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HIGHLIGHTS FEBRUARY 2000

2-1 EFFICACY AND SAFETY OF THE ORAL NEURAMINIDASE INHIBITOR OSELTAMIVIR IN TREATING ACUTE INFLUENZA.

Oseltamivir is effective and thus far safe in treating naturally acquired influenza. The question is when to use it and for whom to use it. Many patients with flu-like symptoms do not have flu. Presence of influenza in the community must be confirmed. Possible indications for use: in the elderly whose immune response to vaccine is suboptimal, for nursing home residents (to reduce likelihood of contagion), during epidemics in which vaccine may be ineffective when antigenically novel viruses appear. JAMA February 2, 2000; 283: 1016-24

2-2 EFFECTIVENESS OF MANUAL PHYSICAL THERAPY AND EXERCISE IN OSTEOARTHRITIS OF THE KNEE

An enthusiastic cooperative effort between physiotherapist and primary-care clinician will delay or prevent need for surgery. Annals Int Med. February 1, 2000; 132: 173-81

2-3 RETINOPATHY AND NEPHROPATHY IN PATIENTS WITH TYPE 1 DIABETES FOUR YEARS AFTER A TRIAL OF INTENSIVE THERAPY: The EDIC Study

Primary care clinicians can successfully maintain intensive therapy to control glycemia and reduce kidney and eye complications. NEJM February 10 2000; 342: 381-89

2-4 MISUNDERSTANDINGS IN PRESCRIBING DECISIONS IN GENERAL PRACTICE: Qualitative Study

Primary care clinicians can reduce misunderstandings and improve clinical outcomes by actively seeking patients' participation in the consultation and asking them to voice their expectations and preferences. BMJ February 19, 2000; 320:484-88 Comment:

2-5 THE ROLE OF CLINICAL SUSPICION IN EVALUATING A NEW DIAGNOSTIC TEST FOR ACTIVE TUBERCULOSIS

A good example leading to calculations of sensitivity, specificity, predictive values, likelihood ratios, and pre- and post-test probabilities. Continued on the next abstract.
JAMA February 2, 2000; 283: 639-45

2-6 SENSITIVITY, SPECIFICITY, PREDICTIVE VALUES.

Editor's review of results of tests based on the preceding article: sensitivity, specificity, predictive value of a positive test, predictive value of a negative test. Calculations are simple and fun, but tricky.

2-7 SUBCLINICAL HYPOTHYROIDISM IS AN INDEPENDENT RISK FACTOR FOR ATHEROSCLEROSIS AND MYOCARDIAL INFARCTION IN ELDERLY WOMEN: The Rotterdam Study

An important additional reason to screen women over age 50. Annals Int Med February 15,2000; 132: 270-78

2-8 ASSESSING THE RISK OF BREAST CANCER

Primary care clinicians have the responsibility to assess and present to their patients valid risk estimates for the risk of breast cancer. This will allow reasonable choices about hormone replacement therapy, mammography, tamoxifen preventive therapy, and genetic testing. NEJM February 24, 2000; 342: 564-

2-9 GENERAL PRACTICE — TIME FOR A NEW DEFINITION

Primary care clinicians not only care for a patient's immediate health problems, but also must consider their social status and know how and when to engage community health resources for the patient's benefit. They prevent illness and palliate as well as attempting diagnosis and cure. Primary care is the most difficult of specialties. Clinicians must integrate biomedicine, medical psychology, and medical sociology.BMJ February 5, 2000: 320: 354-57

2-10 CHOLESTEROL AND STROKES

Primary care clinicians have the responsibility and opportunity to reduce the incidence and progression of carotid atherosclerosis by lipid control, especially by use of statin drugs. As a result, incidence of embolic stroke can be reduced**.** BMJ February 19, 2000; 320: 459-60

2-11 SHOULD DOCTORS GET CME POINTS FOR READING?

Primary care clinicians need help to keep up with the current medical literature. Services which access, read, assess, abstract, condense, and present clinically relevant studies in a clear and easily reviewable format may help**.** BMJ February 12, 2000; 320: 394-95

2-12 PROTHROMBIN AND FACTOR V MUTATIONS IN WOMEN WITH A HISTORY OF THROMBOSIS DURING PREGNANCY AND THE PUERPERIUM

2-13 THE CHALLENGE OF THROMBOPHILIA IN MATERNAL-FETAL MEDICINE

There are many genetic mutations in clotting and anti-clotting factors which predispose individuals to venous thromboembolic disease. These are in addition to acquired risk factors (trauma and stasis). Primary care clinicians should consider these intrinsic risk factors in patients, especially those with recurrent disease. Prophylaxis may be indicated.

NEJM February 10, 2000; 342: 374-80

NEJM February 10, 2000; 342: 424-25

2-14 GOUT

Hyperuricemia is a common, but not obligatory feature of acute gout. BMJ January 15,2000; 320: 132-33

2-15 ESTROGEN REPLACEMENT THERAPY FOR TREATMENT OF MILD TO MODERATE ALZHEIMER DISEASE

A negative study contradicting previous reports. Self-correcting the scientific literature is essential to continue trust from the public as well as clinicians. With constant correction and up-dating, ultimately the scientific approach to medicine is strengthened. JAMA February 23, 2000; 283: 1007-15

2-16 LONG-TERM OUTCOMES OF PERSONS WITH LYME DISEASE

2-17 LONG-TERM OUTCOMES AND MANAGEMENT OF PATIENTS WITH LYME DISEASE

Patients who have been suspected of having Lyme disease and continue to experience non-specific symptoms present a “doctor’s dilemma”. Uncertainty breeds strong disparate opinions. Should these individuals receive antibiotics as a therapeutic trial? The Infectious Disease Society of America says no.

JAMA February 2, 2000; 283: 609-16

JAMA February 2, 2000; 283: 658-59

2-18 CONGENITAL HEART DISEASE IN ADULTS

For those who wish a refresher course. Beautiful illustrations.

NEJM January 27, 2000; 342: 256-63

NEJM February 3, 2000; 342: 334-42

RECOMMENDED READING

2-4 MISUNDERSTANDINGS IN PRESCRIBING DECISIONS IN GENERAL PRACTICE

2-11 SHOULD DOCTORS GET CME POINTS FOR READING?

REFERENCE ARTICLES

2-8 ASSESSING THE RISK OF BREAST CANCER

2-18 CONGENITAL HEART DISEASE IN ADULTS

2-1 EFFICACY AND SAFETY OF THE ORAL NEURAMINIDASE INHIBITOR OSELTAMIVIR IN TREATING ACUTE INFLUENZA.

Previous studies have shown that oseltamivir (*Tamivir*) a specific neuraminidase inhibitor, is effective in preventing and treating experimental influenza. It inhibits replication of a wide variety of influenza A and B viruses. It is effective when given by mouth.

This study evaluated efficacy and safety of oseltamivir in the treatment of naturally acquired influenza.

Conclusion: Oseltamivir reduced duration and severity of acute influenza in healthy adults.

STUDY

1. Randomized, double-blind, multicenter study entered over 600 healthy adults age 18 to 65 (mean = 32).
2. None had been immunized against flu.
3. All had a febrile respiratory illness of no more than 36 hours' duration with temperatures of 38^0 C or more and at least one respiratory symptom (cough, sore throat, or nasal symptoms) and one constitutional symptom (headache, malaise, myalgia, sweats and/or chills, and fatigue).
4. Randomized to: 1) oseltamivir 75 mg twice daily, 2) oseltamivir 150 mg twice daily, or 3) placebo for 5 days.
5. Swabs were taken from nose and throat for culture of the flu virus. Type and subtype of

the flu virus were determined by hemagglutination inhibition assay (**HIA**). For the primary efficacy analysis, laboratory-documented influenza infection was defined as isolation of the virus and/or a 4-fold or greater HIA response.

6. A total of 374 (60%) actually had influenza infection. Outcomes were determined in these patients.
   (*Note over one third of these patients did not have influenza. This would lead to unnecessary treatment in large numbers of patients in primary care. RTJ*)

RESULTS

1. No significant difference in outcomes between the 75 mg group and the 150 mg group.
2. Duration of illness (median hours) in both oseltamivir groups was reduced by more than 30% compared with placebo.
3. Severity of illness (judged by symptom score) was reduced by 38% compared with placebo. Treatment benefit was apparent soon after administration, in some as early as 24 hours.
4. The treated group returned to usual activities 2 to 3 days earlier than the placebo group.
5. Secondary complications such as bronchitis occurred in 7% of the oseltamivir patients vs 15% of controls.
6. Adverse effects: vomiting occurred more often in the oseltamivir groups (15% vs 3%. Only one patient in the oseltamivir group withdrew because of GI events.
7. One patient developed resistance to oseltamivir.

