

PRACTICAL POINTERS

FOR PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

SEPTEMBER 2006

OBESITY Clinical Points

OBESITY Importance of Waist Circumference

MEDICAL THERAPY FOR URINARY STONE PASSAGE

**DIAGNOSIS OF MIGRAINE A mnemonic
NEED OF NEUROIMAGING FOR HEADACHE**

HbA1c MONITORING Pitfalls and Indications

ACUTE APPENDICITIS A Clinical Review

**THE NICE (UK) SUGGESTS THAT USE OF CHOLINESTERASE INHIBITORS FOR ALZHEIMER'S SHOULD
BE LIMITED.**

RESTLESS LEG SYNDROME

A TYPE OF FATIGUE SYNDROME FOLLOWING SEVERE INFECTIOUS DISEASE

ROSIGLITAZONE TO REDUCE RISK OF PROGRESSION OF PRE-DIABETES. A GOOD IDEA?

THE BURDEN OF VALVULAR HEART DISEASE IN THE ELDERLY POPULATION

CDC RECOMMENDS OPPORTUNISTIC HIV TESTING

THE CHANGING FACE OF HIV CARE

**JAMA, NEJM, BMJ, LANCET
ARCHIVES INTERNAL MEDICINE
ANNALS INTERNAL MEDICINE
www.practicalpointers.org**

**PUBLISHED BY PRACTICAL POINTERS, INC.
EDITED BY RICHARD T. JAMES JR. MD
400 AVINGER LANE, SUITE 203
DAVIDSON NC 28036 USA
Rjames6556@aol.com**

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 5 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.
Editor/Publisher.

Practical Pointers is published every month on the internet as a public service. It is available on a more timely basis by e-mail attachment. It contains no advertising. It is completely without bias. There is never any charge.

Requests for "subscription" to rjames6556@aol.com

HIGHLIGHTS and *EDITORIAL COMMENTS* SEPTEMBER 2006

“The Diagnosis Of Obesity Is Rarely Recorded”

9-1 OBESITY—*Time To Wake Up*

“An evidence-base of effective measures for preventing obesity does not exist.”

“Obesity does not need a scientific breakthrough to be treated successfully.”

“In practice, height and weight are often not recorded. The diagnosis of obesity is rarely recorded. BMI is seldom measured in persons of normal weight. Thus, progression to overweight is missed, and with it the opportunity to prevent more than half of the burden of diabetes.”

“The metabolic and vascular benefits of even modest reductions in weight are well described. The most striking benefits, in proportional terms, are from modest weight loss (5% to 10%), when fat is particularly lost from intra-abdominal sites. This amount of loss increases life expectancy an average of 3 to 4 years for overweight patients with type 2 diabetes.”

Read the full abstract for more clinical points.

I believe our number one goal of primary care should be making all persons take responsibility for their own health and well-being by adopting healthy habits.

Some primary care clinicians have a weight problem. This may deter them from confronting obese patients about their problem.

Some clinicians may be discouraged about advising obese patients because of a perceived lack of effectiveness of treatment.

I can think of no more simple, no-cost, and potentially valuable measure to reduce risk of disease than weight loss.

If only it were not so difficult!

Waist Circumference—A Simple, No Cost, Valid, And Important Marker of Risk.

9-2 OBESITY: Body Mass Index and Waist Circumference

“The main difficulty with anthropometric measures is that doctors and the public are not aware of the value of these measures. More sophisticated and expensive measurements are no better for determining body fat.”

“Waist circumference was developed originally as simpler measure—and a potentially better indicator of health risk than BMI. It is at least as good an indicator of total body fat as is BMI. It is the best predictor of visceral (intra-abdominal) fat and total fat.”

“The most clinically telling physical sign of serious underlying disease is increased waist circumference, which is linked to insulin resistance, hypertension, dyslipidemia, a pro-inflammatory state, type 2 diabetes, coronary heart disease, sleep apnea, and gallbladder disease.”

“Abdominal (visceral) fat is metabolically active.”

Read the full abstract for other clinical points.

Primary care clinicians should chart waist circumference and BMI.

A Greater Likelihood Of Spontaneous Passage.

9-3 MEDICAL THERAPY TO FACILITATE URINARY STONE PASSAGE: A Meta-Analysis

Provided these patients do not require renal pelvic decompression (because of a solitary kidney or obstructing pyelonephritis), and if pain relief can be obtained, a trial of conservative non-surgical therapy may be warranted. Many of these stones pass spontaneously, especially small ones (5 mm and under) located distally in the ureter.

