

PRACTICAL POINTERS
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EXPRESSING HUMANISM IN EACH MEDICAL ENCOUNTER (6-1)
FREQUENCY OF FAILURE TO INFORM PATIENTS OF TEST RESULTS (6-2)
LIFESTYLE FACTORS IN NEW-ONSET DIABETES IN OLDER PATIENTS (6-3)
IS MONITORING BONE MINERAL DENSITY WITH DXA IN PATIENTS RECEIVING
ANTIRESORPTIVE THERAPY A “MISUSE OF HEALTH RESOURCES”? (6-4)
QUADRIVALENT HUMAN PAPILLOMA VIRUS VACCINE FOR WOMEN AGE 24-45 (6-5)
THERAPIES FOR CORONARY HEART DISEASE IN PATIENTS WITH DIABETES (6-6)
INFLUENZA A H1N1—INFORMATION FOR HEALTH PROFESSIONALS (6-7)
IMPLICATIONS OF THE EMERGENCE OF A NOVEL INFLUENZA VIRUS (6-8)
WHOOPING COUGH (6-8)
RECENT DEVELOPMENTS IN HYPERTHYROIDISM (6-10)
A NEW SELF-ADMINISTERED COGNITIVE SCREENING TEST FOR ALZHEIMERS (6-11)

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This document is divided into two parts

1) The **HIGHLIGHTS AND EDITORIAL COMMENTS SECTION**

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

EDITORIAL COMMENTS are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 20-year publication of Practical Pointers.

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 6 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.

Editor/Publisher.

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HIGHLIGHTS AND EDITORIAL COMMENTS JUNE 2009

The Other Side of the Coin

6-1 THE SILENT DIMENSION: *Expressing Humanism in Each Medical Encounter*

Professional competence encompasses two sides of the same coin: professional skills (disease oriented) and humanistic values (patient oriented).

“Humanistic medicine” has a number of meanings. It centers around the physician’s comprehension of the patient’s narrative and emotions; compassion, and commitment to act and try to alleviate the patient’s suffering. Humanistic behavior is an essential component of professional medical care. It is often neglected. Sincere humanistic behavior can become an integral part of the encounter, correct current deficiencies, and catch up with the astounding advances in modern biomedicine.

A warm, interested and supportive attitude toward the patient can be adopted with ease at every setting. Inclusion of the humanistic aspect of each physician-patient encounter may significantly alter the current scene. Marked benefits for both physician and patient can be expected, including patient’s satisfaction, trust, and compliance, leading to better health outcomes.

The commentator suggests use of a simple mnemonic for clinicians to capture and apply the essentials of a humanistic physician-patient relationship.

CAPTURES:

Curiosity: about the patient’s personal aspects.

Admire: finding something to admire about the patient.

Perspective: try to see things from the patient’s point of view.

Touch and Use: body language (proximity, holding the patient’s hand, smile) to convey caring and attention.

React: to what the patient says and does, and how. Take notice!

Support: Stress any positive or encouraging aspects to provide support and reassurance

Humanism can be taught and acquired. Lack of training constitutes one of the worst barriers to implementation. A warm, attentive, personal, and caring attitude on the part of the physician can be easily achieved and incorporated into the encounter.

Read the full abstract

I do not recall any discussion about the humanistic aspects of medicine during my training years (admittedly years ago). I believe it is stressed in training programs now. I hope so. Looking back, during my active practice years, I almost always focused more on the disease. I was intent on not

missing any important diagnosis and providing the most effective medical treatment.. If I could do it over again, I would certainly focus equally on the patient side. I believe I would then be a more productive clinician, and my practice would be more enjoyable.

6-2 FREQUENCY OF FAILURE TO INFORM PATIENTS OF CLINICALLY SIGNIFICANT OUTPATIENT TEST RESULTS

Failing to inform a patient about an abnormal outpatient test can be a serious error. Failure to inform and failure to document that the patient has been informed are common and are legally indefensible factors in malpractice claims.

This retrospective medical record review included over 5400 randomly selected records of primary care outpatients (age 50-69) in 23 practices. Selected 11 blood tests and 3 screening tests (mammography, Pap smear, and fecal occult blood test).

Defined a range of “clinically significantly abnormal ” values for each test. These values were well out of the reference range, and almost all physicians would agree that the patient should be informed because the test indicated immediate danger, or had potential implications for health over time.

Good processes for managing test results: 1) all results are routed to the responsible physician; 2) physician signs off on all results; 3) the practice informs patients about all results, normal and abnormal; 4) documents that the patient has been informed; 5) patients are told to call after a certain time if they had not been notified.

Very few practices had explicit rules for managing test results

Recorded 1889 abnormal test results. Of these there were 117 failures to inform, and 18 failures to document. Total of 135 of 1889 (7%)

Low process scores were significantly associated with failure to inform.

In 8 practices, patients were told that “no news is good news”—if patients did not hear about the test, they should assume it was normal. “No news is good news” is a dangerous practice.

Failure to inform could be approached as a systems problem—a problem of organization and incentives—rather than a failing of individual physicians.

Conclusion: Failure to inform patients, or to document informing patients of abnormal test results are common. Use of simple processes for managing results is associated with lower failure rates.

This is a good example of how a systems approach may improve methodology. Primary care practices should adopt good processes, not leave it to the individual physician.

Adding an EMR to poorly organized systems may make things worse.

Patients frequently wait for reports with anxiety. Poor communication remains a major fault in medicine. I believe prompt reporting is a manifestation of caring.

Each Low Risk Lifestyle Risk Factor Was Independently Associated With A Lower Incidence

6-3 LIFESTYLE RISK FACTORS AND NEW-ONSET DIABETES MELLITUS IN OLDER ADULTS

This study determined how lifestyle factors, assessed later in life, relate to new-onset type-2 diabetes (DM-2) in a broad and relatively unselected population of older adults.

Prospectively examined associations of lifestyle factors with incident DM-2 during a 10-year period among over 4800 randomly selected men and women age 65 and over (mean = 73)

Low-risk lifestyle groups were defined by:

- 1) Physical activity level (leisure-time activity and walking pace) above the median
- 2) Dietary score in the top 2 quintiles (higher fiber intake and higher polyunsaturated fat to saturated fat ratio lower trans fat intake, and lower mean glycemic index)
- 3) Never smoked or former smoker over 20 years ago
- 4) Alcohol use (light or moderate)
- 5) Body mass index less than 25
- 6) Waist circumference of 88 cm for women and 92 cm for men, or under

Main outcome measure = incident DM-2 defined by new use of insulin or oral hypoglycemic drugs.

During 10 years, 337 new cases of DM-2 occurred (10 per 1000 person-years).

Each low risk lifestyle risk factor was *independently* associated with a lower incidence of DM-2.

Nine of 10 cases of DM-2 in this older population appeared attributable to the 6 risk factors. If these factors are causal, 9 of 10 cases of DM-2 might have been prevented.

Conclusion: Even later in life, combined favorable lifestyle factors are associated with a markedly lower incidence of new-onset diabetes.

Diabetes not uncommonly begins in older age. Over 10 years, an estimated 10 in 1000 persons (one in every 100) over age 65 would develop new-onset DM-2. On a population basis, this would be a high number. Costs of treatment would be high. I believe many cases could be avoided.

Of course, the risk factors pertain to younger persons as well.

The goal is to go into old age with no risk factors. And to remove those that do exist at the time.

I believe the greatest challenge and the most productive intervention of our new national health care plan is to encourage and monitor adoption of healthy lifestyles. The only means to accomplish this lies in long-term continuous primary care.

The study strengthens the association of benefit of low-to-moderate alcohol intake. Abstinence has been termed a risk factor for years.

“Is Potentially Misleading and A Misuse Of Healthcare Resources”

6-4 MONITORING BONE MINERAL DENSITY DURING ANTIRESORPTIVE TREATMENT FOR OSTEOPOROSIS

Antiresorptive treatment for osteoporosis is usually prescribed for 5 years. It reduces the risk of fractures. It causes adverse effects. Patients and their doctors seek reassurance that the treatment is working.