DISCUSSION

1. The oral neuraminidase inhibitor oseltamivir was an effective treatment for influenza when given within 36 hours of onset.
2. Treatment also reduced days lost from work and the rate of complications of influenza.
3. The problem of resistance to the drug remains, but has been observed to be much less frequent than with amantadine.

CONCLUSION

The data suggest that oral oseltamivir reduces the duration and severity of acute influenza in healthy adults and may decrease the incidence of secondary complications.

JAMA February 2, 2000; 283: 1016-24 Original investigation by the US Oral Neuraminidase Group, first author John J Treanor, University of Rochester, NY

Comment:

Study was financially supported by F. Hoffman La Roche Ltd.

The authors note that over 2100 individuals were screened for enrollment, but only 629 were chosen for entry, and only 374 actually had influenza. This suggests that many patients in primary care might receive oseltamivir needlessly. This would increase use of an expensive drug with risk of adverse effects, and development of resistance. Post-marketing reports of toxicity will be forthcoming.

I could not determine from their data the effect of oseltamivir on the 255 subjects (40%) who entered the trial but did not have influenza. Would there be a response to placebo? I suspect there would be. There was no no-placebo group in the study.

Is the advantage of a few days relief of symptoms and early return to work worth more than $50 for a 5-day supply? Answer must be individualized.

I am sure all will agree that vaccine is still the major preventive measure. In those neglecting to receive immunization, who should be treated if flu-like symptoms occur? We should first establish that the virus is indeed present in the community before suggesting oseltamivir. Then the question is - who should be treated?

For a more detailed review of the neuraminidase inhibitors see: "Influenza Virus Neuraminidase Inhibitors" Lancet March 4, 2000: 355: 827-35. The authors, in their conclusion, make the interesting statement: "Although not currently approved for prevention in most countries, the NA inhibitors do seem to be effective for chemoprophylaxis and could be used for long-term protection of those unable to receive vaccine or not responding to it (eg, the elderly), or when the vaccine is unavailable or ineffective due to antigenically novel viruses. Short-term protection (10 to 14 days) could be considered for outbreak control in institutions."

"Efficacy and Safety of Oseltamivir in Treatment of Acute Influenza: A Randomized Trial Lancet May 27, 2000; 355: 1845 -50 also reports the drug was effective and well tolerated. Further investigation in children, elderly, and other at-risk patients is warranted.

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2-2 EFFECTIVENESS OF MANUAL PHYSICAL THERAPY AND EXERCISE IN OSTEOARTHRITIS OF THE KNEE

Fitness walking, aerobic exercise, and strength training have all been reported to result in functional improvement in patients with osteoarthritis of the knee. Active and passive range-of-motion exercise is also considered an important part of rehabilitation programs.

Physical therapists frequently use manual therapy procedures as part of comprehensive rehabilitation programs to help patients regain joint mobility and function.

This study evaluated the effectiveness of manual physical therapy and exercise for osteoarthritis of the knee. The hypothesis was that manual therapy combined with range-of-motion, strengthening, and cardiovascular exercises would be more effective than placebo for improving function, decreasing pain and stiffness, and increasing the distance walked in 6 minutes.

Conclusion: Combined physical therapy and supervised exercise yielded functional benefits.

STUDY

1. Randomized, controlled trial entered 83 outpatients (mean age = 60) with osteoarthritis of the knee. Fourteen did not complete the study.
2. Randomized to: 1) treatment group received a combination of manual physical therapy applied to the knee as well as to the lumbar spine, hip, and ankle as required, and a standardized knee exercise program, or 2) placebo group given subtherapeutic ultrasound to the knee. (See p 175 and appendix p 180 for details.)
3. Physical therapy was given by physical therapists formally trained in manual therapy.
4. Treatments were given twice weekly for 4 weeks. Follow-up at 8 weeks and 1 year.

RESULTS

1. Clinically significant improvements occurred in the treatment group as compared with the placebo group:
    At 8 weeks in the treatment group:
        A. Six minute walk distance was 170 m longer.
        B. Scores on an osteoarthritis index indicated about a 50% improvement in pain, stiffness, and function.
    At one year in the treatment group:
        A. Fewer knee surgeries (5% vs 20%) At 1 year, no patient who had not undergone surgery was seeking it.
        B. Fewer steroid injections (5% vs 15%)

DISCUSSION

1. Manual physiotherapy and exercise was related to significant improvements in self-perceptions of pain, stiffness, and functional ability, as well as improvement in distance walked in 6 minutes.
2. Benefit was evident at 8 weeks and persisted for 1 year. Some reported relief of symptoms in 2 to 3 weeks.
3. The manually applied treatment allowed therapists to focus on specifically involved structures.
4. Many patients do not receive physical therapy before undergoing knee replacement.

This program represents a cost-effective way to improve function and may delay or defer knee surgery.

CONCLUSION

A combination of physical therapy and exercise yielded functional benefits for patients with osteoarthritis of the knee. This program may delay or prevent the need for surgery.

Annals Int Med. February 1, 2000; 132: 173-81 Original investigation, first author Gail D Deyle, Brooke Army Medical Center, Fort Sam Houston, San Antonio, TX

2-3 RETINOPATHY AND NEPHROPATHY IN PATIENTS WITH TYPE 1 DIABETES FOUR YEARS AFTER A TRIAL OF INTENSIVE THERAPY: The EDIC Study

Intensive therapy of type 1 diabetes with the aim of achieving near normal blood glucose and glycosylated hemoglobin concentrations markedly reduces the risk of micro-vascular complications as compared with conventional therapy. The Diabetes Control and Complications Trial [1] (DCCT; 1400 patients with type 1 diabetes over 6.5 years), was a major study determining this benefit of glycemic control. DCCT ended in 1994.

At the end of DCCT, the EDIC trial began (Epidemiology of Diabetes Interventions and Complications). EDIC assessed whether the benefits of former intensive therapy (as in the DCCT) would persist.

Conclusion: Benefit persisted for 4 years.

STUDY

1. At the end of the DCCT, patients in both the intensively-treated group and conventionally-treated group were offered continued intensive therapy, or beginning intensive therapy.
2. Over 650 were included in each group.
   A. Group A had received conventional therapy during the 6.5 year DCCT trial and then were offered intensive therapy.
   B. Group B received intensive therapy during the 6.5 year DCCT trial. Intensive therapy was continued.
   C. All received therapy under the care of their own physicians.
3. Follow-up = 4 years.

RESULTS

1. Group A (former conventional group (n = 603):

A. During the DCCT trial (6.5 years) this group was treated by "conventional" therapy consisting of one or two injections of insulin daily with one blood test and one urine test daily.

B. This former conventional therapy group then entered the follow-up EDIC trial and were offered the same intensive therapy as those in the intensive therapy group in the DCCT trial.

C. The application of intensive therapy in this group led to improved control. Over the 6.5 years in DCCT glycosylated hemoglobin (GHb) averaged 9.1%. The average over the next 4 years in ECIC was 8.2%
(Ie, beginning intensive therapy in primary care practice may improve glucose control.)

D. During the 4 years, 75% used multiple daily injections of insulin. But only 40% monitored their blood glucose 4 times a day.

E. However, the rate of progression of retinopathy was greater in group A than in the group B - 21% vs 6%.

F. Development of new nephropathy was also more common in group A than in group B- 11% vs 5%.

2. Group B (former intensive group (n = 605)

A. Received intensive therapy during the 6.5 year DCCT trial, then entered the EDIC trial with continued intensive therapy under the care of their personal physician.

B. The median GHb over 4 years was 7.9%, up from 7.3% at entry. (Somewhat more favorable than the 8.2% in group A.)

C. Incidence of retinopathy progression and incidence of new nephropathy was less frequent than in group A.

DISCUSSION

1. During the 4 year EDIC study, the GHb improved in group A (those changed from conventional therapy to intensive therapy). The average GHb was, however, greater than in group B (those continued on intensive therapy).
2. The GHb in group B actually rose over 4 years, but remained lower than the GHb of Group A.
3. The frequencies of progression of retinopathy and nephropathy remained markedly lower in group B despite the increase in GHb from 7.3% to 7.9%
4. When examined in relation to the glycosylated hemoglobin values, the likelihood of progression was strongly associated with the mean glycosylated hemoglobin value during the DCCT and EDIC studies combined. Thus, the benefit of intensive therapy in the intensive group of DCCT persisted for at least 4 years despite rising GHb values. "These findings strongly suggest that intensive therapy that maintains near normal glycosylated hemoglobin

concentrations has a beneficial effect on the long-term complications of diabetes that persists long after the actual period of such therapy."

5. The DCCT previously demonstrated that intensive therapy was more effective when introduced during the first 5 years of diabetes as primary prevention than when introduced as secondary prevention after complications had begun to develop.
6. These findings strongly support the implementation of intensive therapy as early as safely possible and the maintenance of such therapy for as long as possible.