Calcium channel blockers and adrenergic alpha antagonists have been proposed as a way to enhance passage. Use of these drugs is based on our understanding of ureteral smooth-muscle physiology.

This meta-analysis included 9 randomized, controlled trials (over 650 outpatients) in which calcium blockers (eg, nifedipine) or alpha blockers (eg, tamsulosin; *Flomax*) were used. In most patients, the stone was located in the distal third of the ureter.

Control groups were defined as those not having received any additional medical therapy to ease stone passage (eg, no other vasodilators, no antispasmodics or anticholinergic drugs).

Both groups received NSAIDs (eg, diclofenac) for pain control. NSAIDs are highly effective in symptomatic relief of acute renal colic.

Overall, patients given a calcium blocker or an alpha blocker had a 65% greater likelihood of stone-passage than controls. The calculated number needed to treat (NNT) to obtain one passage = 4.

“With the low risk-profile of these drugs, and their wide therapeutic window, our results suggest that physicians should consider a new algorithm for the management of urolithiasis in which treatment begins with a course of medical therapy.”

The investigators suggest that corticosteroids might provide additional benefits.

Conclusion: Medical therapy is an option for facilitation of urinary-stone passage for patients amenable to conservative management.

Is there any reason why a calcium blocker and an alpha blocker could not be combined? And a corticosteroid added, since treatment period is short?

POUNDing Migraine is a Symptom Complex

9-4 DOES THIS PATIENT WITH HEADACHE HAVE MIGRAINE OR NEED NEUROIMAGING?

In assessing patients with headache (**HA**), clinicians are often faced with two important questions. Is the HA migraine.? Does the patient require neuroimaging?

Patients who present with classic visual aura—a slowly evolving scintillating scotoma that moves or passes through the visual field over roughly 30 minutes, then disappears, and is followed by the onset of unilateral disabling HA—constitute an easy diagnosis.

The study suggests 5 questions used as a screening tool for migraine without aura:

- 1) Is the HA pulsating?
- 2) Does it last between 4 and 72 hours (without medication)?
- 3) Is it unilateral?
- 4) Is nausea present?
- 5) Is the HA disabling?

If the answer is “yes” to 4 or 5, the likelihood ratio of migraine is high (LR = 24: migraine vs not-migraine). If 3 are present, LR is 3.5. For 1 or 2, the LR is below 1.0

These authors have constructed a mnemonic based on these 5 criteria: POUNDing

P = PULSATING

hO = HOURS OF DURATION (4 to72)

U = UNILATERAL

N = NAUSEA OR VOMITING

D = DISABLING

Looking for a *combination* of symptoms is important in the diagnosis of migraine.

Neuroimaging is more likely to reveal intracranial pathology if the HA is associated with:

- 1) An abnormal neurological examination.
- 2) A thunderclap HA
- 3) Atypical aura
- 4) Altered mental status
- 5) Associated pathology: cancer; HIV infection.

Testing HbA_{1c} More Often Than Every Several Months May be Misleading

9-5 GLYCATED HAEMOGLOBIN (HbA_{1c}) MONITORING

This article discusses some of the physiology of HbA_{1c} and some common situations in which it may be misleading. With increasing emphasis on achieving lower HbA_{1c} values, clinicians need to understand its limitations.

Glycation of hemoglobin is non-linear over time. Formation of HbA_{1c} occurs over the lifespan of the red cells (~ 120 days). Approximately 50% is present in older cells (aged 90-120 days—the end of lifespan). The other 50% occurs in younger cells (aged 1 -90 days). Thus, HbA_{1c} represents a weighted average of blood glucose over the previous 3 to 4 months. A greater percentage is present in older cells.

The reviewers discuss several situations illustrating how HbA_{1c} may mislead.

Testing HbA_{1c} more often than every several months may potentially cause clinical errors.

HbA_{1c} should *not* be used to diagnose diabetes. Indiscriminate use of HbA_{1c} risks incorrect classification.

Two measurements a year are sufficient in patients who are meeting goals of treatment and who have stable control, and a maximum of 4 to 6 a year in patients whose treatment has changed, or who are not meeting treatment goals.

