF MEDICINE**

Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients


for the SURTAVI Investigators®

Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients


for the SURTAVI Investigators®
SURTAVI Trial (NEJM 2017)

- TAVR with self expanding valve vs surgery (SAVR)
- Intermediate Risk Patients (STS Score 4-8)
- Severe Symptomatic Aortic Stenosis

- Randomized Controlled Non-Inferiority Trial
- Primary Endpoint: Composite of Death or disabling stroke at 24 months

- 1746 patients randomized (1660 underwent valve replacement)
- 87 centers

SURTAVI Trial (NEJM 2017) - Results

- Primary outcome met!

- Death/Stroke at 24 months: 12.6% vs 14%

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Month</th>
<th>TAVR</th>
<th>Surgery</th>
<th>95% CI for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAVR</td>
<td>0</td>
<td>864</td>
<td>796</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>755</td>
<td>674</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>612</td>
<td>555</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>456</td>
<td>407</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>272</td>
<td>241</td>
<td></td>
</tr>
</tbody>
</table>
SURTAVI Trial (NEJM 2017) - Results

Mortality similar (11.4% vs. 11.6%)
• Stroke numerically lower in TAVR (2.6% vs. 4.5%)

The Tradeoff is higher rates of vascular complication and pacemaker implantation
TAVR for Intermediate Risk Patients

KEY POINT:

For intermediate risk patients, TAVR is as effective as surgical repair, but has higher rates of pacemaker implantation and vascular injury.

What should a Primary Care Doctor know about TAVR patients?

ACC CLINICAL DOCUMENT

2017 ACC Expert Consensus Decision Pathway for Transcatheter Aortic Valve Replacement in the Management of Adults With Aortic Stenosis

A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents

Nishimura, et al.
2017 VHD Focused Update

2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines
**Point 1: Risk Evaluation Should Include STS Score (Risk of Mortality), Frailty and Comorbidities**

- **Low risk**
  - STS-PROM <4% and
  - No frailty and
  - No comorbidity and
  - No procedure specific impediments

- **Intermediate risk**
  - STS-PROM 4%-8% or
  - Mild frailty or
  - 1 major organ system compromise not to be improved postoperatively or
  - A possible procedure-specific impediment

- **High risk**
  - STS-PROM >8% or
  - Moderate-severe frailty or
  - >2 major organ system compromises not to be improved postoperatively or
  - A possible procedure-specific impediment

- **Prohibitive risk**
  - PROMM >50% at 1 year or
  - >3 major organ system compromises not to be improved postoperatively or
  - Severe frailty
  - Severe procedure-specific impediments

STS - PROM = Predicted Risk of Mortality (30 Day)
Calculated at [http://riskcalc.sts.org/](http://riskcalc.sts.org/)

---

**Point 2: Intermediate risk patients are now indicated for TAVR (IIa)**

AS indicates aortic stenosis; AVR, aortic valve replacement, and TAVR, transcatheter aortic valve replacement.
Point 3: Long-Term Follow up for TAVR Patients Defined

<table>
<thead>
<tr>
<th>5.4.2 Long-Term Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing</strong></td>
</tr>
<tr>
<td>□ TAVR team at 30 days</td>
</tr>
<tr>
<td>□ Primary cardiologist at 6 months and then annually</td>
</tr>
<tr>
<td>□ Primary care MD or geriatrician at 3 months and then as needed</td>
</tr>
<tr>
<td><strong>Antithrombotic therapy</strong></td>
</tr>
<tr>
<td>□ ASA 75 mg-100 mg daily lifelong</td>
</tr>
<tr>
<td>□ Clopidogrel 75 mg daily for 3-6 months</td>
</tr>
<tr>
<td>□ Consider warfarin (INR 2.0-2.5) if at risk of AF or VTE</td>
</tr>
<tr>
<td><strong>Concurrent cardice disease</strong></td>
</tr>
<tr>
<td>□ Coronary disease</td>
</tr>
<tr>
<td>□ Hypertension</td>
</tr>
<tr>
<td>□ Heart failure</td>
</tr>
<tr>
<td>□ Arrhythmias (especially AF)</td>
</tr>
<tr>
<td>□ Manage cardiac risk factors (including diet and physiological activity)</td>
</tr>
<tr>
<td><strong>Monitor for post-TAVR complications</strong></td>
</tr>
<tr>
<td>□ Echocardiography at 30 days then annually (if needed)</td>
</tr>
<tr>
<td>□ ECG at 30 days and annually</td>
</tr>
<tr>
<td>□ Consider 24 h ECG if bradycardia</td>
</tr>
<tr>
<td><strong>Dental hygiene and antibiotic prophylaxis</strong></td>
</tr>
<tr>
<td>□ Encourage optimal dental care</td>
</tr>
<tr>
<td>□ Antibiotic prophylaxis per AHA/ACC guidelines</td>
</tr>
</tbody>
</table>

Point 4: Endocarditis prophylaxis after TAVR

Patients with Transcatheater valves should receive endocarditis prophylaxis prior to dental procedures

- Infective Endocarditis (IE) has been reported to occur after TAVR at rates equal to or exceeding those associated with surgical aortic valve replacement (AVR)
- TAVR IE is associated with a high 1-year mortality rate of 75%

**Point 5: Anticoagulation after TAVR**

Anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for at least 3 months after TAVR in patients at low risk of bleeding.

- Studies have shown that valve thrombosis may develop in patients after TAVR, as assessed by CT scanning (7-40%).
- Valve thrombosis occurs in patients who received antiplatelet therapy alone but not in patients who were treated with VKA.

**Point 6: Antiplatelet Therapy after TAVR**

Clopidogrel 75 mg daily may be reasonable for the first 6 months after TAVR in addition to life-long aspirin 75 mg to 100 mg daily.
Key Points Regarding TAVR (1/2)

- Risk assessment for patients should include STS Score, Frailty and Comorbidities

- For Patients with Symptomatic Severe Aortic Stenosis (Stage D) whose risk for surgical valve replacement is:
  - **Inoperable**: TAVR has a **CLASS I** indication
  - **High Risk**: TAVR has a **CLASS I** Indication
  - **Intermediate Risk**: TAVR is reasonable (**CLASS IIa**) 
    - Risks for pacemaker placement are high
    - Risk for vascular complications remain elevated
  - **Low Risk**: Surgery is Preferred

Key Points Regarding TAVR (2/2)

- Patients with a TAVR valve should receive prophylaxis for endocarditis (**CLASS IIa**) 

- Anticoagulation with a VKA antagonist (Coumadin) may be reasonable for 3 months after TAVR to prevent valve thrombus (**Class IIb**) 

- Clopidogrel 75 mg daily for 6 months and ASA 81 mg daily for life may be reasonable after TAVR (**Class IIb**)
**What Have We Learned?**

**Dual Antiplatelet Therapy**
- Duration of DAPT after ACS and PCI
- Choice of Antiplatelet Agents
- An Approach to Triple Therapy with Anticoagulation and DAPT
- Timing of Non Cardiac Surgery after PCI

**BioResorbable Stents**
- Bioresorbable Stents are not ready for primetime!

---

**What Have We Learned?**

**Transcatheter Aortic Valve Replacement (TAVR)**
- TAVR is now indicated for intermediate risk patients with Symptomatic Severe Aortic Stenosis
  - Rates of pacemaker implantation and vascular injury are higher with TAVR compared to surgery
- Patients with TAVR valves should receive endocarditis prophylaxis
- Antiplatelet agents and VK antagonists may be considered for use after TAVR implantation
Questions?

References

Guidelines


Trials

Thank You!

Questions / Final syllabus:

Email Krishan Soni @

Krishan.soni@ucsf.edu

415-476-6541
Communication Skills for Enhancing Patient and Provider Outcomes

Disclosures
- I have no conflict of interest
- No disclosures

Agenda
- Agenda Setting
- Conflict
  - Eliciting the other’s perspective
  - Distinguishing Interests vs Positions
  - Responding to emotion
- Teachback

Burnout
Case

- CC: “I need more oxycodone”
- 56 year old woman with a history of chronic pain from a remote motor vehicle accident, s/p 2 lumbar spine surgeries, HTN, and prediabetes, on oxycodone for many years, presenting for follow up.

- “My back is killing me doc. I need more oxycodone. I can’t get through the day without it. I need an early refill.”

What are you likely to say next...

- A. “That sounds terrible. I want to help. Tell me more about your back pain...”
- B. “That sounds terrible. I want to help, but I’m not sure more oxycodone will be the right solution for you. Let’s be sure to talk about other options...”
- C. “That sounds terrible. Before we dive deeper, I’d like to get a list of the other concerns that you have today...”
- D. “That sounds terrible, but I can’t do early refills, it’s our clinic policy. I’m so sorry.”

Agenda Setting

- Get the ENTIRE list of concerns up front

- “Sounds like your back is really bothering you. I want to hear more about that in a moment. Before we dive in, what other concerns do you have that you would like to try to address today during our visit?”