The most common way to monitor response is repeated measurement of bone mineral density (BMD) using dual energy X-ray absorptiometry (DXA), an approach endorsed by guidelines.

A study in this issue of BMJ analyzed the effects of alendronate vs placebo in over 6000 women with low BMD. BMD at hip and spine was measured at 4 time points (before treatment, one, two and three years). Treatment was estimated to be beneficial in the vast majority of women. Overall, in 3 years, the mean increase in hip BMD was 0.030 g/cm^3 . At 3 years, the 95% distribution for the actual overall effects did not overlap zero, ranging from an increase of 0.019 to 0.041 g/cm^3

However, measurements in individuals (within a person) varied considerably more, often showing apparent decreases in BMD. The apparent 95% distribution of change after 3 years ranged from a decrease of 0.031 to an increase of 0.075 g/cm^3

The large within-person variation in BMD is likely to be an understatement, as BMD measurements in practice have considerably more within-person variation than measurements in clinical trials.

To detect significant changes in BMD, the rate of bone gain must be larger than the precision error of DXA measurement. Although gain may be achieved after 5 years of bisphosphonate therapy, the changes in BMD within 1 or 2 years is generally too small to be detected. Even changes of 7% or more may not be reliably shown in individual patients. Not being able to detect a change until 5 years is clearly not clinically useful.

The large variability associated with measurement of BMD in an individual obscures the treatment response. This makes monitoring unnecessary and potentially misleading.

A final nail in the coffin for monitoring BMD is the observation that only a small proportion of reduction in fractures attributable to alendronate is explained by a change in BMD. Only 16% of the

decrease in risk of fracture is attributable to an increase in BMD. Some studies have found reductions in fracture regardless of whether BMD is increased or decreased on treatment.

“The clear implication for clinical practice is that patients may be given inappropriate advice if changes in bone mineral density are used to monitor treatment.”

The national effort to reform medical insurance calls for studies to determine the most cost-efficient diagnostic tests. Testing is overdone. The use of DXA may be a good example.

The Quadrivalent HPV Vaccine Was Efficacious In Women Age 24-45

6-5 SAFETY, IMMUNOGENICITY, AND EFFICACY OF QUADRIVALENT HUMAN PAPILOMAVIRUS (TYPES 6, 11, 16, 18) RECOMBINANT VACCINE IN WOMEN AGE 24-45

Women older than age 25 clearly retain a substantial risk for acquisition of HPV. The extent to which infections occurring in mid-adult life are associated with subsequent risk of precancer and cancer is not clear.

The peak incidence of HPV infection occurs within 5-10 years of first sexual experience. A second peak has been recorded in women age 30-50. Whether this second peak is due to reactivation of latent infections, or new HPV infections is not clear. There is a possibility of new infections.

This international randomized, double-blind, placebo-controlled trial entered 3819 women age 25-45 between 2004-2006. None had a history of genital warts or cervical disease. None were pregnant or immunocompromised.

Randomized to: 1) Aluminum adjuvant quadrivalent vaccine (*Gardasil*; Merck). or
2) Aluminum containing placebo injection. Injections were given at day 1, and months 2 and 6.

Performed gynecological examinations periodically up to 48 months. Specimens were tested by PCR for HPV DNA. Also tested subjects for infection by a serological test (immuno-assay for antibodies to HPV).

At baseline, HPV positivity to either 6, 11, 16, or 18 by immunoassay or DNA testing was 33%. 90% of women were naïve to 3 vaccine types; 66% were naïve to all 4 types.

Almost all women seroconverted. Those who were infected with one type at baseline usually experienced a rise in titer to that type.

Vaccine efficacy:

A. Against incidence of infection (detected by serology) = 93%.

Infection occurred in 3 vaccine subjects vs 40 placebo subjects.

B. Against clinical disease (detected by PCR): one vaccine vs 13 placebo cases.

C. Against combined incidence of infection or clinical disease related to types 16 and 18 = 83%; 4 cases in the vaccine group vs 23 cases in the placebo group.

D. Against types 6 and 11 = 100%; 0 in the vaccine group and 19 in the placebo group.

Adverse effects: 5 persons in the vaccine group and one in the placebo group discontinued because of adverse effects. No serious vaccine-related adverse events were recorded.

“Our results are generalizable to women aged 24-45 years in the general population who have had no (recent) cervical disease and no previous history of external genital disease.”

Conclusion: The quadrivalent HPV vaccine was efficacious in women age 24-45 who were not infected with the relevant HPV types at enrollment.

This trial was conducted in 6 different countries. This is an excellent illustration of international cooperation. I congratulate all concerned.

In those already infected with one type, titers of antibodies to that type rose after administration of the vaccine. Will this help eliminate the infection? Previous studies of HPV stated the vaccine was not therapeutic.

This application is not ready for prime time. We await developments with interest.

This may prove to be a major advance in cancer prevention.

The duration of immunity is not known. Boosters may be required.

Provides Some Guidance To Primary Care Clinicians

6-6 THERAPIES FOR TYPE 2 DIABETES AND (STABLE) CORONARY HEART DISEASE:

A Randomized Trial

What is the optimal treatment for patients with type-2 diabetes (**DM-2**) and angiographically defined, stable coronary heart disease (**CHD**) ?

This randomized trial entered and followed 2368 patients with both DM-2 and CHD.

All had CHD documented on angiography. Ischemia was symptomatic in 82% of patients.

All patients were treated according to current guidelines to target levels of HbA1c less than 7%, LDL-cholesterol less than 100mg /dL, and BP of 130/ 80 or less. Medications included statins, aspirin, beta-blockers, and either ACE inhibitors or angiotensin II blockers.

All received counseling regarding smoking, weight loss, and exercise.

Randomized to:

A. 1) A group pre-selected for CABG (n = 763), or 2) A group pre-selected for PCI (n =1605)

(Selection was by the responsible physician as the most appropriate therapy for each patient.)

B. Both groups were then divided into subsets:

2368 enrolled			
CABG stratum		PCI stratum	
Pre-selected for CABG (n = 763)		Pre-selected for PCI (n = 1605)	
Randomized to	Randomized to	Randomized to	Randomized to
IMT-alone	prompt CABG + IMT	IMT- alone	prompt PCI + IMT
(n = 385)	(n = 378)	(n = 807)	(n = 798)

(Thus, all 2368 patients received IMT. Patients in the CABG stratum had significantly more coronary disease.)

(Patients in the CABG group assigned to IMT-alone were to undergo revascularization with CABG during follow-up only if clinically indicated. Patients in the PCI group assigned to IMT-alone were to undergo revascularization with PCI during follow-up only if clinically indicated.)

C. All subjects were also randomized to: 1) Insulin provision (insulin and/or sulfonylurea), or 2) Insulin sensitization (metformin and/or thiazolidinedione)

Primary endpoint = death from any cause. Secondary endpoint = composite of death, non-fatal MI, and stroke (major CV events).

All patients assigned to IMT-alone underwent careful monitoring, and 42% had changes in the clinical course during 5-years of follow-up that called for later revascularization. At 3 years, 43% of patients in the insulin-sensitization group and 12% of those in the insulin-provision group received medications from the alternative drug class. (Ie, considerable cross-over between groups)

In the insulin-sensitization group, compared with the insulin provision group, mean HbA1c levels were significantly lower, the BMI significantly lower, plasma insulin levels consistently lower, and there were fewer episodes of severe hypoglycemia, less weight gain, and higher HDL-cholesterol levels.

Overall, the rate of death from any cause did not differ significantly between the various groups; 88% survived at 5-years. The rate of freedom from major CV events did not differ significantly between the revascularization groups and the IMT-alone groups, or between the insulin-provision and the insulin-sensitization groups.

However, at 5 years, patients in the CABG stratum who were pre-assigned to prompt surgery had significantly fewer major CV events (especially non-fatal MI) than those in the CABG stratum assigned to the IMT-alone group (22% vs 30%). In contrast, rates of CV events among patients in the PCI stratum who were assigned to prompt PCI did not differ significantly from those in the IMT-alone group.