“As situations of increased hemoglobin turnover are often not stable, if the values of HbA_{1c} are interpreted at all, they should logically be combined with home glucose measurement as an indicator of day to day control.”

Read the full abstract.

“The Diagnosis Is Primarily A Clinical One”

9-6 ACUTE APPENDICITIS: A Refresher Course of Clinical Points

Thirteen clinical points. Most old; some new. Read the full abstract.

Should These Drugs Be Removed From General Use?

9-7 ROLE OF CHOLINESTERASE INHIBITORS IN DEMENTIA: *Needs Rethinking*

Meta-analyses show quite consistently that these drugs have modest beneficial effects compared with placebo—at six months, a mean difference of 2 to 3 points on the Alzheimer’s disease assessment scale (range 0 to 70); of 2.4 points on the assessment of activities of daily living on the progressive deterioration scale (range 0 to 100); and a difference of 2.5 points on the neuropsychiatric inventory scale (range 12 to 120). Caregivers often reported improvements in behavioral disturbances and activities of daily living in patients taking the drugs. But also when their relative-patient was taking a placebo.

Within one year, 9% of Alzheimer's patients who were taking the drugs were admitted to care homes vs 14% of those on placebo. At three years, the numbers were almost identical—42% vs 44%.

The UK National Institute for Health and Clinical Excellence (NICE) is now considering revising the guidelines because the drugs do not provide value for money. Their benefits are, by any criteria, modest.

This has been met with a hostile reception from some segments of the public.

A frequent argument is that the new recommendations are wrong because the medicines are all that the doctors have to offer. "The tragedy is that the only currently licensed medicines for a cruel illness have turned out to be of marginal benefit."

This is more a social, economic issue than medical. The modest and transient benefits of these drugs are well known. On average, they retard progression of dementia by about 6 months. They do not prevent dementia. As the article suggests, over several years, the drugs make little difference in admission to care institutions.

But, the reported outcomes in randomized trials are mean outcomes. Some patients may respond more favorably. They may be outliers. Families may hope for this. I believe, however, that many patients take these drugs for years too long.

Look For Iron Deficiency

9-8 RESTLESS LEG SYNDROME

RLS has a prevalence of 10% to 15% in white adults. It occurs in children and adolescents as well as adults. In over 1/3 of patients symptoms start before age 10. Most are not diagnosed until middle or late adult life. One study has asked whether "growing pains" in children may be a manifestation.

The International Restless Legs Syndrome Study Group suggests 4 criteria for diagnosis:

- 1) The desire to move the extremities, often associated with paresthesias or dysesthesias
- 2) Motor restlessness
- 3) Aggravation of symptoms by rest, and at least temporary relief by activity
- 4) Worsening of symptoms in the evening or night.

Iron deficiency is present in about 1/4 of patients, particularly in older people. The severity of symptoms is proportional to the reduction in iron. Symptoms severity increases as serum ferritin levels become lower. Reduction of iron in parts of the CNS (shown by MRI) and reduced ferritin in the cerebrospinal fluid suggest that iron deficiency may have a role in pathophysiology. The possibility of iron deficiency needs to be investigated and treated. Treatment may reduce symptoms.

Ropinirole (a dopamine agonist often prescribed for Parkinson's disease and for bipolar disorder) is approved for use in RLS in the USA. . It has significant adverse effects, particularly somnolence. It interacts with a number of other drugs.

Both clinician and patients should be aware of all adverse effects. I would not prescribe it for RLS unless the patient has very troublesome symptoms and insists on trying drug therapy.

“A Distinguishable Subset Within The Broad Diagnostic Category Of Chronic Fatigue Syndrome.”

9-9 POST-INFECTIVE AND CHRONIC FATIGUE SYNDROMES PRECIPITATED BY VIRAL AND NON-VIRAL PATHOGENS.

Post-infective fatigue states have been linked to a diverse spectrum of severe infections, although associations between the syndrome and infections are not consistent.

This prospective population-based cohort study delineated the risk factors, symptom patterns, and longitudinal course of prolonged illnesses after a variety of acute infections.

This study, in a rural area of Australia, was based on patients with IgM positive serological results indicating acute Epstein-Barr virus, Q fever, or Ross-River virus infections.

Of the subjects (n = 253; age range 17-63), none had symptoms of the infection for over 6 weeks. None reported pre-existing medical disorders or drug abuse likely to be associated with prolonged fatigue.