CONCLUSION

The reduction in the risk of progressive retinopathy and nephropathy resulting from intensive therapy in patients with type 1 diabetes persisted for at least 4 years despite increasing hyperglycemia.

NEJM February 10 2000; 342: 381-89 Original investigation by the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group (DCCT/EDIC) a large multicenter trial.

1 NEJM 1993; 329: 977-86

Comment:

This was a complicated paper. The abstract may be difficult to follow. Was it worth abstracting? I believe so, because it emphasizes the long-term benefits of glycemic control which can be achieved in primary care practice. I believe glycemic control will be as beneficial in patients with type 2 diabetes. RTJ

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Recommended Reading

2-4 MISUNDERSTANDINGS IN PRESCRIBING DECISIONS IN GENERAL PRACTICE: Qualitative Study

Patients are increasingly being involved in their own health care. To be involved their priorities must be identified and addressed. Consistently, patients prefer doctors who listen and encourage their patients to discuss all problems.

Prescriptions are written in most general practice consultations. Doctor-patient communications about prescribing can be misunderstood and can cause discomfort for both parties and enlarge the continuing problem of non-compliance. Patients' priorities for prescribing are clearly an important focus.

This study identified and described misunderstandings between patients and doctors associated with prescribing decisions.

Conclusion: Misunderstandings and lack of participation by patients cause adverse consequences.

STUDY

1. Selected 35 patients from 20 general practices. Some presented with a new problem for which a prescribing decision was likely or possible; some were patients who wanted to discuss a previously prescribed medicine; some were patients attending emergency surgeries.
2. Asked about their experiences of illness, their expectations of the consultation, and their relationship with their doctor. Later they were asked about what happened in the consultation, and what medicines had been prescribed.
3. The general practitioners were asked about what happened in the consultation, and about their relationship with the patient.
4. Both patients and MDs were asked if they were satisfied with the consultation.

5. Outcome— to uncover any misunderstandings between patients and doctors that had potential or actual adverse consequences.

RESULTS

1. Fourteen categories of misunderstanding were identified. These included: patient information unknown to doctor, doctor information unknown to the patient, conflicting information, disagreement about attribution of side effects, failure of communication about doctor's decisions, and relationship factors.
2. All the misunderstandings were associated with a *lack of patients' participation* in the consultation in terms of voicing their expectations and preferences, or the voicing of responses to doctors' decisions or actions. (*See Boxes p 485 – 86 - 87 for examples of the misunderstandings*.)
3. All were associated with potential adverse outcomes such as non-adherence to treatment. Many were based on inaccurate guesses and assumptions. Doctors seemed unaware of the relevance of patients' ideas about medicines for successful prescribing.

DISCUSSION

1. Misunderstandings arose through lack of exchange of relevant information in both directions, as a result of conflicting information or attributions, and when the patient failed to understand the doctor's diagnostic or treatment decisions.
2. Lack of participation by the patient in the consultation leads to misunderstandings.

3. Models of shared decision making emphasize the need for an exchange of information and the consequences of the failure to do so. Both parties to the consultation have relevant information to exchange, and it is not possible to make judgements about which party contributes most to misunderstandings.
4. This underlines the importance of researching patients' priorities at the consultation level. Asking patients about satisfaction is an insufficient way of assessing outcome of consultations.
5. General practitioners sometimes write inappropriate prescriptions to preserve relationships with their patients.
6. "Many assumptions made by doctors, although reasonable in themselves, are not correct in particular circumstances." Doctors need to check their assumptions at each consultation.
7. The study also identified examples of good practice. One doctor asked patients directly what they thought about taking medicines. One gave deferred prescriptions (ie, to be taken if the symptoms did not improve in a few days). This was as acceptable outcome for patients.
8. Although it is clearly difficult to avoid all misunderstandings, given the time constraints of general practice, some doctors in this study did succeed in doing so.
9. "Given the power imbalance the onus would seem to be on doctors to elicit patients' ideas and expectations. This information is a valuable and necessary contribution to the consultation." "In addition to listening, doctors also need to ask the right questions."

BMJ February 19, 2000; 320:484-88 Original investigation, first author Nicky Britten, King's College, London

Comment:

I believe many qualitative investigations are more meaningful to primary-care practice than the quantitative conclusions of evidence-based medicine. They go beyond evidence-based medicine. Even if the MD knows the best of evidence, applying it to an individual may be difficult or impossible.

Primary care clinicians sometimes face seemingly unsurmountable obstacles in providing good care. In our increasingly culturally diffuse society, we may consult with patients who may be English-language-illiterate, or are ill educated and will have great difficulty in understanding. All patients differ; all present unique concerns. Primary care is the most difficult specialty.

I have made a list of some attributes of a good consultation:

1. At outset, ask the patient to express her concerns. Then listen. Then encourage clarification and expansion of concerns while continuing to listen. Begin to understand the patient's story.
2. Define the problem, and if definable, apply the best of evidence-based medicine. (First learn what the best is, if EBM has presented anything that is applicable.)
3. Fully explain your understanding of the concerns and why you respond the way you do. This

includes explanation of the reason for the prescription , and the importance of compliance with the medication, and its cost and possible harm as well as benefits.

4. Try to make sure the patient understands. Then give him the opportunity to reply and inquire further.
5. Follow-up with repeat consultation or telephone
6. Do all this within 15 minutes.

RTJ

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2-5 THE ROLE OF CLINICAL SUSPICION IN EVALUATING A NEW DIAGNOSTIC TEST FOR ACTIVE TUBERCULOSIS

Since the discovery of *Mycobacterium tuberculosis* by Robert Koch years ago, the diagnosis of TB has focused on demonstrating the organism on acid-fast smear or on culture. Detection of acid-fast bacilli on smear requires more than 10 000 organisms per mL, and does not distinguish between various acid-fast bacilli. Culture can take weeks. The advent of HIV infections has increased the number of mycobacterial infections other than M tuberculosis. This further impairs the reliability of AFB smear to specifically predict TB. “In acute care settings, as many as 8 to 10 patients are suspected to have TB for every confirmed case.” Under pressures of the HIV epidemic and new immigration patterns, the clinical spectrum of the disease has changed.

Presently, the most important criteria for establishing a diagnosis of active TB (defined here as *M tuberculosis* infection) are 1) acid-fast smear and culture, and 2) a case definition. The case definition is based on radiographic signs, physiological symptoms, risk factors, or a combination of these.

Nucleic acid amplification can identify *M tuberculosis* by detecting nucleic acid sequences unique to *M tuberculosis* directly in clinical specimens. This offers accuracy and speed.

This study assessed the performance of a specific nucleic acid amplification test (Enhanced Mycobacterium tuberculosis Direct — E-MTD) against a uniform clinical standard, stratified further by the level of clinical suspicion.

Conclusion: Clinical suspicion of TB was helpful in targeting the areas of the clinical spectrum in which nucleic acid amplification tests can make an important contribution.

STUDY

1. Prospective multicenter trial enrolled a total of 338 patients with symptoms and signs consistent with active TB.
2. Classified patients on clinical grounds as being at low (<25%), intermediate (25%-75%), or high (>75%) relative risk of having active TB. The classification of risk was based on expert physicians’ clinical judgement.

3. Clinical judgement was based on combinations of suggestive chest X-ray, weight loss, cough, chest pain, positive skin test, tuberculosis exposure, immune suppression (eg, HIV), foreign-born, homelessness, and institutional domicile.
4. To provide a uniform definition of TB, the investigators developed criteria to represent a conservative consensus standard for ruling in or ruling out pulmonary TB:
   A. A combination of a high clinical suspicion and at least 2 positive cultures from separate specimens was considered definitive evidence of active TB.
   B. A combination of a low clinical suspicion and sputum specimens consistently negative for TB constituted definitive evidence that the patient did not have TB.
   C. In the absence of these conditions, an expert panel had to agree to classify a patient as having active TB.
5. The "gold standard" of the study (either TB present, or TB absent) was the final comprehensive clinical diagnosis .
6. Determined sensitivity, specificity, and predictive values of the E-MTD test for each of the clinical classifications of relative risk as noted above.

RESULTS

1. Of a total of 338 subjects:

		Clinical Suspicion Level					
		Low (n=224)		Intermediate (n=68)		High (n=46)	
		TB present (n=12)	TB absent (n=212)	TB present (n= 20)	TB absent (n=48)	TB present (n=40)	TB absent (n=6)
E-MTD	positive	10	7	15	0	35	0
E-MTD	negative	2	205	5	48	5	6

2.