Severe hypoglycemia was more frequent in the insulin-provision group (9%)

The fact that the majority of patients in the IMT-alone groups did not require revascularization during 5-years suggests that many may be safely treated with IMT-alone.

Among patients for whom CABG was selected as the intended method of revascularization, the

combination of prompt surgery and an insulin-sensitization strategy was associated with a lower rate of major CV events than any of the other treatment combination groups.

“This data may suggest that insulin-sensitization is preferable for patients with type-2 diabetes and coronary disease.”

This complex trial was difficult to abstract clearly and concisely. I believe it does provide some guidance for primary care clinicians who may be negotiating with patients, in collaboration with their cardiologist consultants, about best therapy for this subset of diabetic patients.

- 1) Insulin-sensitization (metformin and thiazolidinediones) provides advantages over insulin-provision. (The study could not determine adverse effects of thiazolidinediones.)*
- 2) If revascularization is advised, CABG is the preferred intervention. PCI is not recommended.*
- 3) Intensive medical treatment alone is an option. Careful follow-up is required to determine if cross-over to CABG is necessary. As well as cross-over to additional drug therapy.*

A H1N1 Influenza Center At NEJM.Org Will Help Monitor The Disease

6-7 H1N1 INFLUENZA A—INFORMATION FOR HEALTH PROFESSIONALS

In the first 2 weeks in April 2009, cases of an untyped influenza A began to be identified in Mexico and Southern California. By the third week in April, it was established that the illness resulted from a triple recombination of human, avian, and swine influenza viruses. It is an H1N1 virus.

A polymerase-chain-reaction (**PCR**) has been developed, which enables determination whether an illness with the protean manifestations of cough, fever, sore throat, diarrhea, and nausea, could be confirmed as a case.

By May 7 (only one month after the first case) articles appeared providing background information about the novel virus in the USA. The goal was to provide clinical descriptions of patients so that health professionals could make the difficult decision about whether an individual had a suspected case. The decision depends on the presence of typical, but unfortunately variable and non-specific symptoms. Identifying a case by PCR allows epidemiological links to be established.

The ability to clearly define a confirmed case will allow for a careful assessment of the associated illness and its severity. We now have important tools to fight this outbreak: a clear definition, an aware health care system, and an informed public.

Please read the full abstracts.

I believe the identification, tracking, and prompt notification of this disease is a miracle of modern technology and a source of satisfaction to the WHO, the CDC and the Public Health Service

Would outcomes have been different if this technology were available in 1918?

The Current Situation Is Not “1918 Again”. It Is 1918 Continued.

6-8 IMPLICATIONS OF THE EMERGENCE OF A NOVEL H1 INFLUENZA VIRUS

A group of viruses, called triple reassortants of viruses from pigs, humans, and birds (triple reassortant swine influenza A (H1) viruses) has circulated among pigs for more than a decade. These viruses may occasionally be transmitted from pigs to humans, but do not spread efficiently from human to human.

Another group is a recent reassortant of the triple swine influenza A virus (H1) and an Eurasian swine influenza virus. This new virus is the H1N1 currently being transmitted human to human and has spread rapidly to many countries.

It is termed the swine-origin influenza virus (**S-OIV**)

The current situation is not “1918 again”. It is 1918 continued. We are being infected with the remnants of the 1918 virus.

Questions remain:

- 1) Will S-OIV replace human H1 virus as the seasonal virus and evolve antigenic variants every year?
- 2) Will S-OIV further adapt to humans and become more severe?
- 3) Will it return in the fall season and become more severe with higher mortality?
- 4) Will a vaccine be available? Development will be challenging.

6-9 WHOOPING COUGH: *Easily Missed*

Whooping cough (**WC**), caused by *Bordetella pertussis*, should be considered in any adolescent or adult with an acute cough lasting more than 2 weeks, even if the patient has been immunized. The cough may be the only symptom.

A single raised titer of an IgG anti-body to pertussis toxin in oral fluid is validated. It is quick and easy to use in primary care. It is 99% specific.

How is it managed? WC is a notifiable disease. Erythromycin within 3 weeks of onset of symptoms reduces the period of infectivity and may prevent transmission to family members, even though treatment may not affect outcome for the patient. A seven-day course is sufficient.

Prophylaxis with erythromycin should be offered to everyone in households with a vulnerable infant. The illness in infants may be severe and require prompt referral.

6-10 RECENT DEVELOPMENTS IN HYPERTHYROIDISM

Since the 2003 *Lancet* seminar on hyperthyroidism, several reports have enhanced understanding of the end-organ manifestations of hyperthyroidism.

This brief article comments on:

1. Atrial fibrillation in older persons with subclinical hyperthyroidism (SCH) .
2. Relation of SCH to all-cause mortality
3. Treatment of SCH in asymptomatic patients
4. Bone loss associated with SCH
5. Sexual dysfunction in males with hyperthyroidism
6. Antithyroid drugs to treat hyperthyroidism. Methimazole may be preferable to propylthiouracil¹
7. Antithyroid drugs as definitive treatment of Graves disease.
8. Antithyroid drugs prior to radio-iodine treatment
9. Long-term quality of life of patients with Graves disease

Please read the full abstract.

1 *The FDA has recently alerted physicians about the risk of liver failure and death in patients taking propylthiouracil for Graves disease. Of 32 patients taking propylthiouracil who developed a serious liver injury, 13 died, and 11 required liver transplant. Only 5 cases of liver failure from methimazole have been reported. Patients taking propylthiouracil should be closely monitored for signs of liver injury.. Propylthiouracil should be avoided unless there are no other options.*

JAMA "Medical News and Perspective" July 20/29 302; 370-71

This is amazing! Propylthiouracil has been prescribed for decades. There must be many drugs causing serious effects we know nothing about.

A Positive And Valid Screening Test For The Detection Of AD

6-11 SELF ADMINISTERED COGNITIVE SCREENING TEST (TYM) FOR DETECTION OF ALZHEIMER'S DISEASE

Three requirements for widespread use of cognitive tests for use by non-specialists:

1. Minimal operator time to administer

2. Test a reasonable range of cognitive functions

3. Sensitive for Alzheimer's disease (AD)

The TYM ("test your memory") test was designed to fulfill these requirements.

The test is a series of 10 self-administered tasks: orientation, ability to copy a sentence, semantic knowledge, calculation, verbal fluency, similarities, naming, visiospatial abilities, and recall of a copied sentence. Perfect score = 50

A cross sectional study included 94 patients with AD attending a memory clinic, 23 patients with amnesic mild cognitive impairment, and 540 controls.

Controls: Average score was 47 of 50 for ages 18-70. Scores slightly declined after age 70, and significantly declined after age 80.

AD patients: Average score was 33 of 50

With a cut-point of 42 or less, the TYM detected 93% of patients with AD; the MMSE at the established cut point of 23 or less detected 52%.

Patients with mild cognitive impairment averaged 29 of 30 on the MMSE and 45/50 on the TYM. They tended to score worse on anterograde memory.

I abstracted this article to note that a substitute for the MMSE is available. Use of the MMSE is constrained by a copyright.

The TYM is designed as a quick screening test for primary care.

There are several cognitive tests available. They seem similar. More time may be needed to establish the place of TYM—its limitations and usefulness in English-speaking societies

ABSTRACTS JUNE 2009

The Other Side of the Coin

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“Humanistic medicine” has a number of meanings. It centers around the physician’s comprehension of the patient’s narrative and emotions; compassion, and commitment to act and try to alleviate the patient’s suffering. Humanistic behavior is an essential component of professional medical care. It is often neglected. Sincere humanistic behavior can become an integral part of the encounter, correct current deficiencies, and catch up with the astounding advances in modern biomedicine.

A warm, interested and supportive attitude toward the patient can be adopted with ease at every setting. Inclusion of the humanistic aspect of each physician-patient encounter may significantly alter the current scene. Marked benefits for both physician and patient can be expected, including patient’s satisfaction, trust, and compliance, leading to better health outcomes.