Used a self-reported questionnaire assessing 6 symptom domains: acute illness; irritability; fatigue; neurocognitive disturbance; musculoskeletal pain; and mood disturbance.

The case rate for provisional post-infective fatigue syndrome (%):

Six weeks	35
Three months	27
Six months	12
Twelve months	9

Compared with subjects who recovered more promptly (n = 224), the 28 subjects considered to have the post infective fatigue syndrome reported higher scores for the fatigue factor.

Fatigue (of the 6 symptom domains) was the strongest and most consistent correlation with functional impairment (“days out of role in the past month”).

The syndrome was predicted largely by the severity of the acute illness, rather than by demographic, psychological, or microbiological factors.

Prolonged fatigue states after infections are common and disabling. They may persist for 12 months or longer.

I abstracted this study because I believe some patients do indeed develop chronic fatigue after a serious infection. These patients deserve recognition and support. I do not think its cause is psychological. I doubt, however, that it lasts for years.

I believe it differs from what we have heretofore termed “The Chronic Fatigue Syndrome”. It may likely be differentiated by terming this syndrome “The Post-infection Fatigue Syndrome”.

I hope this provocative study will provoke further investigations. The point is clinically important.

Is This A Reasonable Application For Primary Care Practice?

9-10 EFFECTS OF ROSIGLITAZONE ON THE FREQUENCY OF DIABETES IN PATIENT WITH IMPAIRED GLUCOSE TOLERANCE OR IMPAIRED FASTING GLUCOSE

This 3-year study assessed whether rosiglitazone (*Avandia* 8 mg daily) would reduce the frequency of development of type 2 diabetes (**DM2**) in patients with impaired fasting glucose, impaired glucose tolerance, or both (pre-diabetes).

Both placebo and rosiglitazone groups received advice about diet and lifestyle.

	Composite outcome*	Became normoglycemic**
Rosiglitazone	11.6%	38.6%
Placebo	26%	20.5%***

* The composite outcome (development of DM2 or death) contained mainly subjects who developed diabetes. Deaths were infrequent; slightly over 1% in both groups.

** Regression of fasting plasma glucose to less than 100 mg/dL

*** Note that about 1/5 of subjects taking placebo became normoglycemic.

Absolute difference = 15.4% (NNT for 3 years to prevent one composite outcome) = 6;
NNT to achieve normoglycemia in one subject = 5)

Conclusion: Rosiglitazone reduced incident DM2 and increased the likelihood of regression to normoglycemia in adults with impaired fasting glucose or impaired glucose tolerance, or both (pre-diabetes).

This is another example of American's preference to take a "pill for their ill" rather than adopting healthy lifestyles. Pill-taking is so much easier!

Note that at baseline many subjects were obese, sedentary, had hypertension, and smoked. These risks must have been reduced in some subjects during the trial. We are not told how many, or how they were treated. These factors carry more risk than risks of pre-diabetes, and certainly should take precedence over any drug therapy to reduce risk of progression of pre-diabetes into diabetes.

What is the benefit / harm-cost ratio of rosiglitazone?

1) *Benefit: The outcome of the trial does not provide any estimate of clinical benefit (reduction in complications of diabetes or increased years of health). The endpoint of this trial was a substitute (intermediate) endpoint—a chemical outcome (difference in plasma glucose), not a clinical outcome.*

2) *Harm: Will come to some. The drug does cause fluid retention and has a risk of congestive heart failure.*

3) *Cost: By my calculation, based on price quoted by drugstore.com = \$6,263.00 for 3 years. Generic Metformin 1000 mg costs \$177.00 for 3 years.*

The trial implies that reducing the risk of developing diabetes will produce clinical benefits. We do not know by how much. We do not know if continuing rosiglitazone beyond 3 years will reduce progression to DM2. I doubt that many patients would continue rosiglitazone after 3 years. Note that 1/4 of subjects in the trial discontinued the drug during the 3 years. In clinical practice, more will discontinue. This limits applicability. I believe the risk of DM2 will revert to baseline risk when the drug is discontinued.

I would wager that, in clinical practice, patients who rely on a pill to reduce risk of DM2 would be less likely to maintain lifestyle changes to reduce risk. Lifestyle changes would be more permanent. Lifestyle interventions are essential.