- “Yes, I’m hearing your back pain is bad and something we should definitely talk more about. Before we go further, I’d like to get a list of the other concerns you’d like to discuss today.”
Agenda Setting

- Then, inviting further items to complete the list - “Is there something else?” until all concerns are exhausted.

- “Something else” vs “Anything else”
  - Using “Something else” decreased unmet concerns by 78%.
  - Using “Anything else” was no different than controls.

- “I’ve got some samples”
- “I haven’t got any samples.”

- “I haven’t got some samples.”
- “I’ve got any samples.”


Agenda Setting

- Why do it?
  - Fewer “doorknob” questions
  - Patients feel we explain things in a way they can understand
  - Providers feel a greater sense of control of the visit
  - Patient’s don’t often lead with what is most important to them or see that some concerns may be related

- Don’t we already do this?
  - Only 32% of the time...


Interrupting (effective re-direction)

- EEE
  - Excuse – Empathize – Explain
  - Excuse me for a moment. Your back has been painful. Before we talk further about this pain, I’d like to know if you have something else important to address today. This way you and I can figure out how to make the best use of our time.
  - Excuse me, your back pain sounds distressing, but we were only part way through addressing your asthma. How about we finish the asthma and then see if there is time for your back pain?


Case Revisited

- A. “That sounds terrible. I want to help. Tell me more about your back pain...”
- B. “That sounds terrible. I want to help, but I’m not sure more oxycodone will be the right solution for you. Let’s be sure to talk about other options...”
- C. “That sounds terrible. Before we dive deeper, I’d like to get a list of the other concerns that you have today...”
- D. “That sounds terrible, but I can’t do early refills, our clinic policy. I’m so sorry.”
### Case Revisited

- Patient: “Well, I can’t sleep at night. I am waking up and can’t get comfortable.”
- Provider: “The pain affects your sleep. What else?”
- Patient: “Well no, my sheets are all wet at night. In fact, my husband slept on the couch last night”
- Provider: “And was there something else?”
- Patient: “I’m having some trouble walking.”
- Provider: “Okay, what other concerns do you have?”
- Patient: “That’s about it.”

### Agenda Setting

- Ask for “the list”
- Use “What Else”
- If need to interrupt, consider EEE
- Just do it

### Conflict

- Ladder of Inference
- Eliciting the other’s perspective
- Distinguishing interests from positions
- Responding to emotion BEFORE seeking solutions
Conflict

Joint Commission ‘09 ~ 70% of sentinel events traced to a problem with communication

ACP Physician survey (n= 840):
- More than 70% observed disruptive MD behavior at least monthly, 10% daily
- 99% stated conflict negatively impacted pt care

Senior medical professionals interviewed at 2 tertiary care teaching hospitals estimated that half of MD time is spent in conflict


Case

You are seeing Mr. Smith in clinic, a 56 y/o man with LBP
- His pain is acute, fairly severe, he has no red flag symptoms and a normal exam other than paraspinal tenderness
- He requests an MRI and you think it isn’t indicated
- You feel his request is a challenge to your authority
- As the encounter goes on, you start to feel angry that he is putting you in this position and annoyed at how entitled he is
- You start to feel resentful because now you are running behind
- You just want the visit to end
- You refuse the MRI and you both leave the encounter frustrated
- After the visit, you dread having to see Mr. Smith again

The Ladder of Inference

Provider’s View | Mr Smith’s View
---|---
**Conclusion**
I don’t like this patient | I am so glad I have a caring doc

**Reasoning**
Trying to understand entitled patients is a waste of time | My doctor will certainly order one

**Assumptions**
When patients ask for things that aren’t indicated, they are entitled | The only way to really know how to treat this is to get an MRI.

**Directly Observable Data**
Mr. Smith requests an MRI | I’m in so much pain and I want to enjoy my vacation next week that I’ve planned for a year
Trying to climb down the ladder...

- “Sounds like you think an MRI is going to be important here. Help me understand your perspective on that...”

- Try to break the “ICE” – Ideas, Concerns, Expectations
  - “What ideas do you have about what is causing your pain?”
  - “What concerns you the most about this?”
  - “What are you expecting we can accomplish today?”

Positions vs Interests

<table>
<thead>
<tr>
<th>Positions</th>
<th>Interests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positions</td>
<td>Interests</td>
</tr>
<tr>
<td>80:20 rule</td>
<td></td>
</tr>
</tbody>
</table>

Distinguish interests from positions

**Position:** What we say we want

**Interests:** All the things we care about (often intangible)

**Positions**
- “I want an MRI”
- “I want more dilaudid”
- “I want to see a specialist”

**Interests**
- To know when I will feel better
- To do the activities that give me joy
- Reassurance that it’s not cancer
Offer some PEARLS©

- **Partnership:** Let’s work together on this.
- **Emotion:** I imagine how frustrating this is for you.
- **Apology:** I’m sorry to hear how difficult this is.
- **Respect:** I give you a lot of credit for getting through this as you have.
- **Legitimization:** Most people in your position would feel this same way.
- **Support:** I’m going to stick with you through this.

Empathy Enhances Efficiency

<table>
<thead>
<tr>
<th>Made empathic statements</th>
<th>Didn’t make empathic statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internists</td>
<td>17.6 min visits</td>
</tr>
<tr>
<td>Surgeons</td>
<td>12.5 min visits</td>
</tr>
</tbody>
</table>

Levinson et al. A Study of Patient Clues and Physician Responses in Primary Care and Surgical Settings. JAMA. 2000;284:1021-1027

Case Revisited

- Provider: “Sounds like you think an MRI is important here. Help me understand that.”
- Patient: “Well, actually, my wife said I should ask. To be honest, I just want to feel better during my vacation next week and try to find a way to keep this from happening again.”
- Provider: “Sounds like we should focus on controlling your pain and talk about some prevention strategies?”
- Patient: “Yeah”
- Provider: “Let’s work together to find a way to treat your pain so you can enjoy your vacation. Also, having heard your concerns and completing the physical exam, I have a good idea of what is causing your pain and an MRI isn’t going to help us right now. Can I share with you what I think is happening with your back and then talk about pain relief options?”
- Patient: “Yes, please do.”

Conflict

- Climb down the Ladder of Inference
- Elicit the other’s perspective
  - “Help me understand”
  - ICE – Ideas, Concerns, Expectations
- Distinguish interests from positions
- Respond to emotion (before fixing)
"The single biggest problem in communication is the illusion that it has taken place."
—George Bernard Shaw

At the end of a busy clinic session, Dr. Brash angrily heads back to his office. He slams down his stethoscope and exclaims, "Why are patients always so noncompliant? Why don't they do what I tell them to do? They just don't want to be helped!"

"Sounds frustrating," says his colleague sympathetically. "What happened?"

"One of my patients, Ms. Jones, clearly has the classic signs of clinical depression and anxiety. She's even having panic attacks. Last visit I started her on an antidepressant, but this time, six weeks later, she hasn't even touched it! I remember I went over all of the reasons she should be on it, and I even went over side effects. How does she expect to get any better if she doesn't take the medication? I just don't get it!"

6 weeks earlier...

After presenting with fatigue, insomnia, poor concentration, episodic palpitations, chest tightness and occasional SOB and completing an exam...

Dr. Brash: Ms. Jones, I'm going to prescribe a medication for you that will help you feel better. It's an antidepressant and should also help with the anxiety. You should start taking half a pill in the morning, and then after a week, as long as you don't have any side effects, you can go up to a full pill. The most common side effects are feeling a little jumpy, which is why I want you to take it in the morning—but this is only at the beginning and it wears off as you continue to take it.

Dr Brash (cont): Sometimes there's some diarrhea or a little bit of nausea that tend to go away, and then sometimes some sexual side effects. I'm going to send it straight to your pharmacy so you can start taking it tomorrow, and I'll see you back again in six weeks to see how you're doing. Any questions?

Ms. Jones: Uh, I guess not. (As Dr. Brash leaves the room to his next patient, she mumbles to herself) But what about my heart?
ARTful Information Sharing

- **Ask** – for the patient’s perspective/understanding
- **Respond** – to what was said
- **Teach** – your perspective

Provider: “I’ve done a lot of talking. So I know I’ve done a good job of explaining things, what are you going to tell your spouse we talked about today?” **(ASK)**

Patient: Well, I’m going to start this new medicine for my diabetes that I take once a day, but will I be able to afford this medicine? **(ASK)**

Provider: That’s right that its once a day, but it sounds like you are concerned about how much this might cost. **(RESPOND)** As it turns out, I have a different medicine that would likely be cheaper, but is twice a day. **(TEACH)** How does that sound to you? **(ASK)**


Improved Outcomes with Teachback

- Informed consent
  - Increased comprehension of risks, benefits and alternative
- DM2 control
  - Using this approach has an odds ratio of 15.2 for better a1c’s
  - Used in low health literacy patients


Better Transmission

- Dr. Brash: I know I did a lot of talking just now. Just so I know I made myself clear, tell me what you will do when you go home. **(Ask)**
- Ms. Jones: Well, you want me to start this pill once a day in the morning, and to start at the lower dose for one week, but I’m confused. Did I have a heart attack? **(Respond)**
- Dr. Brash: Oh, my apologies. I guess I skipped over that. I can understand why you might be confused. **(Respond)** Fortunately, no, I don’t think you had a heart attack, but a different kind of attack, a panic attack. **(Teach)** What have you heard about panic attacks? **(Ask)**
- Ms. Jones: Oh, yes, my friend has the same thing and he needed medicine too.
Better Transmission

- Dr Brash: Sorry to hear about your friend (Respond). As I mentioned, the medicine will help, but not right away, it will take several weeks and do watch out for the side effects (Teach). What further questions do you have? (Ask)
- Ms Jones: Can I call you if I have any concerns?
- Dr Brash: Of course. I can tell you seem a bit nervous. (Respond). Call anytime and lets plan for a follow up visit in about 4 weeks to see how you are doing (Teach). How does that sound? (Ask)
- Ms Jones: Okay, sounds good.