The commentator suggests use of a simple mnemonic for clinicians to capture and apply the essentials of a humanistic physician-patient relationship.

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Admire: finding something to admire about the patient.

Perspective: try to see things from the patient’s point of view.

Touch and Use: body language (proximity, holding the patient’s hand, smile) to convey caring and attention.

React: to what the patient says and does. Take notice!

Support: Stressing any positive or encouraging aspects to provide support, reassurance, and hope.

The sincere adoption of a few simple attitudes and techniques as summarized by the CAPTURES mnemonic may prompt physicians to focus on the humanistic aspects of patient care as a routine component of the encounter. Adopting a warm, friendly, and real curiosity about your patient’s personal aspects is always a good beginning. Inquiring about the patient’s birthplace, family origins, childhood, profession, children or hobbies will supply a good lead. Then find something to openly admire in the patient. Respect for the patient and commitment will readily follow in all but exceptional cases.

In difficult cases, admit uncertainty, interpret negative tests as a good sign, provide repeated encouragement, and stress the need to watch and wait. Be able to sense the patient’s perspective and

respond with an enhanced commitment and honesty. Honesty is the best policy even when mistakes occur. The physician needs to develop the ability, as well as the habit, to sense how things look to the other person and feel and respond to the caretaker's burden. Joke and laugh a little. Praise minor achievements. Instill some hope.

Humanism can be taught and acquired. Lack of training constitutes one of the worst barriers to implementation. A warm, attentive, personal, and caring attitude on the part of the physician can be easily achieved and incorporated into the encounter.

A humane attitude complements scientific knowledge, professional expertise, and evidence-based decisions. Patients cite "humanism" as the most highly rated aspect of care. They stress strong preferences for good communication, partnership, and autonomy. Such behavior is an important determinant of patient's satisfaction and trust. It may improve compliance with medical advice and medications. And lead to better health outcomes.

Physicians who are gentle, respectful, sensitive, and attentive to their patients are more likely to elicit and understand the whole spectrum of patients' agendas, uncover significant emotional or social problems, and improve the patient's quality of life and prognosis. Health literacy, adherence, and coping improve, not only for patients, but also for their families.

There are many barriers to the expression of empathy and compassion, and sensitivity to the patient's concerns: time; poor continuity of care; and the appearance of alienating factors between patients and physicians. Reality lags far behind. Physicians tend to interrupt patients within seconds of commencing their story, leaving many agendas, mostly personal, unvoiced. Most clues and direct expressions of affect pass unacknowledged. Patients are often frustrated and cite impaired concern and unsatisfactory communication with their physician. Many are deeply disappointed with the caring and empathetic dimensions of today's medicine. Many turn to complementary and alternative medicine.

Deserting the prevailing predominantly bio-medical paradigm in favor of a more balanced approach that recognizes and targets the sick person and the burden of illness as well as the disease is associated with improved health outcomes. Physicians also gain emotionally and can be expected to be more satisfied, less stressed, and less sued.

Conclusion: The sophisticated and rapid advances of modern bio-medicine have not encompassed the humanistic aspects of patient care. Better physician education and increased awareness by physicians are needed to include and express an honest personal, sensitive, and caring attitude in every patient-physician encounter, despite difficulties such as time constraints.

6-2 FREQUENCY OF FAILURE TO INFORM PATIENTS OF CLINICALLY SIGNIFICANT OUTPATIENT TEST RESULTS

Failing to inform a patient about an abnormal outpatient test can be a serious error. Failure to inform and failure to document that the patient has been informed are common and legally indefensible factors in malpractice claims.

This study asks the following questions:

- 1) How commonly do primary care physicians fail to inform patients of clinically significant abnormal outpatient test results?
- 2) Do practices that use certain “good” practices to manage test results have lower failure rates?
- 3) Do practices that use electronic medical records (**EMR**) have lower failure rates?

STUDY

1. Retrospective medical record review included over 5400 randomly selected records of primary care outpatients (age 50-69) in 23 practices. Selected 11 blood tests and 3 screening tests (mammography, Pap smear, and fecal occult blood test).
2. Defined a range of “clinically significantly abnormal” values for each test. These values were well out of the reference range, and almost all physicians would agree that the patient should be informed because the test indicated immediate danger, or had potential implications for health over time.
3. Surveyed physicians about the processes of managing test results.
4. Informed individual physicians about their apparent failure to inform and asked whether they had informed the patient.
5. Reviewers calculated a “process score” ranging from 0 to 5 for each practice
6. Good processes for managing test results were defined 1) all results are routed to the responsible physician; 2) physician signs off on all results; 3) the practice informs patients about all results, normal and abnormal; 4) documents that the patient has been informed; 5) patients are told to call after a certain time if they had not been notified.

RESULTS

1. Recorded 1889 abnormal test results.
2. Of these there were 117 failures to inform, and 18 failures to document. Total of 135 of 1889 (7%)
3. Failures ranged from 0% in 3 practices to 26%.
4. The mean process score was 3.8 on a 0 to 5 scale. Five meaning that the practice routinely used all 5 good processes. Low process scores were significantly associated with failure to inform.
5. Very few practices had explicit rules for managing test results. In 8 practices, patients were told that “no news is good news”—If patients did not hear about the test, they should assume it was normal.
6. Five practices had full EMRs ; 4 had partial; and 14 had none. Failure rates were relatively low in practices with good process, regardless of whether they had full EMR.
7. Use of partial electronic records (paper-based progress notes and electronic test results or vice-versa) was associated with higher failure rates compared with not having an electronic record, or with having an electronic record that included both progress notes and test results.

DISCUSSION

1. “In this study, failing to inform patients of clinically significant abnormal tests results or to document that they have been informed, appears to be relatively common, occurring in 1 of every 14 tests.”
2. Practices that used better processes to manage results had lower failure rates.
3. Partial EMRs (combination of paper and electronic records) had the highest rates of failure.
4. Most practices did not use all 5 of the relatively simple processes. Most do not have explicit rules about notifying patients.
5. “No news is good news” is a dangerous practice.
6. Most physicians believe that patients should be informed of normal as well as abnormal results.
7. Failure to inform could be approached as a systems problem—a problem of organization and incentives—rather than a failing of individual physicians.

CONCLUSION

Failure to inform patients, or to document informing patients of abnormal test results are common. Use of simple processes for managing results is associated with lower failure rates.

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Each Low Risk Lifestyle Risk Factor Was Independently Associated With A Lower Incidence

6-3 LIFESTYLE RISK FACTORS AND NEW-ONSET DIABETES MELLITUS IN OLDER ADULTS

Preventing the onset of type-2 diabetes (**DM-2**) is important. Long-term treatment with metformin may prevent or delay onset of DM-2 in high risk subgroups. Modest changes in diet and exercise prevent DM-2 to a greater extent than metformin, improve a broad range of other metabolic risk factors that are largely unaffected by metformin, and may be more applicable to a broader population than metformin.

This study determined how lifestyle factors, assessed later in life, relate to new-onset DM-2 in a broad and relatively unselected population of older adults.

STUDY

1. Prospectively examined associations of lifestyle factors with incident DM-2 during a 10-year period among over 4800 randomly selected men and women age 65 and over (mean = 73)
2. Low-risk lifestyle groups were defined by:
 - 1) Physical activity level (leisure-time activity and walking pace) above the median
 - 2) Dietary score in the top 2 quintiles (higher fiber intake, higher polyunsaturated fat to saturated fat ratio, lower trans fat intake, and lower mean glycemic index)
 - 3) Never smoked or former smoker over 20 years ago
 - 4) Alcohol use (light or moderate)
 - 5) Body mass index less than 25
 - 6) Waist circumference of 88 cm for women and 92 cm for men, or under
3. Main outcome measure = incident DM-2 defined by new use of insulin or oral hypoglycemic drugs.