	Clinical Suspicion Level		
	Low	Intermediate	High
Sensitivity of E-MTD	83%	75%	87%
Specificity of E-MTD	97%	100%	100%
Positive predictive value of E-MTD	59%	100%	100%
Negative predictive value of E-MTD	99%	91%	91%

[*One of these calculations is in error. Can you determine which one? RTJ* **1**]

DISCUSSION

1. Estimates of clinical suspicion necessarily reflect the population under study, both patients and physicians.
   These values are best understood as estimates of relative, not absolute risk.
2. Factors likely to affect physicians' estimates of relative risk include the customary prevalence of the disease in the practice setting, the clinical spectrum of the disease, the experience of the physician, and the quality of the medical history.
3. About 40% of individuals with an intermediate clinical suspicion of TB were HIV-positive and nearly one third were ultimately diagnosed as having mycobacteria other than M tuberculosis.
   "Conventional diagnostic signs (AFB smear, chest radiograph, advanced symptoms) appeared to offer limited distinction between TB and non-TB groups in this suspicion range."

CONCLUSION

For complex diagnostic problems like TB, clinical risk assessments can provide important information regarding the predictive values more likely to be experienced in clinical practice. In this series a clinical suspicion of TB was helpful in targeting areas of the clinical spectrum in which nucleic acid amplification can make an important contribution.

JAMA February 2, 2000; 283: 639-45 Original investigation, first author Antonino Catanzaro, University of California, San Diego Medical Center, CA.

Comment:

1 I believe this 91% calculation for negative predictive value in the high clinical suspicion group is in error. My recalculation from the table in paragraph 1 of the results section determined the predictive value of a negative test to be 54%.

Although this study is not a practical point for primary care at this time, the article does present calculations which enhance diagnostic accuracy.

I abstracted this article mainly to review the calculations for sensitivity, specificity, and predictive values of a test. Then to revisit likelihood ratios and pre-test probability. I have to refresh my memory of these determinations periodically, or I will lose them. See the following abstracts. RTJ

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2-6 SENSITIVITY, SPECIFICITY, PREDICTIVE VALUES.

The preceding study presented an excellent opportunity to review and calculate these basic attributes of evidence-based medicine. If I do not review them periodically, I lose them.

Many studies published in the flagship journals have sections on statistical analysis. I always skip these. I have had no training in statistics. Indeed, I do not believe primary care clinicians have to be very knowledgeable about statistics. But, understanding a few basics does make reading more enjoyable. RTJ

Sensitivity, specificity, positive predictive values, and negative predictive values are properties only of

a test for a specific target disorder.

SENSITIVITY:

Sensitivity of a test pertains only to patients who *actually have* the target disorder.

It is defined as the percentage of patients who have a positive test among *all those who actually have* the target disorder.

Three easy steps to determine sensitivity of a test:

1. Start by determining the total number of subjects in the study *who have* the target disorder as defined by the "gold standard". (This = true positives + false negatives)
2. Then determine the number of patients who have a positive test for the disorder. (Number of true positive tests.)
3. Then calculate the ratio of the number of true positive tests to the total number of subjects who have the target disorder, expressed as a percentage:

$$\frac{\text{True positives (TP)}}{\text{True positives (TP)} + \text{false negatives (FN)}}$$

Example:

In the preceding study, of the subjects considered at low clinical suspicion of TB (the target disorder):

	Low clinical suspicion group TB present (n=12)
E-MTD test positive	10 (TP)
E-MTD test negative	2 (FN)

1. Total number of subjects who actually had TB = 12.
2. Number with a positive E-MTD = 10
3. The ratio of the number of true positive tests to the total number of subjects with TB = 10/12

   = 83% = sensitivity of the E-MTD test.

SPECIFICITY

Specificity of a test pertains only to patients who *do not have* the target disorder.

It is defined as the percentage of patients who have a negative test among all those *who do not have* the target disorder.

Three easy steps to determine specificity of a test:

1. Start by determining the number of subjects in the study who *do not have* the target disorder. (True negatives + false positives)
2. Then determine the number of subjects who have a negative test for the disorder. (Number of "true negative" tests.)
3. Then calculate the ratio of number of true negative tests to the total number of subjects who do not have the target disorder, expressed as a percentage.

$$\frac{\text{True negatives (TN)}}{\text{True negatives (TN) + false positives (FP)}}$$

Example:

In the preceding study, subjects considered at low clinical suspicion of TB:

	Low clinical suspicion group TB absent (n = 212)
E-MTD test positive	7 (FP)
E-MTD test negative	205 (TN)

1. Total number who did not have TB = 212
2. Total number who had a negative E-TBD test = 205.
3. The ratio of true negative tests to total negative tests = 205 / 212 = 97% = specificity of E-MTD test.

POSITIVE PREDICTIVE VALUE

The predictive value of a positive test pertains only to those patients *who have a positive test* for the target disorder, regardless of whether or not they actually have the disorder.

It is defined as the percentage of subjects who have a true positive test among all those with positive tests. (Ie, true positive tests divided by the sum of true positive tests plus false positive tests.)

Three easy steps to determine the positive predictive value of a test:

1. Start by determining the total number of positive tests. (True positives plus false positives.)
2. Then determine the number of true positive tests.
3. Then calculate the ratio of true positive tests to the total number of positive tests expressed as

a percentage.

$$\frac{\text{True positives (TP)}}{\text{True positives (TP) + false positives (FP)}}$$

Example:

In the preceding study of subjects considered at low clinical suspicion of TB:

	Low clinical suspicion(n=224)	
	TB present (n=12)	TB absent (n=212)
E-MTD test positive	10 (TP)	7 (FP)
E-MTD test negative	---	---

1. Total number of positive tests = 10 + 7 = 17.
2. Number of true positive tests = 10.
3. The ratio of true positive tests to total positive tests = 10/17 = 59% = predictive value of a positive E-MTD test.

The higher the predictive value of a positive test, the more likely it is that the patient with a positive test has the target disorder. In this example, only 10 of 17 (58%) persons tested had a true positive test — too few to be a reliable test in ruling in TB. Indeed, if the predictive value of a positive test ≤ 50%, the test is worthless.

NEGATIVE PREDICTIVE VALUE

The predictive value of a negative test pertains only to those patients *who have a negative test* for the target disorder, regardless of whether or not they actually have the disorder.

It is defined as the percentage of subjects who have a true negative test among all those with negative tests. (Ie, true negative tests divided by the sum of true negative tests plus false negative tests.)

Three easy steps to determine the negative predictive value of a test:

1. Start by determining the total number of negative tests (True negatives + false negatives)
2. Then determine the number of true negative tests.
3. Then calculate the ratio of true negative tests to the total number of negative tests expressed as a percentage.

$$\frac{\text{True negatives (TN)}}{\text{True negatives (TN) + false negatives (FN)}}$$

Example:

In the preceding study of subjects considered at low clinical suspicion of TB:

	Low clinical suspicion group	
	TB	TB

	present (n=12)	absent (n=212)
E-MTD test positive	---	---
E-MTD test negative	2	205

1. The total number of negative tests = 205 + 2 = 207.
2. The total number of true negative tests = 205
3. Ratio of true negative tests to total negative tests = 205/207 = 99% = predictive value of a negative E-MTD test.

The higher the predictive value of a negative test, the more likely it is that a patient with a negative test does not have the target disorder. In this example, 205 subjects (99%) had a true negative test, and only 2 had a false negative test. The negative test was highly reliable in ruling out TB

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CREATING A SIMPLE 2 BY 2 TABLE CLARIFIES THE CALCULATIONS

	TARGET DISORDER		
	Present	Absent	Always place the target disorder at the top Either present or absent
Test positive	True positive Tests (TPT)	False positive Tests (FPT)	Always place the test results at the left.
Test negative	False negative Tests (FNT)	True negative Tests (TNT)	Either positive or negative.

1. Sensitivity is calculated from the left column: $\frac{\text{Number of true positive tests (TPT)}}{\text{Total number of subjects with the target disorder (TPT + FNT)}}$

2. Specificity is calculated from the right column: $\frac{\text{Number of true negative tests (TNT)}}{\text{Total number of subjects without the disorder (TNT + FPT)}}$

3. Positive predictive value is calculated from the top row: $\frac{\text{Number of true positive tests}}{\text{Total of all positive tests (TPT+ FPT)}}$

4. Negative predictive value is calculated from the bottom row: Number of true negative tests

Total of all negative tests (TNT + FNT)

Calculating these characteristics of tests is simple, but can be tricky as a cross-word puzzle. The most important step is to begin by placing the target disease *on top* of the 2 X 2 table and the test *on the side*. You must proceed meticulously in an orderly fashion. It is easy to make a mistake in the calculations. I frequently make mistakes and have to recalculate. Indeed, I have read two recent studies in flagship peer-reviewed journals which misstated predictive values.

Several more calculations are required to determine the highest probability of the diagnostic value of a test: 1) the pre-test probability of the disease in question being present in the population or individual tested. And 2) the likelihood ratios of the test used. Combining 1) with 2) will result in a new, more accurate probability, the post-test probability that the disease is or is not present.