How effectively would reduction in risk of developing DM2 during 3 years reduce risk of cardiovascular complication of DM2? Very little. The number needed to treat pre-diabetes over 3 years with rosiglitazone to prevent one clinical event would be extremely high.

I would not prescribe rosiglitazone for this purpose. I might prescribe metformin to very select patients as a bridge to reduce risk while they improve lifestyles over a year or two. Metformin has some advantages: no hypoglycemia; no weight gain; reduction in triglycerides; reduction in macrovascular events. And cost.

“More Than One In Eight People Aged 75 and Older Have A Moderate Or Severe Valve Disease.”

9-11 BURDEN OF VALVULAR HEART DISEASE

Since the incidence of rheumatic fever has fallen dramatically in developed countries, valvular heart disease (**VHD**) is not usually regarded as a major problem. VHD is now mostly degenerative. It is related to the increasing age of the population. Availability of echocardiography has led to an increase in diagnosis.

This study reassessed the prevalence of VHD in the population and its effect on overall survival.

“The population burden of clinically noteworthy valvular heart disease is considerable in the US population.” Prevalence increased markedly with age—from 0.7% in the young group; to 13.3% in the 75 and older group. Prevalence begins to increase at age 65. “More than one in eight people aged 75 and older have a moderate or severe valve disease.” The estimate of prevalence of VHD in the USA corresponds to a burden in the year 2000 of 4 to 5 million adults.

VHD is not benign. Over 10 years after diagnosis, mortality rates were increased in those with VHD—adjusted risk ratio = 1.36 (valve disease vs no valve disease). Risk of death increased each year.

Conclusion: Moderate or severe VHD is common in the population. It increases markedly with age, and is associated with increased mortality.

This begs the question—What should primary care clinicians do with a patient with VHD? The response depends on many factors (age, type of VHD, co- morbidity, preferences of the patient, availability of expert surgeons)—not an easy decision to make.

Another problem: Does VHD predispose to endocarditis secondary to bacteremia associated with dental manipulations? This has been debated. The increasing prevalence of VHD in the elderly renews the debate. Should patients with VHD receive antibiotic prophylaxis when undergoing invasive dentistry?

“All Patients Should Be Screened Regardless Of Whether They Seem To Be At Risk”

9-12 CDC RECOMMENDS OPPORTUNISTIC HIV TESTING

The CDC has issued new recommendations designed to make voluntary HIV screening on an opportunistic basis a routine part of medical care for all patients aged 13 to 64. The objective is to increase early diagnosis among the estimated 250 000 Americans who are HIV positive, but are not aware of it. This would lead to earlier diagnosis and more effective treatment.

The main recommendations:

- 1) All patients should be screened regardless of whether they seem to be at risk.
- 2) Patients should be able to opt out of screening.
- 3) The need for special consent should be eliminated, and be replaced by a standard requirement for consent.
- 4) Counseling on HIV before and after the test is advisable, but not mandatory.

Making the test a normal part of care is an important step toward removing the stigma associated with testing.

Several questions arise:

Who pays?

Are satisfactory arrangements available for follow-up and treatment?

What is the gold standard for the test used?

What about false positive tests?

Does the primary care clinician have the duty to inform and to warn sexual partners of a patients tested positive?

This reminds me of the old requirements for screening for syphilis which were in place in many states years ago. In North Carolina, it was a requirement for a marriage license.

“Now, More Than Ever, HIV Care Is Primary Care.”

9-13 THE CHANGING FACE OF HIV CARE

Management of HIV infections has advanced dramatically. Related morbidity and mortality has declined—attributed to improved prophylaxis against opportunistic infections, and the introduction of a potent combination of antiretroviral therapies (HAART; highly active antiretroviral therapy).

Some authorities have reported that the life expectancy of patients with HIV is approximating that of the general population. “HIV is becoming a chronic disease.”

The physician of choice has changed. Earlier, infectious disease experts, oncologists, and palliative care specialists treated most patients. Now, as patients with HIV live much longer, they are developing non-HIV conditions (hypertension, cancer, diabetes, and coronary heart disease). In addition, antiretroviral drugs are associated with dyslipidemia, diabetes, and neuropathies. As life expectancy and state of health improves, and life is extended, HIV patients may eat more and become overweight, with the same consequences.