RESULTS

1. During 10 years, 337 new cases of DM-2 occurred (10 per 1000 person-years).
2. Each low risk lifestyle risk factor was independently associated with a lower incidence of DM-2
3. Risk of incident DM-2 according to low-risk lifestyles:

Low-risk lifestyle factors	% of 4883 participants	Hazard ratio*
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1) Physical activity > median		
Dietary score upper 2 quintiles	22	0.54
2) Physical activity > median		
Dietary score upper 2 quintiles		
Never smoked or former smoker	12	0.42
3) Physical activity > median		
Dietary score upper 2 quintiles		
Light-moderate alcohol use	13	0.32
4) Physical activity > median		
Dietary score upper 2 quintiles		
Never smoked or former smoker		
Light-moderate alcohol use	6	0.18
5) Physical activity > median		
Dietary score upper 2 quintiles		
Never smoked or former smoker		
Light-moderate alcohol use		
BMI < 25, or WC < 88 or < 92 cm	3.4	0.11
(* HR compared with participants not in this low-risk group)		

DISCUSSION

1. In this large prospective cohort study of older adults, lifestyle factors assessed later in life, were each independently associated with risk of new-onset DM-2
2. Nine of 10 cases of DM-2 in this older population appeared attributable to 6 risk factors: low physical activity, poor diet, smoking, and alcohol use (none or high), not being overweight, and not having a high waist circumference. If these factors are causal, 9 of 10 cases of DM-2 might have been prevented.
3. Other studies have reported that 1 to 2 drinks a day increase HDL-cholesterol, lower triglycerides, and lower HbA1c and fasting blood glucose.

CONCLUSION

Even later in life, combined favorable lifestyle factors are associated with a markedly lower incidence of new-onset diabetes.

Archives Int Med April 27, 2009; 798-807 Original investigation, first author Dariush Mozaffarian, Harvard School of Public Health, Boston, Mass. This is based on data from the Cardiovascular Health Study

“Is Potentially Misleading and A Misuse Of Healthcare Resources”

6-4 MONITORING BONE MINERAL DENSITY DURING ANTIRESORPTIVE TREATMENT FOR OSTEOPOROSIS

Antiresorptive treatment for osteoporosis is usually prescribed for 5 years. It reduces the risk of fractures. It causes adverse effects. Patients and their doctors seek reassurance that the treatment is working.

The most common way to monitor response is repeated measurement of bone mineral density (**BMD**) using dual energy X-ray absorptiometry (**DXA**), an approach endorsed by guidelines.

Routine monitoring is costly, and—if it does not reduce disease burden—may divert healthcare resources from more deserving causes. Monitoring should detect whether treatment will reduce the risk of fracture in individual patients.

The effectiveness of repeated measurement of BMD to monitor treatment depends on:

- 1) DXA should be able to detect a significant change in BMD within a time scale that enables effective changes in management to occur.
- 2) The change in BMD must predict the reductions in fractures after treatment.

To detect significant changes in BMD, the rate of bone gain must be larger than the precision error of DXA measurement. Although gain may be achieved after 5 years of bisphosphonate therapy, the changes in BMD within 1 or 2 years is generally too small to be detected. Even changes of 7% or more may not be reliably shown in individual patients. Not being able to detect a change until 5 years is clearly not clinically useful.

A large randomized, controlled trial in this issue of *BMJ*¹ analyzed the changes in BMD during the first few years of alendronate therapy (*Fosamax*; Merck). The variation of effect of treatment between women was considerably less than the variation within an individual woman. The large variability associated with measurement of BMD in an individual obscures the treatment response. This makes monitoring unnecessary and potentially misleading.

A final nail in the coffin for monitoring BMD is the observation that only a small proportion of reduction in fractures attributable to alendronate is explained by a change in BMD. Only 16% of the

decrease in risk of fracture is attributable to an increase in BMD. Some studies have found reductions in fracture regardless of whether BMD is increased or decreased on treatment.

How much these findings reflect variation in measurement of BMD or true lack of correlation between changes in BMD and fracture reduction is uncertain.

“The clear implication for clinical practice is that patients may be given inappropriate advice if changes in bone mineral density are used to monitor treatment.”

If true non-responders to antiresorptive treatment do exist, they are rare, and caused mainly by non-adherence to treatment.

BMJ June 27, 2009; 338: 1511-13 Editorial by Juliet Compston, University of Cambridge, UK.

1 BMJ June 27, 2009; 338: 1553 “Value of Routine Monitoring of Bone Mineral Density after Starting Bisphosphonate Treatment” first author Katy L Bell, University of Sydney, Australia.

This study analyzed the effects of alendronate vs placebo in over 6000 women with low BMD.

Most patients also took supplementary vitamin D and calcium. BMD at hip and spine was measured at 4 time points (before treatment, one, two and three years).

Treatment was estimated to be beneficial in the vast majority of women. The mean actual increase in hip BMD was 0.030 g/cm^3 . At 3 years, the 95% distribution for the actual effects did not overlap zero, ranging from an increase of 0.019 to 0.041 g/cm^3

However, measurements in individuals (within a person) varied considerably more, often showing apparent decreases in BMD. The apparent 95% distribution of change after 3 years ranged from a decrease of 0.031 to an increase of 0.075 .

The large within-person variation in BMD is likely to be an understatement, as BMD measurements in practice have considerably more within-person variation than measurements in clinical trials.

6-5 SAFETY, IMMUNOGENICITY, AND EFFICACY OF QUADRIVALENT HUMAN PAPILOMAVIRUS (TYPES 6, 11, 16, 18) RECOMBINANT VACCINE IN WOMEN AGE 24-45

Women older than 25 clearly retain a substantial risk for acquisition of HPV. The extent to which infections occurring in mid-adult life are associated with subsequent risk of precancer and cancer is not clear.

In a cohort of 1600 women in Columbia, the 5-year cumulative risk of cervical HPV infection of any type decreased from 43% in women age 15-19 to 22% in those aged 30-44 (*due to an immune response*). There is a reduced, but not insignificant risk in the older cohort.

The peak incidence of HPV infection occurs within 5-10 years of first sexual experience. A second peak has been recorded in women age 30-50. Whether this second peak is due to reactivation of latent infections, or new HPV infections is not clear. There is a possibility of new infections.

Changes in sexual behavior in the past 30 years, characterized by rising age at first marriage, and an increase in divorce rates, have led to more widespread premarital sexual intercourse, and acquisition of new sexual partners around middle age.

In the US, nearly 40% of men and women who have married are divorced by age 55; 25% of these people remarry at least once.

Thus, the potential of HPV infection and disease exists in women in their 3rd, 4th, and 5th decades. These women could benefit from prophylactic HPV vaccination.

The prophylactic quadrivalent HPV vaccine (types 6, 11, 16, 18) is highly effective in prevention of cervical epithelial neoplasia related to these types, as well as cervical adenocarcinoma in situ, in women who are naïve to the respective HPV types (especially 16 and 18). There is also a high efficacy against genital warts related to types 6 and 11.

Women who are naïve to all 4 types (negative by both serological and DNA testing with PCR) derive full benefit in protection against all 4 types. Women who are infected with one or more types will derive partial protection.

This phase III trial assessed the efficacy, safety, and immunogenicity of the quadrivalent vaccine in women age 24-45.

STUDY

1. An international randomized, double-blind, placebo-controlled trial entered 3819 women age 25-45 between 2004-2006. None had a history of genital warts or cervical disease. None were pregnant or immunocompromised.
2. Randomized to: 1) Aluminum adjuvant quadrivalent vaccine (*Gardasil*; Merck). or
2) Aluminum containing placebo injection. Injections were given at day 1, and months 2 and 6.
3. Performed gynecological examinations periodically up to 48 months. Specimens were tested for HPV DNA by PCR Also tested subjects for infection by a serological test (immuno-assay for antibodies to HPV).
4. Coprimary efficacy endpoints: Combined incidence of infection (detected by serology)

of at least 6 months duration, and cervical and external genital disease due to 1) HPV 6, 11, 16, and 18 and due to 2) only HPV 16 and 18 (detected by PCR). The primary immunogenicity endpoint was serum antibody response to HPV after administration of 3 doses.