Agenda

- Agenda Setting
- Conflict
  - Eliciting the other’s perspective
  - Distinguishing Interests vs Positions
  - Responding to emotion
- Teachback

Pair Share Teachback

Thank you
Avoid These Potential Pitfalls

1. Docusate
2. Chemotherapy Near End of Life
3. Oxygen in Non-Hypoxic Patients with Dyspnea

Docusate for Constipation

- Study: Double-blind RCT
  - 74 patients, 3 inpatient Canadian hospices
  - Randomized to 10 days of:
    - Senna 1-3 tabs/day + docusate 100 mg BID
    - Senna 1-3 tabs/day + placebo BID

Disclosures

I have no financial disclosures to report.
Study Results

- Docusate group had marginally larger volume of stool $p=0.06$; stool consistency was slightly different between groups
- No difference in:
  - Average number of bowel movements/day
  - Patients’ perceptions of the difficulty or completeness of defecation
  - Pain
  - Percent of patients requiring additional bowel intervention (74% placebo; 69% docusate)
- Additional issues: tastes horrible, pill burden

Docusate for Constipation (continued)

No appreciable benefit of adding Docusate to Senna in hospice patients

- What works for constipation:
  - Always rx laxative with opioid
  - Start with Senna, then add Miralax, Lactulose, etc
  - Suppository or enema (avoid Fleet's) if $>3-4$ days
  - Hydration and activity
  - Consider Methylnatrexone for opioid-induced constipation if above not working

Chemotherapy Near End of Life

- Goals of chemotherapy for patients with metastatic cancer:
  1. Live longer
  2. Live better
- Study: Association of chemo in last 6 months of life with caregiver-reported quality of life in last week of life and survival

Prigerson HG. Jama Oncol 2015; 1(8):778-784
Chemotherapy Near End of Life

- 661 patients with advanced metastatic cancer who had progressed on prior therapy
- MD estimate of < 6 months to live
- ½ of patients were on chemo at enrollment
- Median survival 4 months
- Patients with good functional status were more likely to receive chemo

Study Results

- No improvement in QOL for patients with moderate or poor baseline functional status
- Chemo associated with worse QoL for patients with better functional status at baseline
- No difference in survival (though study not designed for this)

Think twice about whether to support palliative chemotherapy for patients with metastatic cancer who are near the end of life.

Supplemental Oxygen for Dyspnea In Non-Hypoxic Patients

- Palliative oxygen therapy widely used for dyspnea
- Potential benefits: placebo effect, family feels like “doing something”
- Potential burdens: ties patient down, social stigma, uncomfortable, nosebleeds, fire risk

Supplemental Oxygen Trial

- Study:
  - Double-blind RCT
  - 239 outpatients in US, Australia and UK with life-limiting illness, refractory dyspnea, and PaO2 >55 mmHg
  - Randomized to RA or O2 at 2 LPM x 7 days
  - Instructed to use O2 at least 15 hours/day

Abernethy A. Lancet 2010;376(9743):784-93
**Study Results**

- No difference between supp O2 vs RA by NC in:
  - Mean AM Breathlessness scores
  - Mean PM Breathlessness scores
  - Quality of Life

Compared with RA NC, oxygen by NC provides no benefit for dyspnea in patients who are not hypoxemic.

---

**What Works for Dyspnea**

- Treat the underlying cause
  - Pleural effusion, PE, pna, ascites
- Opioids
  - Low dose, Safe even in COPD
- Position
- Breathing training
- Fan and/or fresh air
- Cold cloth to face
- Acupuncture in COPD

---

**Practical Pearls**

1. Prognostication
2. Role of Palliative Care
3. Advance Care Planning

---

**Prognostication**

- Helps patients and providers to determine realistic, achievable goals of care and proceed with interventions consistent with those goals

  "If your heart stops, do you want electrical shocks and chest compressions to try to get your heart beating again?"

- Helps patients with life planning
- Most people want to know!
- Younger patients (often with cancer):
  - Usually clearer trajectory
- Older adults:
  - Absence of a dominant terminal condition
  - Age + Functional + Cognitive + Multimorbidity
Life Expectancy

<table>
<thead>
<tr>
<th>Life Expectancy</th>
<th>Clinical Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4-6 weeks</td>
<td>Methylphenidate over SSRI for depression</td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>Discontinue statins</td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>Refer to hospice</td>
</tr>
<tr>
<td>&lt;1-2 years</td>
<td>Nonoperative management of AAA</td>
</tr>
<tr>
<td>&lt;2-3 years</td>
<td>Tight BP control in diabetes unlikely to prevent stroke, MI</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>Bio-prosthetic heart valve over mechanical</td>
</tr>
<tr>
<td>&lt;9 years</td>
<td>Discontinue tight blood sugar control in diabetes</td>
</tr>
</tbody>
</table>

Key Clinical Decisions and Life Expectancy

Multiple Domains Impact Prognosis

- Functional Status
- Comorbid Medical Conditions
- Cognition
- Nutrition
- Polypharmacy
- Psychological Status
- Social Support
- Geriatric Syndromes

How Should We Prognosticate?

Great Variation Even by Same Age!

![Graph showing life expectancy for women across different age groups and percentiles.](Walter LC. JAMA 2001; 285:2750-56)
How Should We Prognosticate?

Clinical Judgement

Life Tables

Prognostic Indices

1. How old is your patient? 
2. What is the sex of your patient? 
3. What is your patient’s BMI? 
4. Which best describes your patient’s health in general? 
5. Does your patient have chronic lung disease, such as emphysema or chronic bronchitis? 
6. Does the lung disease limit usual activities such as household chores or work or require home oxygen? 
7. Has your patient ever had cancer (excluding minor skin cancers)? 
8. Does your patient have congestive heart failure? 
9. Does your patient have diabetes or high blood sugar? 
10. Which best describes your patient’s cigarette use? 

11. During the past 12 months, how many times was your patient hospitalized overnight? 
12. Because of a physical, mental or emotional problem, does your patient need the help of others in handling routine needs such as everyday household chores, eating, money management, shopping, or getting around for other purposes? 
13. Because of a health or memory problem, does your patient have difficulty managing money, such as paying bills and keeping track of expenses? 
14. Because of a health or memory problem, does your patient have difficulty with bathing or showering? 
15. Because of a health problem, does your patient have difficulty pushing or pulling large objects like a living room chair?

Total Lee Index Points: 12
Total Schmoo Index Points: 15

Your best guess of 5 year mortality risk: 0.3 95%

eprognosis.ucsf.edu
10 year mortality risk: 87%

Communication on Prognosis
- Ask for permission and preferences for how information is relayed
- Use ranges
- “In other people in a similar situation to you....”

Palliative Care
- Specialized medical care by a team of doctors, nurses, social workers, chaplains and other specialists for people with serious illnesses.
- Focuses on providing patients with relief from the symptoms, pain, and stress of a serious illness—whatever the diagnosis.
- The goal is to improve quality of life for both the patient and the family.