See *Practical Pointers* next month. . RTJ

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2-7 SUBCLINICAL HYPOTHYROIDISM IS AN INDEPENDENT RISK FACTOR FOR ATHEROSCLEROSIS AND MYOCARDIAL INFARCTION IN ELDERLY WOMEN: The Rotterdam Study

Overt hypothyroidism is associated with hypercholesterolemia, hypertension, and cardiovascular disease. Subclinical hypothyroidism (elevated TSH with normal free thyroxine) is prevalent in elderly women. Is it also associated with cardiovascular disease?

The same question concerns thyroid autoimmunity.

This study examined whether subclinical hypothyroidism and thyroid autoimmunity are associated with myocardial infarction (MI) and aortic atherosclerosis in elderly women.

Conclusion: Subclinical hypothyroidism and thyroid autoimmunity were associated with MI and atherosclerosis.

STUDY

1.Population-based observational study in a district of Rotterdam entered over 1100 women (mean age = 69).

2. At baseline, measured thyroid status, aortic atherosclerosis by lateral X-ray of the lumbar spine to determine calcification, and evidence of MI by history and ECG.

3. Follow-up of another 3 to 6 years for incident MI.

4. Defined subclinical hypothyroidism as an elevated TSH (> 4.0 mU/L) and a normal serum

free thyroxine (11 to 25 pmol/L [0.9 to 1.9 ng/dL]).

5. Tested for antibodies to thyroid peroxidase. Levels greater than 10 IU/mL considered abnormal.

RESULTS

1. Subclinical hypothyroidism was present in 11% of subjects. It was associated with a greater prevalence of aortic atherosclerosis and MI (when adjusted for multiple other risk factors).
    Aortic atherosclerosis present— odds ratio of hypothyroidism = 1.7
    MI present on follow-up — odds ratio of hypothyroidism = 2.3
2. In absolute terms (my calculations from table 3 p 275) subclinical hypothyroidism was associated with an increased risk of MI or atherosclerosis by 6 of 100 women as compared with euthyroid women.
3. Risks were stronger for women who had subclinical hypothyroidism plus associated antibodies to thyroid peroxidase vs those with subclinical hypothyroidism alone. (Odds ratios 3.1 and 1.9)
4. No association was found between thyroid autoimmunity itself and cardiovascular disease.
5. The population attributable risk associated with incident MI was calculated as 14%, a percentage within the range of that for known major risk factors.

DISCUSSION

1. Among all women in the sample, 1% had overt clinical hypothyroidism.
2. Subclinical hypothyroidism was highly prevalent among elderly women in this cohort. It was associated with increased prevalence of aortic arteriosclerosis, history of MI, and incident MI on follow-up.
3. Women who had evidence of thyroid autoimmunity combined with subclinical hypothyroidism had a higher prevalence of MI.

CONCLUSION

Subclinical hypothyroidism was highly prevalent in elderly women, and was strongly and independently associated with aortic atherosclerosis and myocardial infarction.

Annals Int Med February 15,2000; 132: 270-78 Original investigation by the Rotterdam Study, first author A Elisabeth Hak, Erasmus University Medical School, Rotterdam, the Netherlands

Comment:

This strengthens the recommendation for screening women over age 50 for subclinical hypothyroidism. RTJ

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REFERENCE ARTICLE

2-8 ASSESSING THE RISK OF BREAST CANCER

Recent developments in the ability to predict and alter breast cancer (BC) risk warrant a new look at the role of assessment of this risk in primary care. Primary care physicians must become adept at evaluating BC risk and counseling women about its effect on medical decisions. Heretofore, older age has been considered the main risk factor.

Important medical decisions depend on a woman's underlying risk: whether to use hormone replacement therapy (HRT); at what age to begin mammographic screening; and whether to use a SERM (selective estrogen receptor modulator — tamoxifen or raloxifene) to reduce risk of BC.

Hormone replacement therapy:

Increases risk of BC by 30% to 40%. But most experts argue that benefits (delay of bone mass loss, possible benefit in lowering risk of coronary heart disease) of HRT outweigh the risks. However, for women at increased risk of BC, the benefit/harm ratio may shift. Conversely, individuals at lower risk of BC may be reassured that benefits of HRT outweigh the risks. As risk of BC increases, the relative benefit of SERMs increases as compared with HRT.

Mammography:

Decisions about mammography in women age 40-49 remain controversial for several reasons: a) Screening is less likely to detect BC at an early stage (breast density is generally higher in younger women); b) cure rates may be lower; c) The increased breast density leads to more false positive tests causing anxiety, reexaminations, and more biopsies; d) Fewer women benefit because BC is less common in this age group.

In addition, costs of screening younger women are higher. The goal is to maximize the benefits of mammography while minimizing the harms. Choosing women at higher risk of BC will increase the benefit/harm cost ratio of screening.

Tamoxifen to prevent BC:

Tamoxifen (Nolvadex, a SERM) is currently the only drug approved by the FDA to reduce risk of BC. Assessment of BC risk is important in making decisions about use for this purpose. There are adverse effects of the drug: venous thrombosis, endometrial cancer, and cataracts. As the absolute risk of BC in an individual increases, the benefit of tamoxifen increases.

How to evaluate BC risk:

Several factors have been consistently associated with increased risk. Several factors may interact. Evaluating risk conferred by combinations is challenging.

Established risk factors for BC:	Relative risk
Age > 50 vs < 50	6.5
Family history	
First degree relative	1.4 – 13.6
Second-degree relative	1.5 – 1.8
Age at menarche <12 vs > 12	1.2 – 1.5
Age at menopause >55 vs < 55	1.5 – 2.0
Age at first live birth >30 VS <30	1.3 – 2.2
Benign breast disease	
Breast biopsy (any histologic findings	1.5 – 1.8
Atypical hyperplasia	4.0 – 4.4
Hormone replacement therapy	1.0 – 1.5

Average risk:

Understanding average risk provides a necessary context for individual assessments. The average lifetime risk in the US women at birth is 12% (one in 8). The longer a woman lives without BC the lower her risk of BC in the remainder of her lifetime. A 50 year old woman who has not had BC has an 11% chance (one in 9) of developing it in her remaining years; likewise, a 70 year old women who has not had BC has a 7% chance (one in 14).

Models currently available to predict risk:

1) The most commonly used was developed by Gail et al. from the Breast Cancer Detection Demonstration Project. This model incorporates the number of first degree relatives with BC (0, 1, or 2); age at menarche (<12, 12 to 13, or ≥14); age at first live birth (< 20, 20 to 24, 25 to 29, or ≥ 30 or nulliparous); and number of breast biopsies (0, 1, or 2). It predicts cumulative risk up to age 90. (See table 1, p 566). (*Clinical examples of risk predictions are given in table 3.p 567*)

2) A second risk model (*Claus — See table 4, p 568*) relates risk to number of relatives with BC, whether they are 1st degree of 2nd degree, and their age at diagnosis. This model is applicable only if the individual has first or second degree relatives with BC.

What about genetic-susceptibility testing?

Two major BC susceptibility genes have been identified — BRCA1 and BRCA2. Women with mutations in either of these genes have a lifetime risk of BC of 60% to 85%. And a lifetime risk of ovarian cancer of 15% to 40%. Several characteristics make the mutations more likely: Family history of early onset BC; combined BC and ovarian cancer; and Ashkenazi Jewish ancestry. Testing for

mutations in these 2 genes is important in predicting BC risk in two sets of circumstances: 1) In families with known mutations testing another family member can separate women who carry the mutation from those who do not. Women who do not carry the mutation are at the same risk as women without a positive family history. 2) In families with an increased risk (as determined by the above models) genetic testing (if positive for the mutations) will identify individuals at much higher risk. Even if negative, however, they remain at higher risk because of their positive family history.
(*See table 5, p 569 for family-risk factors for carrying the BRCA1 and BRCA2 mutations which are reasonable for suggesting screening for an individual woman.)* For women from families without risk factors for a mutation, genetic testing is unlikely to provide useful information.

For women with risk factors for carrying a BRCA mutation, first determine if she is interested in pursuing genetic testing. If so a list of specialized centers can be found at http://cancernet.nci.nih.gov/genesrch.shtml

NEJM February 24, 2000; 342: 564-70 Review article, first author Katrina Armstrong, University of Pennsylvania School of Medicine, Philadelphia, PA.

Comment:

I believe many women will be concerned about their individual risk for BC. The article gives some guidance. If your patient is indeed at increased risk, offer: 1) earlier and more frequent clinical and mammographic screening, 2) avoidance of HRT, 3) use of a SERM, and 4) consideration of testing for BC susceptibility genes. RTJ

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2-9 GENERAL PRACTICE — TIME FOR A NEW DEFINITION

In the past, medical development focused largely on hospitals, organ specialization, and high technology. Now, general practice[1] has developed into a cornerstone of the healthcare system.