5. Infection of 6 months' or more duration was defined as detection of the same HPV-DNA type in cervical or anogenital swabs at two or more consecutive visits spaced at least 6 months apart.
6. Disease was defined as neoplasia, cancer, or warts.
7. Follow-up = a mean of 2.2 years. The trial is expected to last 4 years.

RESULTS

1. At baseline, HPV positivity to either 6, 11, 16, or 18 by immunoassay or DNA testing was 33%. 90% of women were naïve to 3 vaccine types; 66% were naïve to all 4 types.
2. Almost all women had sexual intercourse before enrollment. Mean age at first experience was 19.
3. Almost all women seroconverted. Those who were positive for one type at baseline usually experienced a rise in titer to that type.
4. Vaccine efficacy:
 - A. Against incidence of infection (detected by serology) of at least 6 months' duration = 93%. Infection occurred in 3 vaccine subjects vs 40 placebo subjects.
 - B. Against clinical disease (detected by PCR): one vaccine vs 13 placebo cases.
 - C. Against combined incidence of infection of 6 months' duration or clinical disease related to types 16 and 18 = 83%; 4 cases in the vaccine group vs 23 cases in the placebo group. Against types 6 and 11 = 100%; 0 in the vaccine group and 19 in the placebo group.
5. Adverse effects: 5 in the vaccine group and one in the placebo group discontinued because of adverse effects. No serious vaccine-related adverse events were recorded.

DISCUSSION

1. In adult women age 24-45, the HPV vaccine efficacy against infection, and cervical and external genital disease, is high (mainly due to efficacy against infection).
2. The quadrivalent vaccine already has a proven benefit in girls and women age 9-26.
3. The present report used a combined endpoint of HPV infection of 6 months or longer duration + HPV-related anogenital disease. The composite endpoint allowed a more rapid assessment of efficacy due to the sometimes lengthy interval between HPV infection and disease. The current study was designed as an efficacy bridging study. A longer study will be more revealing.

4. Most of the cervical HPV-related disease was diagnosed as CIN 1, which is considered a morphological manifestation of HPV infection.
5. Maximum effect from prophylactic vaccination will be achieved in women who are not already infected and who are susceptible to infection related to vaccine types. At entry, almost all women in the trial were susceptible to 3 or 4 of the types in the vaccine. A quadrivalent vaccine could potentially benefit women against infection with HPV of types with which they are not infected.
6. The public health effect of the vaccine in women age 24-45 may be smaller than that recorded in younger girls and women.
7. "Our results are generalizable to women aged 24-45 years in the general population who have had no (recent) cervical disease and no previous history of external genital disease."

CONCLUSION

The quadrivalent HPV vaccine was efficacious in women age 24-45 who were not infected with the relevant HPV types at enrollment.

Lancet June 6, 2009; 373: 1949-57 Original investigation, first author Nubia Munoz, National Institute of Cancer, Bogata, Columbia.

Trial supported entirely by Merck.

Provides Some Guidance To Primary Care Clinicians

6-6 THERAPIES FOR TYPE 2 DIABETES AND (STABLE) CORONARY HEART DISEASE:

A Randomized Trial

What is the optimal treatment for patients with type-2 diabetes (**DM-2**) and angiographically defined stable coronary heart disease (**CHD**) ?

This trial evaluated two cardiac treatment strategies and two glyceimic treatment strategies in patients who were receiving uniform glyceimic control (with a target HbA1c of less than 7%) and intensive therapy for cardiac risk factors. The hypotheses of the trial were: 1) Prompt revascularization would reduce long-term rates of death and cardiovascular events as compared with medical therapy alone, and 2) A strategy of insulin sensitization would reduce long-term events and death as compared with a strategy of insulin provision.

STUDY

1. Randomized trial entered and followed 2368 patients with both DM-2 and CHD between 2001-2005

at 49 clinical sites in 6 countries. Follow-up to December 2008 (mean of 5 years).

2. All had CHD documented on angiography: > 50% stenosis of a major coronary artery associated with a positive stress test, or > 70% stenosis in a patient with classical angina. All patients had to be candidates for percutaneous coronary intervention (**PCI**) or coronary artery bypass grafting (**CABG**). Ischemia was symptomatic in 82% of patients. None had left main coronary disease, or class III or IV heart failure.

3. Randomized to:

A. 1) A group pre-selected for CABG (n = 763), or 2) A group pre-selected for PCI (n = 1605)
(Selection was by the responsible physician as the most appropriate therapy for each patient.)

B. Both groups were then divided into subsets:

2368 enrolled			
CABG stratum		PCI stratum	
Pre-selected for CABG (n = 763)		Pre-selected for PCI (n = 1605)	
Randomized to	Randomized to	Randomized to	Randomized to
IMT-alone	prompt CABG + IMT	IMT- alone	prompt PCI + IMT
(n = 385)	(n = 378)	(n = 807)	(n = 798)

(Patients in the CABG stratum had significantly more coronary disease. All 2368 patients received IMT.)

(Patients in the CABG group assigned to IMT-alone were to undergo revascularization with CABG during follow-up only if clinically indicated. Patients in the PCI group assigned to IMT-alone were to undergo revascularization with PCI during follow-up only if clinically indicated.)

C. All subjects were also randomized to: 1) Insulin provision (insulin and/or sulfonylurea), or 2) Insulin sensitization (metformin and/or thiazolidinedione)

4. All patients were treated according to current guidelines to target levels of: HbA1c less than 7%, LDL-cholesterol less than 100mg /dL, and BP of 130/ 80 or less. Medications included: statins, aspirin, beta-blockers, and either ACE inhibitors or angiotensin II blockers.

5. All received counseling regarding smoking, weight loss, and exercise.

6. Patients were followed regularly for a mean of 5 years. Analysis of outcomes on an intention-to-treat basis.

7. Primary endpoint = death from any cause. Secondary endpoint = composite of death, non-fatal MI, and stroke (major CV events).

RESULTS

1. In the prompt intervention groups, revascularization (either PCI or CABG) was performed within 6 months in those who were pre-selected to these interventions.

2. At 5 years, 42% of those assigned to IMT-alone groups had undergone clinically indicated

revascularization. At 3 years, 43% of patients in the insulin-sensitization group and 12% of those in the insulin-provision group received medications from the alternative drug class.

(Ie, considerable cross-over between groups)

3. In the insulin-sensitization group, compared with the insulin provision group, mean HbA1c levels were significantly lower, the BMI significantly lower, plasma insulin levels consistently lower, and there were fewer episodes of severe hypoglycemia, less weight gain, and higher HDL-cholesterol levels.
4. Overall, the rate of death from any cause did not differ significantly between the various groups; 88% survived at 5-years. The rate of freedom from major CV events did not differ significantly between the revascularization groups and the IMT-alone groups, or between the insulin-provision and the insulin-sensitization groups.
6. At 5 years, however, patients in the CABG stratum who were pre-assigned to prompt surgery had significantly fewer major CV events (especially non-fatal MI) than those in the CABG stratum assigned to the IMT-alone group (22% vs 30%).
7. In contrast, rates of CV events among patients in the PCI stratum who were assigned to prompt PCI did not differ significantly from those in the IMT-alone group.
8. Severe hypoglycemia was more frequent in the insulin-provision group (9%) than in the sensitization group (6%).

DISCUSSION

1. The study was designed to reflect how physicians might confront treatment decisions in practice.
2. Among those in the CABG stratum, prompt revascularization significantly reduced major CV events as compared with those assigned to IMT-alone. Among those assigned to the PCI stratum prompt revascularization did not reduce major CV events as compared with the IMT-alone group.
3. “Our findings suggest that patients who have diabetes, evidence of myocardial ischemia, and extensive multivessel disease would benefit from prompt surgical revascularization (CABG) mainly because of a lower rate of non-fatal myocardial infarction.”
4. For patients with less extensive coronary disease for whom PCI was judged to be more appropriate, prompt revascularization did not reduce the risk of CV events as compared with IMT-alone
5. All patients assigned to IMT-alone underwent careful monitoring, and 42% had changes in the clinical course during 5-years of follow-up that called for later revascularization.