ABSTRACTS SEPTEMBER 2006

“The Diagnosis Of Obesity Is Rarely Recorded”

9-1 OBESITY—*Time To Wake Up*

- We live in a “toxic” environment which increases risk of obesity. Among preventable causes of disease and premature death, obesity is overtaking smoking.
- Obesity affects almost every aspect of life and medical practice. Early treatment and prevention offer multiple long term health benefits. Doctors in all medical and surgical specialties can contribute.
- Although the principles of achieving energy balance are known, an evidence-base of effective measures for preventing obesity does not exist.
- In primary care practice, obese people take up a greater proportion of time than non-obese people. Obese patients need more referral, and are prescribed more drugs than people with normal weight. Resources are being spent mainly treating the secondary consequences of obesity. Preventing obesity is not encouraged.
- Uniquely among chronic diseases, obesity does not need a scientific breakthrough to be treated successfully. The barriers to successful management are political and organizational, along with a lack of resources.
- Obesity is often neglected in evidence-based approaches to managing its consequences. Clinical practice focuses on secondary prevention for chronic diseases.
- In practice, height and weight are often not recorded. The diagnosis of obesity is rarely recorded. BMI is seldom measured in persons of normal weight. Thus, progression to overweight is missed, and with it the opportunity to prevent more than half of the burden of diabetes.
- Despite the importance of obesity in secondary prevention of coronary heart disease, it is poorly managed, even in high risk patients.
- Benefits of treatment of cardiac risk factors are greater for overweight and obese persons because their risks are higher.

- Waist circumference is a better assessor of metabolic risk than BMI because it is more directly proportional to total body fat and the amount of metabolically active fat. The most clinically telling physical sign of serious underlying disease is increased waist circumference. It is linked to insulin resistance, dyslipidemia, a pro-inflammatory state, type 2 diabetes, and coronary heart disease. Most hypertension, previously considered “essential” is secondary to obesity.
- A large waist circumference is the strongest anthropometric predictor of vascular events and diabetes. It predicts risk independently of BMI and is a better predictor than waist / hip ratio.
- The metabolic and vascular benefits of even modest reductions in weight are well described. The most striking benefits, in proportional terms, are from modest weight loss (5% to 10%), when fat is particularly lost from intra-abdominal sites. This amount of loss increases life expectancy an average of 3 to 4 years for overweight patients with type 2 diabetes.
- Estimated benefits of 10% weight loss:
 - BP down about 10/10 in hypertensive patients
 - Fall of up to 50% in fasting glucose in newly diagnosed patients with diabetes.
 - > 30% fall in fasting or two-hour insulins
 - > 30% increase in insulin sensitivity
 - 40-60% fall in incidence of type 2 diabetes.
 - Fall of 10% in total cholesterol.
 - Fall of 15% in LDL-cholesterol.
 - Fall of 30% in triglycerides.
 - Rise of 8% in HDL-cholesterol.
 - > 20% fall in mortality.
 - > 30% fall in deaths from diabetes
 - > 40% fall in deaths related to obesity.

BMJ September 23, 2006; 333: 640-42 “Practice” the first of a series “ABC of Obesity” first author David Haslam, clinical director for the National Obesity Forum (UK)

=====

Waist Circumference—A Simple, No Cost, Valid, And Important Marker of Risk.

9-2 OBESITY: Body Mass Index and Waist Circumference

- Body mass index (**BMI**; weight in kg / height in meters²) has traditionally been used to identify

individuals who are most likely to be overweight or obese. Generally a high value indicates excessive body fat, and consistently relates to increased health risks.

- Waist circumference was developed originally as a simpler measure—and a potentially better indicator of health risk than BMI. It is at least as good an indicator of total body fat as is BMI. It is the best predictor of visceral (intra-abdominal) fat and total fat. It gives a better prediction of disease risks than waist / hip ratio.
- The most clinically telling physical sign of serious underlying disease is increased waist circumference, which is linked to insulin resistance, hypertension, dyslipidemia, a pro-inflammatory state, type 2 diabetes, coronary heart disease, sleep apnea, and gallbladder disease.
- Abdominal (visceral) fat is metabolically active. Visceral fat content is strongly related to waist circumference: one kg in person with circumference of 80 cm; 2.3 kg in those with circumference of 100 cm.
- Waist circumference should be measured midway between the lower rib margin and the iliac crest, with a horizontal tape at the end of gentle expiration.
- Waist circumference is minimally related to height, so correction for height does not improve its relation with intra-abdominal fat or ill health.