"At the end of the millennium academic general practice is now established in all developed countries. General practice is recognized as a specialty equally important as, and complementary to, other specialties. Participation in specific training programmes has therefore become mandatory for anyone who wishes to become a specialist in this field."

"General practitioners know that elements of the patient's personality and his or her relations to society have a major role in disease and illness. These elements should be taught, but teaching the psychological and social aspects of medical care still rests more on common sense than on hard evidence."

These editorialists suggest a new definition of general practice:

The general practitioner is a specialist trained to work in the front line of a healthcare system and to take the initial steps to provide care for any health problem(s) that patients might have. The general practitioner takes care of individuals in society, irrespective of the patient's type of disease or other personal and social characteristics, and organises the resources available in the healthcare system to the best advantage of the patients. The general practitioner engages with autonomous individuals across the fields of prevention, diagnosis, cure, care, and palliation, using and integrating the sciences of biomedicine, medical psychology, and medical sociology.

BMJ February 5, 2000: 320: 354-57 Editorial, first author Frede Olesen, University of Aarhus, Denmark

Comment:

1. I think of "General Practice" as including pediatrics, family practice, and primary care adult medicine (internal medicine). Many Ob-Gyn clinicians also include some degree of adult medicine in their practice. Practical Pointers concerns mainly adult primary care.

Several definitions of primary care and general practice have been described. I believe it is the most difficult of specialties to master and do well. Every patient presents unique problems beyond the reaches of evidence-based medicine. The editorialists' comment about common sense rings true.

In addition to knowing the patient's individual story, some knowledge of her family and social surroundings are required to adequately establish a "connection".

To be a good clinician, the generalist must know the abilities and limitations of specialists in his area — know when, and to whom to refer. She must also get to know the fabric of the healthcare and social resources in the community by introducing herself, and developing a relationship with the local nursing, hospice, pharmacy, social-service, and public health professionals . And she should also establish a relationship with key persons in secondary and tertiary referral centers.

Above all she must be an advocate for her patient.

What a daunting task ! RTJ

2-10 CHOLESTEROL AND STROKES

Cholesterol Lowering is Indicated for Strokes Due To Carotid Atheroma.

Strong correlations between lipoprotein concentrations and the risk of stroke have never been clearly established. There is no significant direct relation between an increased risk of stroke and increased plasma total cholesterol or low HDL-cholesterol. Indeed, an inverse relation exists between total

cholesterol and cerebral hemorrhage. (Ie, low total associated with higher incidence of cerebral hemorrhage.)

Virtually all coronary heart disease can be ascribed to coronary atheroma. But. only half the incidence of stroke is due to large vessel atheroma. Non-atheromatous causes (cardiac arrhythmia, small cerebral artery disease, cortical degeneration) are responsible for most of the rest.

No large randomized trials designed specifically to assess the effect of cholesterol lowering on risk of stroke have been completed. We need to consider surrogate data from coronary prevention trials and carotid regression trials to assess the value of lipid control in preventing ischemic stroke.

The three largest secondary prevention trials of coronary heart disease showed that lowering LDL-cholesterol reduced the incidence of stroke and coronary heart disease to a similar extent (about 30%). But, the benefit was for non-fatal strokes. It was not possible to conclude that cholesterol lowering reduced stroke mortality. Benefit was confined to non-embolic stroke and transient ischemic attacks. Strokes related to large vessel atheroma are the most likely to be reduced by lipid control.

More relevant are the findings of carotid regression trials. High resolution ultrasound has clearly established that thickening of the carotid intima and media are predictors of stroke. Reduction of LDL-cholesterol and small increases in HDL-cholesterol prevent, over a 4-year period, progression in carotid wall thickening and reduce the development of new lesions. [1]

"All patients under 75 recovering from a stroke with evidence of carotid atheroma as the cause, or with a history of coronary heart disease should be considered for treatment with a statin to reduce the risk of recurrences. Patients with carotid atheroma identified angiographically should also be considered for statin therapy."

Prevention should be directed to patients with raised total cholesterol and LDL-cholesterol concentrations, particularly when diabetes and hypertension coexist.

BMJ February 19, 2000; 320: 459-60 Editorial by Michael F Oliver, National Heart and Lung Institute, London

Comment:

1. Lipid control with statins has beneficial stabilizing effects on vascular endothelium which may occur within months or a year or two. I believe this is more likely to benefit the elderly than any anatomical regression of atheromatous lesions. On this basis, lipid-screening and treatment of aged persons with a reasonable life-expectancy is a worthwhile clinical application. No need to believe we must wait until anatomical regression takes place.

The 3 main causes of ischemic stroke (emboli of cardiac origin, emboli from carotid atheroma, and cerebral small vessel disease related to hypertension) are likely to be associated with each other in older

patients. If the patient with ischemic stroke has established carotid atherosclerosis, we should not assume automatically that the stroke results from carotid emboli. If the patient with ischemic stroke has atrial fibrillation we should not automatically assume the stroke results from the cardiac emboli. All three risk factors should be treated simultaneously. RTJ

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2-11 SHOULD DOCTORS GET CME POINTS FOR READING?

Yes: Relaxing Documentation Doesn't Imply Relaxing Accountability

"Practicing medicine without reading is unthinkable." Reading is extensively used in searching for information to solve clinical problems. Yet most programs of continuing medical education give little credit for reading. What evidence do we have that it is an effective way of learning?

The AMA (www.ama-assm.org) introduced reading as a required activity in 1990 — defined as reading "authoritative" medical literature — that is peer reviewed journals or textbooks. For the past 2 years doctors have been able to earn category 1 credits for reading articles specially designed for continuing education, structured as a learning experience and following specific rules.[1]

As computers become part of doctors' office equipment, access to data bases should enable doctors quickly to find the most updated and reliable answers to their clinical problems. "In essence, this in no different from reading journals, books, or self produced notes."

"It is well known from quality improvement work that it is what you measure that gets people's attention (irrespective of its importance). And that should warn us not to exclude reading from credit point systems."

"The most frequent stimulus for learning is reading the medical literature, followed by management of a current patient or problem. Reading has the same likelihood of leading doctors to a commitment to change their practice as attending group educational activities and completing self assessment programmes."

"Focusing less on control and more on learning should be the way forward."

BMJ February 12, 2000; 320: 394-95 Editorial by Hans Asbjorn Holm, Norwegian Medical Association, Oslo

1. JAMA 1999; 282: 909-10 "Continuing Medical Education. JAMA Reader's Choice"

Comment:

I abstracted this article because I believe it touches on the importance of services which select and digest information dedicated to each specific specialty from the medical literature. Practical Pointers is slanted toward adult primary care. I believe most clinicians in this specialty would, on reviewing the current flagship journals, choose the same articles *Practical Pointers* chooses as being relevant to

practice. (Ie, information which would lead primary care clinicians to add an application to their practice, delete it, or apply it with due caution.)

The process of *Practical Pointers* proceeds in an organized manner: Flagship journals are currently available by personal subscription. The journals are scanned, relevant articles read, highlighted, and condensed into a shortened readable abstract. A highlight of the abstract permits a quick scan to allow the reader, if interested, to go on to the abstract or the original article. The relevant information in *Practical Pointers* abstracted from all issues of 6 major journals (24 issues each month) can be read in a few hours.

Each year articles which are abstracted are archived and made easily accessible on print text or on the Internet. The Internet has a wonderful advantage of providing immediate links to the full text of the journal articles.

I believe busy primary care clinicians simply do not have the time or energy to constantly keep up with the current literature. They will benefit from a service which selects and pre-digests relevant information. They need help in remembering and easily recalling needed information. Even if the busy clinician takes time to browse several journals regularly, information which may be applicable might well be easily forgotten or misplaced. An abstract service which enables clinicians to easily retrieve and quickly review needed information to refresh the memory will be a valuable aid. RTJ

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2-12 PROTHROMBIN AND FACTOR V MUTATIONS IN WOMEN WITH A HISTORY OF THROMBOSIS DURING PREGNANCY AND THE PUERPERIUM

The risk of venous thromboembolism (**VTE**) is 5 times higher among pregnant women as among non-pregnant women of similar age. VTE is a major cause of mortality and morbidity among women during pregnancy and the puerperium.

During pregnancy, changes occur which may promote coagulation, decrease anticoagulation, and inhibit fibrinolysis. Risk is higher in women with acquired or genetic risk factors for thrombosis.

Two genetic mutations are associated with increased tendency to VTE:

1. Factor V Leiden is the most common inherited abnormality in patients with thromboembolic disease. It is present in 29% of patients with a first episode of VTE and up to 50% of those with recurrent VTE. [G1691A; a simple substitution of guanine for adenine (*or is it adenine for guanine? Someone help me out.*) results in a single amino-acid substitution in the protein.]
2. Prothrombin mutation: a single amino-acid substitution in the prothrombin molecule increases prothrombin concentrations. [G20210A; a simple guanine- adenine substitution.]