5. The fact that the majority of patients in the IMT-alone groups did not require revascularization during 5-years suggests that many may be safely treated with IMT-alone.
7. Among patients for whom CABG was selected as the intended method of revascularization, the combination of prompt surgery and an insulin-sensitization strategy was associated with a lower rate of major CV events than any of the other three treatment combination groups.
8. The study could not distinguish between the effects of thiazolidinediones and/or metformin, or the combination.
- 9 Intensification of medical therapy and consistent monitoring led to improved control of cardiac risk factors across the board.
10. The mean HbA1c was lower by less than 0.5% in the insulin sensitization group compared with the insulin-provision group. “It is unlikely that our results were due solely to differences in glycemic control.”
11. “This data may suggest that insulin-sensitization is preferable for patients with type-2 diabetes and coronary disease.”

SUMMARY

Overall, a strategy of prompt coronary revascularization in patients who had been treated with intensive medical therapy for diabetes and stable ischemic disease, did not significantly reduce the rate of all cause mortality or of major CV events.

Overall, insulin-sensitization and insulin-provision had the similar cardiovascular outcomes during a 5-year period.

Among patients for whom CABG was deemed to be the appropriate treatment, prompt surgery reduced the rate of major CV events as compared with IMT-alone, particularly among patients who were assigned to insulin-sensitization therapy.

In the PCI stratum, revascularization with PCI did not reduce the rate of death or major CV events when added to intensive medical therapy.

NEJM June 11, 2009; 360: 2503-15 Original investigation by the Bypass Angioplasty Revascularization Investigation 2 Diabetes Study Group (BARI 2D), sponsored by the National Institutes of Health.

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A H1N1 Influenza Center At NEJM.Org Will Help Monitor The Disease.

6-7 H1N1 INFLUENZA A—INFORMATION FOR HEALTH PROFESSIONALS

In the first 2 weeks in April 2009, cases of an untyped influenza A began to be identified in Mexico and Southern California. By the third week in April, it was established that the illness resulted from a triple recombination of human, avian, and swine influenza viruses. It is an H1N1 virus.

A polymerase-chain-reaction (**PCR**) has been developed, which enables determination whether an illness with the protean manifestations of cough, fever, sore throat, diarrhea, and nausea, could be confirmed as a case.

Clinicians and epidemiologists can now make case assignments to define and track the outbreak and determine disease severity.

By May 7 (only one month after the first case) articles appeared providing background information about the novel virus in the USA. The goal was to provide clinical descriptions of patients so that health professionals could make the difficult decision about whether an individual had a suspected case. The decision depends on the presence of typical, but unfortunately variable and non-specific symptoms. Identifying a case by PCR allows epidemiological links to be established.

Suspected cases should trigger contact tracing, quarantine, and consideration for treatment with neuraminidase inhibitors. If cases are missed, the affected people will circulate among the population, and the illness will spread more rapidly.

The ability to clearly define a confirmed case will allow for a careful assessment of the associated illness and its severity. We now have important tools to fight this outbreak: a clear definition, an aware health care system, and an informed public.

At present, it seems unlikely that this outbreak will lead to widespread severe illness and deaths. However, this may be just the first wave. The illness may recur in the Southern Hemisphere during their winter, and again in the Northern Hemisphere when our winter comes.

A H1N1 Influenza Center at NEJM.org will help monitor the disease. It is available to all.

We await a vaccine.

NEJM June 18, 2009; 360: 2666-67 Editorial, first author Lindsey R Baden.

The WHO and the CDC also present up-to-date information.

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The Current S-OIV Is Only The Latest Influenza Virus, Not The Last.

6-8 IMPLICATIONS OF THE EMERGENCE OF A NOVEL H1 INFLUENZA VIRUS

A group of viruses, called triple reassortants of viruses from pigs, humans, and birds (triple reassortant swine influenza A (H1) viruses) has circulated among pigs for more than a decade. This group of viruses may occasionally be transmitted from pigs to humans, but does not spread efficiently from human to human.

Another group is a recent reassortant of the triple swine influenza A virus (H1) and an Eurasian swine influenza virus. This new virus is the H1N1 currently being transmitted human to human and has spread rapidly to many countries.

It is termed the swine-origin influenza virus (**S-OIV**)

Both viruses are H1 hemagglutinin viruses. H1 viruses first appeared in humans and swine in 1918. They have subsequently evolved in both species into divergent H1 viruses.

The current situation is not “1918 again”. It is 1918 continued. We are being infected with the remnants of the 1918 virus.

Most adults have substantial immunity to the H1 variants that circulated from 1918-57 and from 1977 to present. Whether cross-reacting antibodies from previous H1 infections provide protection against S-OIV is not known. There may be partial protection.

About 2/3 of the persons infected with the new virus were 18 years or younger. This age distribution is typical of seasonal influenza. School children are the group with the highest rates of influenza. They spread the virus to household contacts.

Clinical manifestations are typical of seasonal influenza. Nausea and diarrhea are more common.

Hospitalized patients had risk factors: very young age, chronic medical conditions, or pregnancy. Pneumonia may be present. Deaths have occurred infrequently.

Questions remain:

- 1) Will S-OIV replace human H1 virus as the seasonal virus and evolve antigenic variants every year?
- 2) Will S-OIV further adapt to humans and become more severe?
- 3) Will it return in the fall season and become more severe with higher mortality?
- 4) Will a vaccine be available? Development will be challenging.

Younger persons may require two injections to develop adequate immunity. Older persons, with some immunity already present, may require only one.

Whether the S-OIV vaccine will cause adverse events (eg, the Guillain-Barre syndrome) is not known.

The emergence and spread of S-OIV brings out the best and the worst of contemporary society;

The best: Within days of the first case of S-OIV infection in the US, the scientific community had a complete genetic sequence of the hemagglutinin. Internet dissemination made this available to everyone. Drug susceptibility was determined.

S-OIV is (*thus far*) susceptible to oseltamivir and zanamivir, but not to amantadine or rimantidine.

The worst:

Inflammatory political posturing illustrated the need for effective communication by physicians and scientists and the public. Some have asked. Why don't you close the borders? Misguided culling of pigs occurred in Egypt. (S-OIV is not epidemic in pigs; only in humans.)

“The current S-OIV is only the latest influenza virus, not the last.”

NEJM June 18, 2009; 360: 2667-68 Editorial by Robert B Belshe, Saint Louis University , St. Louis, MO.

6-9 WHOOPING COUGH: *Easily Missed*

Whooping cough (WC), caused by *Bordetella pertussis*, should be considered in any adolescent or adult with an acute cough lasting more than 2 weeks, even if the patient has been immunized. In China, WC is referred to as “the one hundred day cough”. The cough lasts an average of 3 months. It remains an endemic disease. It may occur repeatedly during a lifetime.

The diagnosis is frequently missed because its prevalence is (incorrectly) thought to be low. The classical “whoop” may be absent. The cough may be the only symptom.

MDs may be unaware that there is a simple diagnostic serological test.

Why does it matter? A persistent cough and cough without explanation causes distress and anxiety. The patient may be subject to inappropriate investigations

How is it diagnosed? *B pertussis* is difficult to culture. The sensitivity of culture falls off during the first 3 weeks. It may be further reduced by antibiotic treatment and previous immunization. Serology is the recommended diagnostic test. A single raised titer of anti-bodies to pertussis toxin in oral fluid is validated. It is quick and easy to use in primary care. It has recently been made available in the UK. Specificity of the test is 99% (1 % false positives).

How is it managed? WC is a notifiable disease. Erythromycin within 3 weeks of onset of symptoms reduces the period of infectivity and may prevent transmission to family members, although treatment may not affect outcome for the patient. A seven-day course is sufficient.

Prophylaxis with erythromycin should be offered to everyone in households with a vulnerable infant. The illness in infants may be severe and require prompt referral.