A New Paradigm

Old

Life Prolonging Care → Medicare Hospice Benefit

New

Life Prolonging Care → Palliative Care → Hospice Care
Palliative Care Improves Value

Quality Improves
- Reduction in symptom burden
- Improved quality of life
- Longer length of life
- Increased family satisfaction
- Better family bereavement outcomes
- Care matched to patient centered goals

Costs Reduce
- Lower hospital cost/day
- Less use of ER, hospital, ICU
- Reduction in 30d readmissions
- Labs, imaging, pharmaceuticals

Early Palliative Care Intervention

- Study:
  - Non-blinded, RCT (single site)
  - Ambulatory patients with newly diagnosed met NSCLC
  - Immediate PC + onc vs onc
  - Primary outcome: change in QOL at 12 weeks


Study Results

- Baseline characteristics did not differ between groups
- Intervention group:
  - Better QOL scores
  - Less depression
  - More documentation of resuscitation preferences
  - Less aggressive care at the end of life
  - Lived two months longer

Palliative Care appears beneficial for patients with newly diagnosed metastatic NSCLC.
Access to Palliative Care

Advance Care Planning

- An ongoing process of discussing care preferences and making care plans between patients (and their caregivers) and providers
- Should include discussion of person’s priorities, beliefs, and values AND prognostic information
- May or may not lead to completion of advance directive
- Both physicians and patients think it’s important

Benefits of ACP

- Patients who have advance care planning or EOL conversations with their provider are:
  - Less likely to:
  - More likely to:
    - Receive outpatient hospice and be referred to hospice earlier (Zhang et al. 2009, Wright et al. 2008)
    - Have their wishes known and followed (Detering et al. 2010; Houkin 2014)
    - Have caregivers who are satisfied with the quality of their loved one’s death (Detering et al. 2010)

Audience Poll

In my practice, I aim to have advance care planning conversations with:

1. None of my patients
2. All my patients over 65 years old
3. My patients who are terminally ill
4. Both 2 and 3
5. All my patients regardless of age
ACP Practices in Primary Care

- Systematic review of 10 studies (5 US) among PCPs providing care for patients living in the community or an assisted living
- ACP most frequently done with patients with cancer, Alzheimer’s dementia, or other terminal illness
- Of patients who died of non-sudden deaths, one-third had ACP
- Provider-reported ACP rates higher than patient-reported ones
- Lack of systematic approach; hard to judge when to initiate
- Patients want to discuss, even if healthy; feel it is responsibility of provider to bring up

Glaudermans et al. (2015) Fam Practice

ACP Documentation

- Include on problem list; be specific
- Health systems streamlining EMR ACP documentation
- Ideally, complete advance directive and medical order (for patients with less than 1y prognosis; in states where available)

www.polst.org

ACP Billing

- ACP CPT codes NEW in 2016
  - “ACP includes the explanation and discussion of advance directives such as standard forms (with completion of such forms, when performed), by the physician or other qualified
  - 99497: first 30 min F2F (wRVU 2.40; $85.99)
  - 99498: each additional 30 min F2F (wRVU 2.09; $74.99)
  - Include pertinent diagnoses; can bill more than once/yr

ACP Tools

www.prepareforyourcare.org
Miscellaneous PC Pearls

- “Easier to stay ahead of [insert symptom], than catch up”
- Symptom management and ACP are processes
- “Patients (and families) aren’t always looking to be "fixed," often they just want someone to listen to them, validate them, and bear witness to their story.”

Summary

- Potential Pitfalls
  - Consider avoiding Docusate, chemotherapy near end of life, and oxygen in non-hypoxic patients

- Practical Pearls
  - Consider the role of prognostication, specialty-level palliative care services, and advance care planning in taking the best care possible of your seriously ill patients and families.

- Additional Resources:
  - https://www.capc.org/fast-facts/
Hepatitis C
New Medications, New Hope and New Opportunities for Primary Care

October 12, 2017

Rena K. Fox, MD
Professor of Clinical Medicine, UCSF

Disclosures:
Grant support – Gilead Sciences, Inc

In this talk, 10 drugs will be discussed, 4 of which are manufactured by Gilead.

Learning Objectives

1. Evidence based and guideline recommended screening for hepatitis C virus (HCV) infection
2. Identify treatment options for HCV genotypes
3. Recommend HCV therapeutic protocols based on individual patient factors, including prior treatment history and complicating comorbidities
4. Understand the need for adherence on HCV treatment
5. Recognize the need for cirrhosis and HCC monitoring after patients achieve HCV cure

HCV Disease Outcomes in the US
Projected Prevalence of Decompensated Cirrhosis and HCC Rises Through 2020

- Although the overall prevalence of HCV infection is decreasing, the prevalence of cirrhosis is increasing.
- Decompensated cirrhosis more common after 1995.
- HCC rose steeply after 1990, predicted to peak in 2019 at 14,000/year.

HCV mortality higher than from top 60 other infections combined

- From 2003-2013, number of HCV deaths surpassed the major 60 other nationally notifiable infectious conditions combined.
- Mortality from other conditions (e.g., TB, pneumococcal disease) is declining while HCV mortality rising.
- HCV deaths mainly among ages 55-64 yo.

Deaths from liver cancer increased at the highest rate of all cancers

- HCC has second highest rise in incidence, second only to thyroid cancer.
- Death rates from HCC highest of all cancer sites.
- During same time, death rates decline from all cancers combined.

Rising Number of New Infections

- Estimated Actual New Cases of HCV:
  - 2011: 16,500
  - 2012: 24,700
  - 2013: 29,700
  - 2014: 30,500

Screening and Initial Evaluation

Screening Recommendations – from the CDC and USPSTF

Risk Based Screening: 1 or more Risk Factors
- IDU
- Transfusion before 1992
- Clotting factors before 1987
- HIV or HBV
- Chronic Hemodialysis
- Elevated ALT

Birth Year Screening: Born 1945-1965


Primary Care Evaluation of HCV

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Every 6 mos *1st contact*</th>
<th>Annually</th>
<th>As needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV RNA (viral load)</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV Genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC/Plt/Scr</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>PT/INR</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>BMP / LFTs</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>HIV Ab</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBe Ab</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBS Ag, HBS Ab</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal US</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunizations</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HCV Treatment
**Viral Cure (SVR) Associated With Reduced Risk of Death, Transplant and HCC**

- Meta-analysis of over 23,000 patients from 129 studies
- Achieving SVR vs. no SVR was associated with substantial benefits
- 62% to 84% reduction in all-cause mortality, 90% reduction in liver transplantation, 68% to 79% reduction in HCC


**5-Yr Risk of All-Cause Death by SVR**

<table>
<thead>
<tr>
<th>SVR</th>
<th>No SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>20%</td>
</tr>
<tr>
<td>Cirrhotic Pts HIV- Coinfected</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

**5-Yr Risk of HCC by SVR**

<table>
<thead>
<tr>
<th>SVR</th>
<th>No SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>4.5%</td>
</tr>
<tr>
<td>Cirrhotic Pts HIV- Coinfected</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

**US HCV Treatment During Interferon-Ribavirin Era**


**Direct Acting Antivirals (DAAs)**

- Against specific HCV targets

**DAA Regimens and Abbreviations**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir</td>
<td>SOF</td>
</tr>
<tr>
<td>Sofosbuvir + Simeprevir</td>
<td>SOF + SIM</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>LDV/SOF</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir + Dasabuvir</td>
<td>PRD/OSD</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir</td>
<td>PRD/OX</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>ELB/GRZ</td>
</tr>
<tr>
<td>Oxlatavir + Sofosbuvir</td>
<td>DAC + SOF</td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir</td>
<td>SOF/VEL</td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir/Voxilgravir</td>
<td>SOF/VEL/VOX</td>
</tr>
<tr>
<td>Glecaprevir/Fibrentasvir</td>
<td>GLE/PIB</td>
</tr>
</tbody>
</table>

**Sites**

- NS3
- NS4a
- NS5
- NS5 A
- NS5 B
### DAA Regimens and Trade Names

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir</td>
<td>Sovaldi</td>
</tr>
<tr>
<td>Sofosbuvir + Simeprevir</td>
<td>Sovaldi + Olysio</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>Harvoni</td>
</tr>
<tr>
<td>Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir</td>
<td>Viekira Pak</td>
</tr>
<tr>
<td>Paritaprevir/Ritonavir/Ombitasvir</td>
<td>Technivie</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>Epclusa</td>
</tr>
<tr>
<td>Daclatasvir + Sofosbuvir</td>
<td>Daklinza + Sovaldi</td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir</td>
<td>Vosevi</td>
</tr>
<tr>
<td>Glecaprevir/Pibrentasvir</td>
<td>Mavyret</td>
</tr>
</tbody>
</table>

### Genotype 1a
#### Treatment Naive

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF x 8 weeks</td>
<td>93% - 97%</td>
<td>≤ 6 mill AND F0 - F2 AND HIV neg</td>
</tr>
<tr>
<td>GLP/PIC x 8 weeks</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>SOF/VEL x 12 weeks</td>
<td>98 - 99%</td>
<td></td>
</tr>
<tr>
<td>LDV/SOF x 12 weeks</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>LDV/SOF x 12 weeks + Ribavirin</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td>GLP/PIC x 12 weeks</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>GLP/PIC x 16 weeks</td>
<td>97%</td>
<td></td>
</tr>
</tbody>
</table>

### Genotype 1b
#### Treatment Naive

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF x 8 weeks</td>
<td>95% - 97%</td>
<td>≤ 6 mill AND F0 - F2 AND HIV neg</td>
</tr>
<tr>
<td>GLP/PIC x 8 weeks</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>SOF/VEL x 12 weeks</td>
<td>98 - 99%</td>
<td></td>
</tr>
<tr>
<td>LDV/SOF x 12 weeks</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>LDV/SOF x 12 weeks + Ribavirin</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td>GLP/PIC x 12 weeks</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>GLP/PIC x 16 weeks</td>
<td>97%</td>
<td></td>
</tr>
</tbody>
</table>

### Genotype 2
#### Treatment Naive

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP/PIC x 8 weeks</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>SOF/VEL x 12 weeks</td>
<td>99 - 100%</td>
<td></td>
</tr>
<tr>
<td>DAC + SOF x 12 weeks</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>
### Genotype 3
Treatment Naive