Both substitutions are associated with increased tendency to coagulation.

This investigation assessed the frequency of these mutations in women with VTE associated with pregnancy and the puerperium.

Conclusion: Presence of the mutations was more common in women with VTE than in control women.

STUDY

1. Case-control study :
   Cases: 119 women with a history of VTE during pregnancy and the puerperium
   Controls: 233 matched women without history of VTE in pregnancy.
2. Measured the mutated factors including the above.

RESULTS

1. Prevalence	Cases	Controls
Factor V Leiden	44%	8%
Prothrombin mutation	17%	1%
Both combined	9%	0

2. Only 5 patients with Factor V Leiden were homozygous for the mutation. None of those with the prothrombin-mutation were homozygous.
3. Several other risk factors for thrombophilia were also more common in the case patients: deficiencies of 1) antithrombin, 2) protein C, and 3) protein S.
4. The predicted incidence of VTE among those with factor V Leiden was 0.25%; those with the prothrombin mutation, 0.5%; among those with both, 4.6%.
5. Women with *recurrent* VTE had significantly higher prevalence of the 2 defects combined than did women with a first episode.

DISCUSSION

1. "We confirmed the importance of factor V Leiden as a risk factor for venous thromboembolism during pregnancy and the puerperium." It is independent of other determinants of risk.
2. The combination of factor V Leiden and the prothrombin mutation led to a disproportionately higher risk than with either factor alone.
3. Nevertheless, the predictive value of factor V Leiden and other inherited markers for the purpose of screening for thrombotic risk is low among pregnant women.

4. “A significant increase in the probability of thrombosis can be demonstrated only in cases in which a women has a combined defect. “

CONCLUSION

A prothrombin gene mutation and factor V Leiden individually are associated with an increased risk of venous thromboembolism during pregnancy and the puerperium. The risk in women with both mutations is disproportionately high.

NEJM February 10, 2000; 342: 374-80 Original investigation, first author Andrea Gerhardt, Heinrich Heine University Medical Center, Dusseldorf, Germany.

Comment:

This may seem somewhat out of touch with ordinary primary care clinical medicine. I do believe it is of interest because it is becoming more evident that many persons with VTE do have abnormalities in their clotting factors. Identification of the defects may lead to prophylaxis. RTJ

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2-13 THE CHALLENGE OF THROMBOPHILIA IN MATERNAL-FETAL MEDICINE

There has been a dramatic increase in the number of identifiable causes of thrombophilia: mutations of factor V (Factor V Leiden), prothrombin mutation, and deficiencies of several factors which, in normal concentrations, inhibit coagulation (protein C, protein S, and antithrombin).

These disorders underlie about 50% of episodes of VTE associated with pregnancy. They are collectively present in at least 15% of Western populations. Their presence alone does not necessarily lead to a clinical event. VTE is multicausal, resulting from an interaction between congenital and acquired risk factors.

Pregnancy is an acquired risk factor. It is associated with increased coagulation and decreased fibrinolysis in preparation for the challenge of delivery. These thrombophilic changes are translated into risk of clinical disorders, of which pulmonary embolism is the most important to the mother. The post-phlebitic syndrome also results from repeated episodes of venous thrombosis.

"About 70% of women in whom VTE occurs during pregnancy and the puerperium have major risk factors: obesity, operative delivery, personal or family history of thromboembolism, or congenital thrombophilia. It is essential to establish the risk of thromboembolism in women during pregnancy and to determine whether they need thromboprophylaxis. "

Clinical events are multicausal.

Pharmacological intervention in pregnancy to prevent VTE focuses on use of heparin. Heparin does not cross the placenta. Warfarin does. But heparin is associated with osteoporosis, heparin-induced thrombocytopenia, and allergy. The risk of these seems substantially lower with use of low molecular

weight heparin. Heparin and low dose aspirin are effective in the treatment of the acquired antiphospholipid-antibody syndrome.

All pregnant women with a personal or family history of VTE should be screened for risk factors. Screening should be extended to women with a history of second-trimester pregnancy loss, severe or recurrent pre-eclampsia, or intrauterine growth restriction, although whether anti-thrombotic therapy will prevent these complications is not known

Drug prophylaxis against VTE is warranted for pregnant women with thrombophilia who have had a previous thromboembolic event.

NEJM February 10, 2000; 342: 424-25 Editorial by Ian A Greer, University of Glasgow, UK

Comment:

The classical triad of stasis, injury, and hyper-coagulability is expanding to include more known causes of increased tendency to coagulation.

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2-14 GOUT

Gout is underdiagnosed and presents diagnostic and treatment challenges. The diagnostic criteria proposed almost 40 years ago are still helpful: 1) a clear history of at least two attacks of painful joint swelling with complete resolution within 2 weeks, 2) a clear history or observation of podagra, 3) presence of a tophus, and 4) a rapid response within 48 hours to colchicine. Two of these criteria are required for a clinical diagnosis. A definitive diagnosis is made if crystals of sodium monourate are seen in synovial fluid or in tissues.

Hyperuricemia is a common but not obligatory feature. It is important to realize that the serum urate concentration may be normal in an acute attack.

The main predisposing factors for gout in men are: family history, obesity, excessive alcohol intake, high purine diet, and raised triglyceride concentrations.

Patients may be broadly classified as overproducers or undersecretors of urate, under secretion being the most common. This may be due to genetic factors, but it is usually drugs — including alcohol — which cause the low renal clearance. This is a particular problem in elderly people taking thiazide diuretics and low dose aspirin who have concomitant impaired renal function. Acute attacks are less common in elderly people in whom gout presents insidiously as a chronic arthritis associated with subcutaneous tophaceous deposits on the fingers, toes, or elbows. It may be misdiagnosed as rheumatoid arthritis.

Idiopathic hyperuricemia occurs more often than clinical gout. A flair of osteoarthritis in a patient with hyperuricemia can lead the unwary into applying the wrong diagnosis.

Pseudogout often presents with a hot swollen knee in an elderly patient with preexisting osteoarthritis. It is readily distinguished by the presence of birefringent crystals of calcium pyrophosphate in the synovial fluid, or by demonstrating chondrocalcinosis on X-ray.

An acute hot joint in a patient receiving chemotherapy for lymphoproliferative malignancy may be due to gout secondary to the acute tumor lysis syndrome.

NSAIDs are the first line of therapy. They should be given in full doses unless there is a contraindication (peptic ulcer disease, background of renal impairment, hypertension, or heart failure). Colchicine is poorly tolerated by the elderly. Intraarticular steroids and systemic steroids are useful in elderly patients with impaired renal function.

Allopurinol should be used for long-term prophylaxis but should not be started until one month after an acute episode. In older people the dose should be kept low, rising to a maximum of 100-300 mg daily. The target urate levels should be 40 to 70 mg/L.

Recurrent attacks despite what seems to be adequate prophylactic treatment are almost always associated with continued alcohol abuse or poor compliance with treatment, especially in men.

BMJ January 15,2000; 320: 132-33 Editorial by R D Sturrock, Royal Infirmary, Glasgow

Comment:

I enjoy a short refresher article which stands alone, not linked to a study in the same issue. The clinical application is obvious. RTJ

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2-15 ESTROGEN REPLACEMENT THERAPY FOR TREATMENT OF MILD TO MODERATE ALZHEIMER DISEASE

Several reports from small clinical trials have suggested that estrogen may be useful for the treatment of Alzheimer disease (AD).

This randomized controlled multicenter trial entered 120 women (mean age 75) with mild to moderate AD. All had a Mini-Mental State Examination score between 12 and 28. All had had a hysterectomy.

Randomized to 2 dosages of conjugated equine estrogen (Premarin; 0.625 and 1.25 mg) or placebo. Follow-up = 1 year.

Results: The Clinical Global Impression of Change score and specific cognitive domains such as memory, attention, and language as well as mood, motor function, and activities of daily living did not differ between groups. The only exception was the Clinical Dementia Rating Scale which suggested worsening among those taking estrogen.

Thus, the study did not support the role of estrogen for treatment of AD.

JAMA February 23, 2000; 283: 1007-15 Original investigation by the Alzheimer's Disease Cooperative Study, first author Ruth A Mulnard, University of California, Irvine.