BMJ June 13, 2009; 338: 1443-44 "Practice", a brief reminder by Anthony Harnden, University of Oxford, Oxford UK

6-10 RECENT DEVELOPMENTS IN HYPERTHYROIDISM

Since the 2003 *Lancet* seminar on hyperthyroidism, several reports have enhanced understanding of the end-organ manifestations of hyperthyroidism.

Subclinical hyperthyroidism (**SCH**):

In mild (ie, subclinical) hyperthyroidism, serum levels of free thyroxine, tri-iodothyroxine, or free tri-iodothyroxine, are within the broad range of normal, but the serum thyroid-stimulating hormone (**TSH**) is subnormal, often less than 0.1 mU/L. Studies in the past 2 decades have shown that subclinical hyperthyroidism causes atrial fibrillation (**AF**) in people over age 60. Even TSH levels between 0.1 and 0.5 (very mild over activity) in individuals over age 65 are associated with AF.

In a meta-analysis, SCH was associated with a 40% increase in all-cause mortality especially in men, with a significant increased risk beginning at age 60.

"These findings suggest that very mild hyperthyroidism should be treated, even in asymptomatic older patients."

Bone loss:

Previous studies have suggested that bone loss in SCH occurs only in postmenopausal women. However, premenopausal women could potentially be at risk of bone loss, though not to the degree of postmenopausal women. Further studies are needed to see if this finding can be replicated. TSH itself may have a positive effect in maintaining bone health by directly inhibiting osteoclastic function, independent of its regulation of thyroid function.

Other symptoms of hyperthyroidism:

One study reported that untreated patients with Graves disease, who had high levels of anxiety due to the disease, had (on PET scan) increased glucose metabolism in the limbic system of the brain, known for its role in emotional activity.

Another study reported that adult men with hyperthyroidism had sexual dysfunction, which improved with treatment.

A third study reported that thyroid myopathy improved when the hyperthyroidism was treated. Recovery could be enhanced by medical therapy plus resistance training.

Treatment:

Outside the USA, anti-thyroid drug therapy is preferred as first-line treatment. Methimazole or carbimazole are favored over propylthiouracil due to their simple one-a-day dosing, and higher adherence. All 3 regimens were equally effective in mild to moderate hyperthyroidism.

In a randomized trial of initial therapy of Graves disease, 369 patients received 12 weeks of 300 mg of propylthiouracil, or methimazole, 30 or 15 mg. All 3 regimens were equally efficacious in mild to moderate disease. Patients with severe disease (free thyroxine > 7 ng/dL) were more likely to achieve euthyroidism after 4 weeks with the higher dose of methimazole

A higher rate of side-effects was observed in the propylthiouracil group vs the methimazole 15 mg group. (52% vs 14%). This reaffirms propylthiouracil's role as second-line therapy except in pregnant women in whom propylthiouracil is preferred because methimazole may have teratogenic effects.

In addition to restoring euthyroidism in patients with Graves disease, anti-thyroid drugs, used for 12 to 18 months, may induce remission (euthyroidism in the absence of drug treatment for one year). A titration regimen (gradually tapering to the lowest possible dose that maintains euthyroidism) was associated with fewer adverse effects than a block-replacement regimen (blocking hormone production together with a replacement dose of L-thyroxine). Remission rates were similar between the two groups. Eighteen months seems to be the optimum duration of therapy.

Antithyroid drugs are often used to pretreat patients before radioiodine ablative therapy, especially in the elderly. A 2007 meta-analysis of the effects of anti-thyroid drugs on subsequent radioiodine ablation showed that propylthiouracil was associated with a high risk of treatment failure. Previous small randomized trials showed no effect of methimazole on the efficacy of radioiodine ablation.

After treatment of Graves' disease with surgery or antithyroid drug therapy, thyroid-stimulating antibody (TSAb)¹ concentrations progressively decreased over 18 months after, and ultimately disappeared in most patients. In contrast, after radioiodine ablation, TSAbs levels actually increased

during the first year, and were less likely to disappear over 5-years, with only 60% of patients achieving undetectable levels.

Thirteen to 20 years after therapy with surgery, radioiodine, or antithyroid drugs, there were no differences in quality of life regardless of the therapy. However, many years later, these otherwise healthy patients had diminished quality of life compared with a large Swedish population, especially in mental performance and vitality. Is this an effect of a previous episode of hyperthyroidism on the CNS, suboptimum thyroid hormone replacement, of a consequence of patients' self-perception as someone afflicted by a chronic disease? Or is Grave's disease a manifestation of a chronic systemic autoimmune disorder?

There is much we do not understand

Lancet June 6, 2009; 373: 1930-32 Comment, first author Julia Kharlip, Johns Hopkins University School of Medicine. Baltimore, MD

1 I had to refresh my memory about thyroid-stimulating antibody. It is also termed the thyroid-stimulating immunoglobulin, and the long-acting thyroid stimulator. It is an auto-antibody that binds to thyroid stimulating hormone (TSH) receptors on the gland, producing long-acting stimulation. It is found in Graves disease. Assays of TSAb have been advocated for use in patients with subclinical hyperthyroidism and unilateral ophthalmopathy. There are several types of TSH receptor binding antibodies. Some are inhibitory and have been implicated in cases of Hashimotos's throiditis.

Source: Google.

A Positive And Valid Screening Test For The Detection Of AD

6-11 SELF ADMINISTERED COGNITIVE SCREENING TEST (TYM) FOR DETECTION OF ALZHEIMER'S DISEASE

Three requirements for widespread use of cognitive tests for use by non-specialists:

1. Minimal operator time to administer
2. Test a reasonable range of cognitive functions
3. Sensitive for Alzheimer's disease (**AD**)

The TYM ("test your memory") test was designed to fulfill these requirements.

The test is a series of 10 self-administered tasks: orientation, ability to copy a sentence, semantic knowledge, calculation, verbal fluency, similarities, naming, visiospatial abilities, and recall of a copied sentence. Perfect score = 50.

This study evaluated the test in detection of AD.

STUDY

1. A cross sectional study included 94 patients with AD attending a memory clinic, 23 patients with amnesic mild cognitive impairment, and 540 controls.
2. Controls were recruited from relatives accompanying patients to the clinic. All were tested by the TYM to calculate normal values for each decade.
3. Compared scores of TYM with scores of the mini-mental state examination (MMSE) of AD patients with age-matched controls.
4. Also tested subjects with mild cognitive impairment.

RESULTS

1. The TYM was filled in quickly and efficiently by controls with minimum supervision. Average time was 5 minutes. A perfect score = 50
3. Controls: Average score was 47 of 50 for ages 18-70. Scores slightly declined after age 70, and significantly declined after age 80.
4. AD patients: Average score was 33 of 50
5. The area under the curve for differentiating AD from controls was 0.95.
6. With a cut-point of 42 or less, the TYM detected 93% of patients with AD; the MMSE at the established cut point of 23 or less detected 52%.
7. Patients with mild cognitive impairment averaged 29 of 30 on the MMSE and 45/50 on the TYM. They tended to score worse on anterograde memory.

DISCUSSION

1. The TYM test was quick to use.
2. Compared with controls, patients with AD scored much poorer on the TYM averaging 33/50.
3. Subjects with mild memory problems (amnesic mild cognitive impairment) scored an average of 45/50 on the TYM with a trend towards problems with antegrade memory.
4. Scores of subjects over age 70 (average 77) differed little from younger subjects. This suggests that it is a useful test to detect older patients with AD.
5. The MMSE has been the standard short cognitive test for 30 years. It has many strengths. It fails some of the requirements for a brief screening test
6. The TYM has high sensitivity for detecting AD. It has a wider scoring range than the MMSE,

with over 13 points between the average control and the average patient with AD. It has a brief but rigorous scoring system. It is simple.

CONCLUSION

The TYM can be completed quickly and accurately by normal controls. It is a positive and valid screening test for the detection of AD.

BMJ June 13, 2009; 338: 1426-28 Original investigation, first author Jeremy Brown, Addenbrooke's Hospital, Cambridge, UK

A website is being expanded to improve application of the TYM.

1 www.TYMtest.com

2 Go to Google for another test: Addenbrooke's cognitive examination—revised

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