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLE/PIC x 16 weeks</td>
<td>95%</td>
</tr>
<tr>
<td>SOF/VEL x 12 weeks</td>
<td>97-98%</td>
</tr>
<tr>
<td>DAC + SOF x 12 weeks</td>
<td>97%</td>
</tr>
</tbody>
</table>

### 3 Major Factors in Choosing HCV Treatment Regimen

- Genotype/subtype
- Treatment History
- Degree of fibrosis

### Resistance Associated Variants (RAVs)

- Amino acid substitutions within HCV proteins that create drug resistance, usually affecting
  - NS3/4 Protease inhibitor drugs
  - NS5A inhibitor drugs
- Genotype 1a, Genotype 3 patients at baseline
- Patients previously treated

### Sofosbuvir/Velpatasvir
ASTRAL-1: GTs 1, 2, 4, 5, 6 for 12 wks

- Total
- New Cirrhotic
- Cirrhotic
- Treatment Naive
- Treatment Experienced

Sof/Vel x 12 wks vs Sof + Riba x 24 wks
ASTRAL-3 Trial - Genotype 3


Total, N=277
Treatment Naïve, Non-cirrhotic
98 93 91 89 90
73 71 58 0

Patient Factors
- Not offered linkage to care with an HCV treater
- Alcohol/Drug use
- Missed appointments
- Fear of side effects due to previous information about interferon
- Contraindications to treatment (eg. medical or psychiatric comorbidities)

Provider Factors
- Under-diagnosis of HCV
- Knowledge gaps about new HCV treatments and recommendations
- Resistant to treat past substance abusers
- Lack of access to specialist help
- Cultural inertia
- Time constraints

Other
- Lack of awareness of infection
- Access to care/loss of insurance
- Payer restrictions
- Cost concerns

Pre-Treatment Considerations

Whom to treat

- Everyone should be considered for treatment
- Most urgent for patients at increased risk of:
  - Decompensation and death
  - Morbidity, symptoms
  - Transmitting virus to others
  - Rapid progression

Barriers to Optimizing Treatment
Factors Influencing HCV Treatment Decisions

- Viral Genotype
- Subtype
- Viral load
- Treatment History
  - naïve or experienced
  - resistance mutations
  - prior treatments
- Fibrosis stage
  - cirrhosis, Childs score A, B or C
  - pre- or post-transplant
- Comorbidities
  - HCV coinfection
  - extrahepatic manifestations (cryoglobulinemia, etc)
  - renal function
  - drug-drug interactions
- Payer requirements
- Financial Insurance approval

Staging and Assessment of Fibrosis

Why test for fibrosis?
- Determine treatment urgency
- Assess need for additional care
- Cirrhosis requires additional management

How to test for fibrosis?
- Gold standard: liver biopsy
- Serum markers– Fibrosure, APRI, Fib-4
- Elastography (FibroScan®, MRE)
- Imaging may detect cirrhotic features

Calculators for Fibrosis

APRI

FIB-4

Patient adherence

- Adherence is crucial
- Factors that may complicate adherence, such as active substance use, depression, neurocognitive disorders, and lack of social support, should be noted
- Address issues of adherence before initiating medications.
- Providers should incorporate strategies for measuring and supporting adherence within their clinics.
Selected Potential Drug–Drug Interactions

<table>
<thead>
<tr>
<th>Concomitant Medication</th>
<th>SOF</th>
<th>SM</th>
<th>LDV</th>
<th>P/RTV/GRB+OSV</th>
<th>DCV</th>
<th>GZREB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid-reducing agents*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethinyl estradiol-containing products</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDE5 inhibitors</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin antimicrobials</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedatives</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St John's wort</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Acid-reducing agents*: 
- Concomitant medication with contraindicated use with the listed drugs.

Considerations for Referral
- HCV/HIV coinfection
- Decompensated cirrhosis
- Renal disease
- Drug–drug interactions
- Retreatment after a DAA regimen failure
- Comorbidities

Whole Sale Costs

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cost per pill</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbasvir/Grazoprevir x 12 wks</td>
<td>$650</td>
<td>$44,400</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir x 8 wks</td>
<td>$1125</td>
<td>$63,000</td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir x 12 wks</td>
<td>$890</td>
<td>$74,760</td>
</tr>
<tr>
<td>Ombitasvir/Paritaprevir/Ritonavir+Dasabuvir x 12 wks</td>
<td>$991</td>
<td>$83,319</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir x 12 wks</td>
<td>$1125</td>
<td>$94,500</td>
</tr>
<tr>
<td>Daclatasvir + Sofosbuvir x 12 wks</td>
<td>$750 + $1000</td>
<td>$147,000</td>
</tr>
</tbody>
</table>

Incremental Costs of HCV

- Patients with HCV: $9681 per patient per year
- HCV with decompensated cirrhosis: $27,845 per patient per year
- HCV with hepatocellular carcinoma: $43,671 per patient per year
- HCV with liver transplant: $93,609 per patient per year

http://www.hepatitis.uw.edu/page/treatment/drugs
TREATMENT IS COST-EFFECTIVE

1. “Real world” SVR rates comparable to clinical trials
2. HCV treatment for genotype 1 patients at all fibrosis stages, Ledipasvir/Sofosbuvir was cost effective.
3. Cost-effective yes, but affordable no.
4. Advanced fibrosis no longer always required by payors


PRICE OF SOFOSBUVIR IN SELECTED COUNTRIES

HILL ET AL JOURNAL OF VIRUS ERADICATION 2016; 2:28-31

MANAGING MEDICATION AUTHORIZATION DENIAL

- Don’t give up after first prior authorization denied
- Carefully read reason for denial
  - Mild fibrosis
  - Not the preferred drug
  - Missing data
- Payor creates eligibility criteria and drug preference
- Appeal or peer to peer available
- Access pt assistance programs

MONITORING ON HCV TREATMENT

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 wks</th>
<th>12 wks after finishing</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV AHA</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Or every 6 weeks until undetectable. Stop treatment if not undetectable by 6 wks</td>
</tr>
<tr>
<td>CRBO</td>
<td>X</td>
<td></td>
<td></td>
<td>Every 2 weeks if on RBV</td>
</tr>
<tr>
<td>LTIL</td>
<td>X</td>
<td></td>
<td></td>
<td>Stop if AST/ALT 10x</td>
</tr>
<tr>
<td>GFR</td>
<td>X</td>
<td></td>
<td></td>
<td>Every 2 weeks if used or drug interactions</td>
</tr>
<tr>
<td>PTX</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SOURCE: HCVRGUIDELINES.ORG
Long-term Monitoring

Regardless of SVR:

Patients with advanced fibrosis should be screened for liver cancer every 6 months.

Patients who are active IV drug users should be screened for reinfection and receive counseling.

Adverse Events

- Discuss most common adverse events and management strategies in pre-education session.
- Headaches, Fatigue, Nausea, Insomnia – less than 10%.
- Anemia – still a concern with Ribavirin.

HBV Reactivation During HCV Treatment

- FDA Drug Safety Communication
  - 24 cases of HBV reactivation (including 3 cases of acute liver failure) over a 31 month period
  - Boxed Warning requirement issued

Opportunities for Primary Care
Primary Care can provide most of the spectrum of HCV care

Such as:
• Screening and diagnosis
• Performing initial evaluation after diagnosis
• Caring for patient with chronic liver disease
• Performing pre-treatment assessment
• Prescribing and managing DAA treatment of uncomplicated cases
• Managing compensated cirrhosis

Linkage to Care

Any patient with HCV RNA should be referred to a medical provider who can further evaluate and manage the patient’s HCV infection, such as:

1) A primary care clinician (physician, nurse practitioner, or physician assistant) with interest and experience evaluating and treating HCV patients
2) An infectious diseases specialist with HCV evaluation and treatment competence
3) A hepatology or gastroenterology specialist

Why Gaps Occur in Linkage of Care

• Provider failure to offer follow-up appointment
• Patient failure to follow-up on the referral
• Lack of medical insurance
• Substance abuse problems that interfere with making or keeping the appointment

Untreated HCV From The Interferon Era

• Many patients diagnosed in the interferon era were ineligible or were counseled not to undergo treatment
• Many patients in the interferon era failed or didn’t tolerate treatment
• These patients should be re-evaluated for DAA treatment now
Recommended for Referral

- Decompensated cirrhosis
- Extrahepatic manifestations
- HIV-HCV coinfection
- DAA treatment failure
- Renal insufficiency
- Drug-Drug interactions

Conclusions

- Compelling evidence for use of DAA - extremely high cure rates, short duration, few side effects
- Ease of regimen - many regimens are one pill per day and ribavirin-free regimens now exist
- Resistance testing is required for some genotypes with some regimens, and some retreatment situations
- Major barriers are access to an HCV prescriber and insurance coverage - yet coverage is very dynamic
- Goal of eliminating HCV needs participation from specialists and generalists
- Systems need to be in place to make HCV screening and linkage to care more reliable
Update in Hospital Medicine 2016-2017