Comment

What is the practical value of reporting a negative study? Previous studies have reported encouraging effects of estrogen on Alzheimer's. The scientific literature must continue to be self-correcting despite the resulting confusion experienced by the public as well as the health-care community. Without correction, myth persists, and the public continues to be deceived. With constant correction and updating, ultimately the scientific approach to medicine is strengthened. RTJ

2-16 LONG-TERM OUTCOMES OF PERSONS WITH LYME DISEASE

Lyme disease (**LD**) is the most common vector-borne disease in the US. Few data exist about long-term outcomes of patients who have been treated for the disease. There has been controversy about the consequences of the infection. Some patients advocacy groups and physicians believe that LD is a very serious and difficult-to-treat illness. Others believe that a majority of patients remains relatively healthy regardless of the stage of the illness at the time of presentation, and suggest that for many patients who have persistent or recurrent subjective complaints, either a misdiagnosis of LD was made, or LD is not the cause of the symptoms.

Some studies report subsequent development of either recurrent or persistent non-specific symptoms (eg, fatigue or arthralgia) even after having been treated with antibiotics. Such patients occasionally receive repeated or prolonged courses of antimicrobial therapy despite advice from national authorities that such treatment is not warranted.

This study assessed the long-term outcomes of patients who had been diagnosed as having Lyme disease in the past.

Conclusion: The frequency of various symptoms which could be attributed to Lyme disease was no more common in patients than in matched controls.

STUDY

1. An observational study:

A. Randomly selected over 678 patients who had been reported to the Connecticut Department

of Health as having suspected LD one to 11 years prior. About 1/3 were children, 2/3 adults. 85% of the subjects had been treated for LD with antimicrobial agents.

B. Determined self-reported symptoms and ability to perform certain daily activities since diagnosis and treatment. (A median of 4 years later.)

2. Case-control study:

A. In addition to the observational study, randomly selected 212 patients from the study group and matched them with 212 control subjects without a history of LD.

Patients with a single erythema migrans lesion at least 5 cm in diameter (with or without concurrent symptoms) were classified as having early localized disease.

Patients with multiple erythema migrans were classified as having early disseminated disease.

Patients with early neurological disease (cranial nerve palsy, aseptic meningitis, peripheral neuropathy, or cardiac disease (acute A-V block) *and* serological evidence of infection with *B burgdoferi* were also classified as having early disseminated LD.

Patients with arthritis, encephalopathy, or polyneuropathy *and* serological evidence of *B burgdoferi* infection were classified as late stage LD.

Patients who had only non-specific symptoms (fatigue, arthralgia) who did not have serological evidence of infection were classified as not having LD

3. Outcome measures – reports of symptoms and ability to perform daily activities.

RESULTS

1. Only 64% of patients classified as having had LD met the national surveillance case definition for LD. (*Citation # 14*):

2. Observational study: (n = 678; median age of adults = 36 years ; children = 8 years)

A. 71% believed they were cured; 9% believed they were not cured; 20% not sure. Most of the unsure patients said they were unsure whether LD was curable.

B. Of the patients who believed they were not cured, more had underlying co-morbid disease.

C. Patients who met the surveillance case definition of LD were more likely to believe they were cured.

D. Overall, only 19% of the increases in symptoms or difficulty in daily living were the LD. Most attributed them to aging or a co-morbid disease.

E. There was a statistically significant association between whether patients believed they were cured and in increases in symptoms and difficulty in daily living.

3. Case-control study

A. Although many patients who had been diagnosed as having LD reported increased

symptoms or difficulties in daily living, the proportions were similar to those reported by the matched control subjects.

DISCUSSION

1. Only about 2/3 of the subjects referred as having LD actually met the surveillance definition. And almost 90% of those who met the surveillance definition had erythema migrans.
2. "Our data indicate that the outcomes of most persons diagnosed as having Lyme disease who are treated with antimicrobial agents are excellent."
3. Although many patients reported increased frequencies of some symptoms and increased difficulties in daily living, relatively few attributed these problems to the LD.
4. The symptoms and difficulties of daily living were no more common in the group with LD and in control patients.
5. Among adults reported to have LD, scores of health-related quality of life tests were similar to those of other generally healthy populations.
6. The diagnosis of LD in many patients who do not meet the case definition of LD was based on a positive serology for *B burgdorferi.* But this test has a poor specificity (many false positives) and it is likely that the diagnosis was inaccurate. The frequency of reported symptoms and difficulty in daily living were consistently lower in patients who met the case definition than in those who did not meet the definition.
7. This study does not indicate that all patients with LD have favorable outcomes. Indeed, there is good evidence that some may experience complications – especially those not treated promptly and those with a genetic predisposition to develop auto-immune mediated arthritis.
8. The generally excellent outcomes should reassure patients and physicians that the prognosis for most patients with LD who receive conventional antimicrobial treatment is excellent.

CONCLUSION

Although many patients with a history of treated Lyme disease reported increases in symptoms and difficulties in daily living, the frequencies of these reports were similar to those of matched controls without Lyme disease.

JAMA February 2, 2000; 283: 609-16 Original investigation, first author Elyse G Seltzer, Yale University School of Medicine, New Haven, Conn.

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2-17 LONG-TERM OUTCOMES AND MANAGEMENT OF PATIENTS WITH LYME DISEASE

(*This editorial comments and expands on the preceding study*.)

Serological methods of diagnosis of *B burgdorferi* infection have not been well standardized. In the absence of a criterion standard blood test, the diagnosis is based on a characteristic clinical picture in the appropriate epidemiological setting (often supported by serological data).

For patients with classic presentations, there is widespread agreement about the initial diagnosis and antibiotic management. However, without a serologic criterion standard, there is no valid way to address issues of asymptomatic or atypical infection for long-term outcomes.

"Uncertainty breeds strong disparate opinions." "As long as Lyme disease is defined primarily by its clinical characteristics, legitimate disagreement will exist between those who accept only the narrow case definition, limited to those patients with well recognized Lyme disease manifestations, and those who believe that *B bergdorferi* also may be an important contributor to other, less well-defined illnesses, particularly when accompanied by positive (albeit imperfect) serological test results."

For the highly motivated patient seeking a diagnostic label for persistent symptoms, it is not difficult to find a physician who, reasoning that the response to a course of antibiotics represents a therapeutic trial, is willing to treat for the unlikely possibility of Lyme disease.

The preceding study addressed this "doctors dilemma".

The study adds support to the champions of evidence-based medicine and validates the position of the Infectious Disease Society of America which tries to discourage use of antibiotics for patients whose clinical presentation is non-specific and who do not meet the accepted case definition standard. "Empirically treating patients who have common frustrating illnesses such as fibromyalgia and chronic fatigue syndrome (even those with positive serologic tests for B bergdorferi) with prolonged courses of parenteral antibiotics can be condemned as unwarranted, expensive, and contributing to the problem of antibiotic resistance."

Despite the directives to be more stringent in diagnosing and treating Lyme disease, physicians will continue to deal with the troublesome fact that there is no test to rule out Lyme disease and that some patients will be persistent in their search for physicians willing to treat their chronic symptoms empirically. "Physicians faced with symptomatic patients rather than with a practice guideline will continue to ask
themselves, 'What if the patient is right, and really has an atypical presentation of Lyme disease ?' "

A new generation of tests for antibodies to *B bergdorferi* is in the works, and may be a help.

JAMA February 2, 2000; 283: 658-59 Editorial by Pierce Gardner, State University of New York at Stony Brook School of Medicine.

Comment:

I abstracted these papers on Lyme disease because I believe the "doctor's dilemma" extends to many symptomatic patients who strongly believe their condition is due to one of a variety of diseases for which there is no "Gold standard" for diagnosis and who persist in their search for empiric treatment. This is especially true in this era of "alternative and complementary medicine". It requires a strong backbone to resist giving in to the patients wishes, even if no harm is expected from the costly alternative. The art of medicine confronts many unexpected dilemmas.

See also: "The Lyme Disease Vaccine: Conception, Development, and Implementation" Annals Int Med April 18, 2000; 132: 661-68 A recombinant protein vaccine derived from an outer surface of the spirochete outer surface protein vaccine in now approved by the FDA. Phase trials report substantial efficacy in preventing asymptomatic and clinical disease without lasting adverse effects.

"The most interesting aspect of the vaccine is that the induced immune response takes effect within the tick vector itself before the causative spirochete ever enters the human host. (*Ie, the human antibody enters the tick and neutralizes the spirochete.)* "This intravector mode of action opens the door to a new method of preventing insect-borne illnesses in humans."

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REFERENCE ARTICLE

2-18 CONGENITAL HEART DISEASE IN ADULTS

This 2-part review is divided into acyanotic conditions (part 1) and cyanotic conditions (part 2). The illustrations are excellent.

Acyanotic: atrial septal defect, ventricular septal defect, patent ductus arteriosus, aortic stenosis, pulmonary stenosis, and aortic coarctation.

Cyanotic: tetrology of Fallot, Ebstein's anomaly, transposition of the great arteries, and Eisenmenger's syndrome.

NEJM January 27, 2000; 342: 256-63

NEJM February 3, 2000; 342: 334-42 first author M Elizabeth Brickner, University of Texas Southwestern Medical Canter, Dallas.