Year in Review

• Updated literature
• August 2016 – August 2017

Process:
• CME collaborative review of journals
  • Including ACP J. Club, J. Watch, etc.
• Independent analysis of article quality
• Thank you to Brad Monash, Ed Vasilevskis, Rachel Thompson, Chad Miller

Update in Hospital Medicine 2016-2017

Chose articles based on 3 criteria:
1) Change your practice or teaching
2) Modify your practice or teaching
3) Confirm your practice or teaching

• Hope to not use the words:
  • Student’s t-test, meta-regression, Mantel-Haenszel statistical method, etc.
  • Focus on breadth, not depth

Update in Hospital Medicine 2016-2017

• State one change in diagnostic testing you will make in clinical practice.
• Describe a new approach to treatment you can use in your clinical practice.
• List one new technique to approach patient care in patients who are at or near the end of life.
• Appreciate the challenges of keeping updated on the literature.
Update in Hospital Medicine 2016-2017

- Major reviews/short takes
- Case-based format
- Multiple choice questions
- Promote retention

Syllabus/Bookkeeping

- No conflicts of interest
- Final presentation available by email
  sharpeb@medicine.ucsf.edu

PE in Syncope

**Question:** How common is PE in patients admitted to the hospital with syncope?

**Design:** Prospective study, 11 hospitals in Italy
Hospitalized for syncope, age > 18 years
Standard evaluation for syncope

- Applied simplified Wells & d-dimer to all patients
- If "high-risk" → CT angiogram or V/Q scanning
- Of 2584 screened, 560 admitted* to the hospital
- Average age 76 years old

**Results**

- Cause of syncope identified in 355 patients (63.4%)
- PE ruled out by Wells/d-dimer in 330 pts. (58.9%)

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE in Syncope (overall)</td>
<td>17.3 % (95% CI 14.2%-20.5%)</td>
</tr>
<tr>
<td>PE in Syncope (no cause)</td>
<td>25.4 % (95% CI 19.4%-31.3%)</td>
</tr>
<tr>
<td>PE in Syncope (other cause)</td>
<td>12.7 % (95% CI 9.2%-16.1%)</td>
</tr>
</tbody>
</table>

- Main or lobar PE in ~ 67%
- Tachypnea, tachycardia, hypotension, signs of DVT more common in those with PE

**PE in Syncope**

**Question:** How common is PE in patients admitted to the hospital with syncope?

**Design:** Prospective, admitted for syncope; Wells & d-dimer for PE, then CTA or V/Q

**Conclusion:** PE in syncope was 17.3% overall; 25.4% in pts. with no other cause; 67% main/lobar
Tachypnea, tachycardia, shock, DVT more common in patients with PE

**Comments:** Only admitted patients; admit criteria Many would have had PE workup separately; Within 48 hours of admission; real PEs? May be an overestimate; consider applying Wells/d-dimer in syncope

---

**Short Take: Diagnosis of Asthma**

In a prospective cohort study, 701 adults diagnosed with asthma in the previous 5 years underwent spirometry, bronchial challenge, and/or tapering of asthma medications.

Asthma was ruled out in 33.1%. Most had not had spirometry.

Most were felt to have something benign as the cause (e.g. allergic rhinitis).


---

**Short Take: Blood Culture Yield**

In a prospective multicenter observational study, cohort study, 1,943 hospitalized patients who had blood cultures drawn (for any reason) were followed.

Among patients with 1) poor food consumption and 2) shaking chills, the incidence of true bacteremia was 47.7%.

In patients with 1) normal food consumption and 2) no chills, the incidence of true bacteremia was 2.4%.


---

**Short Take: Blood Culture Yield**

Normal food consumption had a negative likelihood ratio of 0.18 (95% CI, 0.17-0.19) for excluding true bacteremia.

The presence of shaking chills had a positive likelihood ratio of 4.78 (95% CI, 4.56-5.00) for true bacteremia.

Question: What is the optimal duration of antibiotics in patients hospitalized with CAP?
Design: Randomized, controlled; non-blinded, non-inferiority trial
Hospitalized for CAP, age > 18 years-old

- All patients treated for 5 days
- Randomized to stopping vs. continuing antibiotics

<table>
<thead>
<tr>
<th>Stop</th>
<th>Continue</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No fever for 48h</td>
<td>• Duration determined by MD</td>
</tr>
</tbody>
</table>


Results

- A total of 312 patients, 40% class IV or V (not ICU)
- Most received a fluoroquinolone (80%)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>5 Days</th>
<th>Longer</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Success (10d)</td>
<td>56.3%</td>
<td>48.6%</td>
<td>0.18</td>
</tr>
<tr>
<td>Clinical Success (30d)</td>
<td>91.9%</td>
<td>88.6%</td>
<td>0.33</td>
</tr>
<tr>
<td>Mortality (30d)</td>
<td>2.1%</td>
<td>2.2%</td>
<td>0.99</td>
</tr>
<tr>
<td>Median Duration of Abx</td>
<td>5 days</td>
<td>10 days</td>
<td>0.001</td>
</tr>
</tbody>
</table>

- A total of ~70% got 5 days in the intervention group
- No difference for sicker patients
- Readmissions at 30 days lower in shorter-course

A total of 323 patients with CAP (U.K.) had sputum collected on admission. All samples were tested with real-time PCR for 26 respiratory viruses and bacteria.

A pathogen was confirmed in 87% of patients. *H flu* (40.2%) and *Strep pneumo* (35.6%) were the most common bacteria.

Viruses were present in 30% but 82% of these were co-detections with bacteria.

**Case Summary**

**Definitely**
1. Recognize PE may be common in patients admitted with syncope.

**Consider**
1. Up to 1/3 of adults diagnosed with asthma may not have asthma.
2. Hospitalized patients who are eating well and do not have chills are unlikely to be bacteremic.
3. Shorter courses of antibiotics (5 days) in patients with CAP who are afebrile with stable vital signs.

---

**PPIs in Bleeding Ulcers**

**Question:** For patients with peptic ulcer bleeding, what is the optimal route for the PPI?

**Design:** Systematic review & meta-analysis; RCTs peptic ulcer bleeding (most high-risk); Oral vs. IV PPI (BID or other)

- **High-risk peptic ulcers**
  1) Active bleeding
  2) Visible vessel
  3) Adherent clot

---

**Results**

- Low risk for publication bias

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Oral</th>
<th>IV</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-day Bleeding</td>
<td>5.6%</td>
<td>6.8%</td>
<td>NS</td>
</tr>
<tr>
<td>30-day Bleeding</td>
<td>7.9%</td>
<td>8.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality</td>
<td>2.1%</td>
<td>2.4%</td>
<td>NS</td>
</tr>
<tr>
<td>Length of Stay (d)</td>
<td>4.58</td>
<td>5.23</td>
<td>NS</td>
</tr>
</tbody>
</table>

**PPIs in Bleeding Ulcers**

**Question:** For patients with peptic ulcer bleeding, what is the optimal route for the PPI?

**Design:** Syst review & meta-analysis; 7 RCTs ulcer bleeding; oral vs. IV PPI

**Conclusion:** No difference in recurrent bleeding at 7 or 30 days; no difference in mortality or length of stay

**Comment:** Variable quality, only 7 studies; all RCTs; Acid suppression equivalent with PO

- Adds to prior data where intermittent = bolus/infusion PPI dosing
- Can start with IV BID but change to PO when able


**Short take: Nano-Nose**

A complex artificial intelligence nanoarray was used to analyze 2808 breaths from 1404 patients with different illnesses (e.g. cancer, infection, etc.). The nanoarray identified unique volatile organic compounds (VOCs).

The analyzer was able to accurately identify the illness 86% of the time.


**Short take: Hydrocortisone, Vit C, Thiamine**

In a retrospective before-after clinical study, a total of 94 patients with sepsis were included. Forty-seven (47) received usual care and 47 received hydrocortisone, vitamin C, and thiamine in addition to usual care.

- The hospital mortality in the vitamin C group was 8.5% (4/47) compared to 40.4% (19/47) in the usual care group.
- SOFA scores decreased faster in the vitamin C group and they weaned off pressors earlier.


**High-Flow Nasal Cannula**

**Benefits**
- Patient comfort
- Mobilize secretions
- Decreased entrapment of room air
- Washout of dead space
- PEEP
- Deliver ~ 100% FO2

Heated and humidified oxygen delivered at rates of up to 60L/min

Update in Hospital Medicine
High-Flow Nasal Cannula

Question: What are the benefits of high-flow nasal cannula in hypoxic respiratory failure?

Design: Syst-rev & meta-analysis; 18 studies, 3,881 patients with hypoxic resp. failure; compared to NIPPV and usual oxygen therapy

Conclusion: HFNC may decrease intubation in hypoxic respiratory failure vs. usual oxygen delivery

No difference when compared to NIPPV; no change in ICU LOS or ICU mortality

Comments: Statistical heterogeneity; many causes

Likely better than usual oxygen treatment; no worse than NIPPV, more comfortable

Can be standard for patients with hypoxic respiratory failure

Delirium in Palliative Care

Question: Should haloperidol or risperidone be used to treat delirium in palliative care?

Design: Single center, randomized, controlled trial, 11 hospice services; all patients with delirium

Conclusion: Haloperidol & risperidone may increase delirium; more extrapyramidal side effects

Haloperidol may increase mortality

Comment: Some methodologic issues; dosing

May cause harm & increase mortality

Other studies in delirium mixed regarding benefit of antipsychotics

Likely should avoid if possible


Case Summary

Definitely

1. Change to PO PPI when able in patients with high-risk peptic ulcer bleeding.

Consider

1. A future state where breath samples will be analyzed using nanotechnology.

2. High-flow nasal cannula may be better than usual oxygen delivery

3. Avoiding antipsychotics when treating delirium in palliative care

Case Summary

Definitely
1. Recognize PE may be common in patients admitted with syncope.

Consider
1. Up to 1/3 of adults diagnosed with asthma may not have asthma.
2. Hospitalized patients who are eating well and do not have chills are unlikely to be bacteremic.
3. Shorter courses of antibiotics (5 days) in patients with CAP who are afebrile with stable vital signs.

Update in Hospital Medicine

Short Take: Feed a Cold?

“What should I do about eating when I am sick? I’ve always been told to feed a cold; starve a fever...

...Is there truth to that??”


Short take: Feed a Cold?

Genetically identical mice were infected with a bacteria (Listeria) or a virus (influenza) and then either force-fed or starved.

<table>
<thead>
<tr>
<th>Survival (10 d)</th>
<th>Force-Fed</th>
<th>Starved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral Infection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Short take: Feed a Cold?**

Genetically identical mice were infected with a bacteria (*Listeria*) or a virus (influenza) and then either force-fed or starved.

<table>
<thead>
<tr>
<th>Survival (10 d)</th>
<th>Force-Fed</th>
<th>Starved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Infection</td>
<td>0%</td>
<td>60%</td>
</tr>
<tr>
<td>Viral Infection</td>
<td>78%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Glucose appeared to be the key driver of mortality in bacterial infections. It is unclear if there are implications for humans.

Sports Injuries of the Knee and Shoulder
UCSF Primary Care Medicine: Principles and Practice

Carlin Senter, MD
Associate Professor
Primary Care Sports Medicine
UCSF Medicine and Orthopaedics

October 13, 2017

Learning objectives

Upon completion of this session, participants should be able to:
1. Name 4 exam maneuvers to identify a meniscus tear.
2. Name 6 clinical criteria to identify knee osteoarthritis.
3. Identify indications for surgery for patient with meniscus tear
4. List 4 causes of anterior knee pain
5. Name 2 causes of shoulder pain when both active and passive range of motion are limited.
6. Identify a full thickness rotator cuff tear on physical exam.
7. Explain treatment for rotator cuff disease.

Case #1

60 y/o woman presents with 3 months of medial knee pain worse with playing tennis. (+) swelling. No instability. No frank locking. Pain is worse with weight bearing. Better with rest, ice, and NSAIDs.

Exam: Neutral knee alignment when standing. Knee is not warm. There is tenderness of the medial joint line + medial femoral condyle + medial tibial plateau. Small effusion. ROM 0°-120, limited by pain. (+) crepitus. (+) medial McMurray, medial knee pain with squat and Thessaly tests. No ligamentous laxity.
Diagnosis?

A. Medial meniscus tear  
B. ACL tear  
C. Medial compartment osteoarthritis  
D. Gout  
E. Septic arthritis  
F. Medial meniscus tear and medial compartment osteoarthritis

4 tests for meniscus tear

1. Isolated joint line tenderness  
2. McMurray  
3. Thessaly  
4. Squat

Joint line tenderness

Medial: Sensitivity 83%, Specificity 76%  
Lateral: Sensitivity 68%, Specificity 97%  
(Konan et al. Knee Surg Traumatol Arthrosc. 2009)


Meniscus: McMurray

Sensitivity medial 65%, Specificity medial 93%  
Meniscus: Thessaly

Sensitivity 90%, Specificity 98% (Harrison BK et al. CJSM, 2009)
Sensitivity 51-67%, Specificity 38-44% (Snoeker BAM et al. JOSPT, 2015)

Video used with permission from Anthony Luke, MD

Meniscus: squat

Sensitivity 75-77%, Specificity 36-42%
(Snoeker BAM et al. JOSPT, 2015)

Clinical criteria for diagnosis of knee OA

<table>
<thead>
<tr>
<th>Clinical and laboratory</th>
<th>Clinical and radiographic</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee pain + at least 3 of 5:</td>
<td>Knee pain + at least 3 of 5:</td>
<td>Knee pain + at least 3 of 5:</td>
</tr>
<tr>
<td>Age &gt;50 years</td>
<td>Age &gt;50 years</td>
<td>Age &gt;50 years</td>
</tr>
<tr>
<td>Stiffness &lt;30 minutes</td>
<td>Stiffness &lt;30 minutes</td>
<td>Stiffness &lt;30 minutes</td>
</tr>
<tr>
<td>Crepitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bow tenderness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bow enlargement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No palpable warmth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR &lt;40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF &lt;40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFA OA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% sensitive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% sensitive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% sensitive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Case #1

60 y/o woman presents with 3 months of medial knee pain. (+) swelling, and instability. No frank locking. Pain is worse with weight bearing. Better with rest, ice, and NSAIDs.

Exam: Neutral knee alignment when standing. Knee is not warm. There is tenderness of the medial joint line + medial femoral condyle + medial tibial plateau. Small effusion. ROM 0-120, limited by pain. (+) crepitus. (+) medial McMurray, medial knee pain with squat and Thessaly tests. No ligamentous laxity.
What do you recommend?

A. Refer for arthroscopic debridement of cartilage and meniscus
B. Nonoperative knee OA program
C. Refer for total knee arthroplasty

Surgery vs PT for meniscal tear and OA

• Multicenter RCT
• 351 patients with meniscus tear + mild-moderate OA
• Meniscus sx (clicking, popping, catching, giving way, joint line pain, pain with twisting)
• Avg. age 60 years
• 50% men, 50% women
• Primary outcome = change in WOMAC physical-function score between groups at 6 mo

Results

Conclusions

- 30% crossed over from PT to APM at 6mo
  - These people had WOMACs that didn’t improve until crossover
- No sig difference in adverse events
- PT and APM are reasonable options with similar outcomes for these patients (with allowed cross over if not achieving relief with PT)
- Starting with conservative approach is reasonable


What if this same patient had an isolated degenerative meniscus tear and no clinical signs or symptoms of knee OA?

- 60 y/o woman with 3 months gradual onset medial knee pain.
- Exam
  - Small effusion
  - Isolated joint line tenderness
  - No bony tenderness, no crepitus
  - (+) McMurray, Thessaly, squat
Degenerative meniscus tear, no OA

- FIDELITY studies suggest no benefit from arthroscopic partial meniscectomy, even with mechanical symptoms (locking/catching), over sham arthroscopic surgery.
- Limitations
  - Definition of degenerative meniscus tear?
  - No radiographic OA but these patients had some mild cartilage wear seen in surgery

Take home points: knee OA, meniscus tears

- Degenerative meniscus tear is part of the natural history of osteoarthritis
- Treat as osteoarthritis initially with non surgical knee OA program
- Imaging: Start with x-ray. Consider referral vs MRI if exam c/w meniscus tear and not improving with PT
- Could consider arthroscopic meniscus surgery if weight loss, PT, medications, injections not helping or if patient prefers surgical treatment
Who to refer for knee arthroscopy?

- Younger patients (less likely degenerative)
- Traumatic onset of symptoms
- Locked or locking knee
  - Bucket handle meniscus tear
  - Loose body
- Not improving despite conservative treatment
- Patient prefers surgery to conservative treatment

Case #2

25 y/o woman with sharp anterior knee pain x 1 month since returned from backpacking trip in the Sierras. Might have some swelling. No locking but the knee is popping. Feels unstable when walking down stairs. Pain worse up/down stairs. Painful when gets up from sitting. Doesn’t wear orthotics.

What is the most likely diagnosis?

1. Patellofemoral pain syndrome
2. Patellar chondromalacia
3. Osteochondral lesion of patellofemoral joint
4. Osteoarthritis of patellofemoral joint
5. Patellar tendinopathy
6. Quadriceps tendinopathy
7. Pes anserine bursitis
Ddx subacute-chronic anterior knee pain

1. Patellofemoral pain syndrome
2. Patellar chondromalacia
3. Osteochondral lesion
4. Osteoarthritis of patellofemoral joint
5. Patellar or quadriceps tendinitis or tendinopathy
6. Pes anserine bursitis

Case #4: Inspection

Patellofemoral pain syndrome: miserable malalignment syndrome

- Femoral anteversion (inward rotation of femur)
- Squinting patella (inward patellar rotation)
- Patella alta
- Increased Q-angle
- Excessive outward tibial rotation

Case #2: Other tests identify tightness and weakness

- Ober (too tight?)
- Hip abduction strength (weak?)
- One-legged standing squat (weak? Pain?)
Ober’s Test for tight IT Band

Passive hip abduction and extension.
Hip extension → ITB positioned over greater trochanter of femur.

Hip abduction strength

http://www.youtube.com/watch?v=9Iy-QscuGmo&feature=player_detailpage

One-legged standing squat

- Patient standing on unaffected leg
- Do 3 slow 1-legged squats
- Watch for stability, valgus angulation of knee, ask about pain
- Switch and perform on affected leg
- Sign of weak hip abductors, weak core
- Can bring out pain of patellofemoral pain
One-legged standing squat

Case #2: Physical exam
- Valgus knees while standing
- No effusion
- Tender lateral patellar facet
- Nontender joint lines
- ROM 0-135
- Meniscus testing (-)
- No ligamentous laxity
- (+) Ober bilaterally
- 4/5 hip abductor strength bilaterally
- Unstable 1-legged squat with valgus knee angulation

http://www.kneeguru.co.uk/KNEEnotes/node/763

Case #2 treatment
- Physical therapy rx
  - Strengthen hip abductors
  - Strengthen quadriceps
  - Stretch ITB, quads, hamstrings
- Correct alignment: consider OTC orthotics with arch support if pes planus
- Activity: avoid running, squats, lunges, stair-running, downhill hiking until improved.
- If not improved with above → x-rays and if those normal then MRI (or refer to sports medicine)

Shoulder Problems
Case #1

50 y/o RHD woman with type 2 diabetes presents with 3 months of severe R shoulder pain. No injury. Waking up at night due to pain. Shoulder feels very stiff. She is having trouble reaching behind and raising arm above head.

On exam she has no muscle atrophy and no point tenderness. There is decreased active and passive range of motion of the right shoulder. Her rotator cuff strength is 5/5 though difficult to perform due to limited range of motion and pain.

R shoulder x-rays are normal.

How would you treat this patient?

A. Provide R shoulder sling to use for comfort.
B. Provide shoulder steroid injection to reduce pain.
C. Obtain shoulder MRI.
D. Refer to surgeon for arthroscopy.

Adhesive capsulitis

[Image: http://www.aurorahealthcare.org/healthgate/images/si55551230.jpg]

Shoulder: diagnosis driven exam

[Diagram: Active ROM Decreased, Passive ROM Decreased, Frozen shoulder Normal, X-ray Abnormal, GH joint arthritis Abnormal]

Abduction

Shoulder active range of motion

Forward flexion

External rotation

Internal rotation

Limited ER key finding

Adhesive capsulitis is a clinical diagnosis

- No need for MRI
- X-rays helpful to rule out glenohumeral joint arthritis

X-rays courtesy of Dr. Ben Ma
3 stages of adhesive capsulitis

Freezing
3-9 months ↑ pain ↓ ROM Pain at rest, sleep

Frozen
4-12 months ↓ pain Stable, decreased ROM

Thawing
12-42 months Gradual ↑ ROM Resolution

Average time to resolution: 1-3 years

Treatment for adhesive capsulitis

- Associated w/diabetes: A1c or fasting blood sugar
- Pain control: NSAIDs or injected corticosteroids
  - Does not change disease course
  - Does help significantly with pain control
- +/- physical therapy to help restore ROM
- Capsular distention injections
- Surgery (rarely)


Case #2

57 y/o RHD man presents with R shoulder pain that started after he slipped and fell 3 months ago. Pain at R deltoid. He tried physical therapy without benefit. Waking at night from sleep due to pain.

Exam: Point tenderness just below the acromion. AROM intact with pain on abduction between 60 and 120 degrees. Difficulty fully abducting the R arm. Moderate pain with resisted internal and external rotation of the shoulder. (+) External rotation lag test, (+) internal rotation lag test.

What is the most likely cause of his shoulder pain?

A. Frozen shoulder
B. Glenohumeral joint arthritis
C. Rotator cuff tendinitis (tendinopathy)
D. Partial thickness rotator cuff tear
E. Full thickness rotator cuff tear
Shoulder: diagnosis driven exam

Active ROM
- Normal
- Decreased

Passive ROM
- Normal
- Decreased

X-ray
- Normal
- Abnormal

GH joint arthritis
- Normal
- Abnormal

Frozen shoulder

Rotator cuff disease
- Labral tear
- Biceps tendinitis
- AC joint OA

Rotator cuff disease in primary care

- The 3rd most frequent musculoskeletal reason patients present to the office
- The most common cause of shoulder pain in patients in the US primary care settings


What is rotator cuff disease?

- Impingement
- Tendinitis/tendinopathy
- Partial thickness tear
- Full thickness tear

Rotator cuff disease treatment

Most do well with conservative treatment
- Impingement
- Tendinitis, tendinopathy
- Partial thickness tear
- Full thickness tear → Consider ortho referral.

PT

+/- Injection
+/- Medication
Physical exam maneuvers that increase likelihood of full thickness rotator cuff tear

1. External rotation lag test
2. Internal rotation lag test

Strength test: External rotation lag test

Positive LR 7.2, Negative LR 0.57 for full thickness rotator cuff tear

JAMA. Rational clinical exam: Does this patient have rotator cuff disease? Aug 2013.

Strength test: Internal rotation lag test

Subscapularis = internal rotation lag test

Positive LR 5.6, negative LR 0.04 for full thickness rotator cuff tear

JAMA. Rational clinical exam: Does this patient have rotator cuff disease? Aug 2013.

Case #3

- 30 y/o RHD man fell off bike 3 months ago, injured R shoulder
- Went to PT but continues to have pain
- Anterior shoulder
- Only feels pain if moves shoulder in certain directions quickly
- Does not wake him from sleep at night
Physical examination

- No atrophy
- Tender biceps tendon, nontender AC joint
- AROM R shoulder is intact with a bit of pain at end of full flexion
- (-) Painful arc, (-) Drop arm tests
- (-) Internal and external rotation lag tests
- (+) O’Brien’s test

Case #3 differential diagnosis

- Labral tear
- AC joint separation
- Rotator cuff tear
- Shoulder dislocation
- Fracture
  - Humerus or clavicle

Glenoid labrum

O’Brien’s Test for Labral Tear

- Arm forward flexed to 90°
- Elbow fully extended
- Arm adducted 10° to 15° with thumb down
- Downward pressure
- Repeat with thumb up
- Suggestive of labral tear if more pain with thumb down
- Sens = 59-84%, Spec = 28-92%
SLAP tears

- **Superior Labrum Anterior to Posterior**
  - Many different types, classifications
  - Diagnosis: MR arthrogram
  - Treatment:
    - Trial of physical therapy
    - Surgery: debridement vs repair
  
  NOT a disease of older people (do not consider as etiology for shoulder pain in most >50 y/o as labrum degenerates naturally)

Take home points

1. 4 tests for meniscus tear
   1. Joint line tenderness
   2. McMurray
   3. Squat
   4. Thessaly

Take home points

2. Diagnostic criteria for knee OA

| Clinical and laboratory | Clinical and radiographic | Clinical
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee pain ≥ 6 mos</td>
<td>X-ray OA</td>
<td>Knee pain ≥ 6 mos</td>
</tr>
<tr>
<td>Radiographic OA</td>
<td>Knee X-ray OA</td>
<td>Radiographic OA</td>
</tr>
<tr>
<td>Knee line tenderness</td>
<td>Knee tenderness</td>
<td>Knee line tenderness</td>
</tr>
<tr>
<td>No palpable warmth</td>
<td>Synovitis</td>
<td>No palpable warmth</td>
</tr>
<tr>
<td>Normal flexion &lt; 90°</td>
<td>Normal flexion &lt; 90°</td>
<td>Normal flexion &lt; 90°</td>
</tr>
<tr>
<td>Jumper's stretch</td>
<td>Jumper's stretch</td>
<td>Jumper's stretch</td>
</tr>
<tr>
<td>II/III+</td>
<td>II/III+</td>
<td>II/III+</td>
</tr>
</tbody>
</table>

- Without knee OA
  - Degenerative tear → try non operative treatment first
  - Acute tear → refer for surgical consult
  - Bucket handle tear → urgent MRI, surgical consult, NWB

- With knee OA → non operative treatment first
Take home points

4. Differential diagnosis for anterior knee pain
   - Patellofemoral pain syndrome
   - Patellar chondromalacia
   - Osteochondral lesion of patellofemoral joint
   - Osteoarthritis of patellofemoral joint
   - Patellar tendinopathy
   - Quadriceps tendinopathy
   - Pes anserine bursitis

5. Name 2 causes of shoulder pain when both active and passive range of motion are limited.
   - Arthritis of the glenohumeral joint
   - Adhesive capsulitis (frozen shoulder)

6. Identify a full thickness rotator cuff tear on physical exam.

7. Explain treatment for rotator cuff disease
   Most do well with conservative treatment
   - Impingement
   - Tendinitis, tendinopathy
   - Partial thickness tear
   - Full thickness tear → Consider ortho referral.
Thank you!

Carlin Senter, MD
Carlin.Senter@ucsf.edu