- Levels of health risks associated with waist circumference (cm) in white men and women:

Men		Women		Health risk*
Cm	Inches	Cm	Inches	
< 94	< 37	< 80	<31	Low
94 to 101.9	37 to 39	80 to 87	32 to 34	Increased
102 and above	40 and above	88 and above	35 and above	High.

(* Risk of type 2 diabetes, coronary heart disease, and hypertension.)

- Different ethnic groups may have different cut-off levels of waist circumference. Some African and Asian groups have greater risk of coronary heart disease at the same cut-off levels.

- Identifying people who are overweight, and particularly those with accumulation of excessive visceral fat, is essential for directing interventions. BMI and waist circumference are well validated and available to all health professionals. Both are simple. Waist circumference is arguably better, but both are simple. Change is best monitored by following body weight.
- BMI and waist circumference are collinear, so combining the two measures adds little to risk prediction.
- Each kg of weight loss is equivalent to a reduction of 1 cm in waist circumference. However, there is greater measurement error in waist circumference. BMI is the best measure for monitoring change.
- Loss of 10% of bodyweight (not necessarily a return to normal BMI) is associated with multiple metabolic and vascular benefits.
- The main difficulty with anthropometric measures is that doctors and the public are not aware of the value of these measures. More sophisticated and expensive measurements are no better for determining body fat.

BMJ September 30, 2006; 333: 695-98 “Practice” the second of a series “ABC of Obesity” first author Thang S Han, University College London Hospitals, UK

Go to [www.consumer.gov/weightloss/bmi .htm](http://www.consumer.gov/weightloss/bmi.htm) for an easy to use chart determining BMI by inches and pounds.

=====

A Greater Likelihood Of Spontaneous Passage.

9-3 MEDICAL THERAPY TO FACILITATE URINARY STONE PASSAGE: A Meta-Analysis

The lifetime risk of urinary stone (US) is between 5% and 12%. About half of these patients will have a recurrence within 5 years. It is a chronic disease with substantial economic consequences and great public health importance.

Although some stones might be asymptomatic, many are painful and commonly present to emergency departments. Provided these patients do not require renal pelvic decompression (because of a solitary kidney or obstructing pyelonephritis), and if pain relief can be obtained, a trial of conservative

non-surgical therapy is warranted. Many of these stones pass spontaneously, especially small ones (5 mm and under) located distally in the ureter.

Calcium channel blockers and adrenergic alpha antagonists have been proposed as a way to enhance passage. Use of these drugs is based on our understanding of ureteral smooth-muscle physiology.

Medical therapy is underused in part because there are now minimally invasive techniques (ureteroscopy and lithotripsy) which allow resolution. But they are invasive and costly, and associated with risks.

This meta-analysis assessed the efficacy of medical therapy.

Conclusion: Medical therapy is an option for facilitation of stone passage for patients amenable to conservative management.

STUDY

1. Meta-analysis included 9 randomized, controlled trials (over 650 outpatients) in which calcium blockers (eg, nifedipine) or alpha blockers (eg, tamsulosin; *Flomax*) were used. In most patients, the stone was located in the distal third of the ureter.
2. Control groups were defined as those not having received any additional medical therapy to ease stone passage (eg, no other vasodilators, no antispasmodics or anticholinergic drugs).
3. Both groups received NSAIDs (eg, diclofenac) for pain control. NSAIDs are highly effective in symptomatic relief of acute renal colic.
4. Some trials used alpha blocker alone; some alpha blocker + corticosteroids; some calcium blocker alone; some calcium blocker + steroids. In some trials corticosteroids were used in both treatment and placebo groups. (The incremental benefit of corticosteroids was small.)
5. Primary end point = proportion of patients who passed stones.

RESULTS

1. Overall, patients given a calcium blocker *or* an alpha blocker had a 65% greater likelihood of stone-passage than controls.
2. The calculated number needed to treat (NNT) to obtain one passage = 4.
3. Treatment duration ranged from 7 days to 6 weeks. Mean time to passage ranged from 6 days in several treatment groups to 20 days in controls. In the majority of trials the stone was passed more quickly in the treated group.
4. Some of the trials reported less need for analgesics in the treatment group.

DISCUSSION

1. This suggests that pharmacotherapy helps with passage of stones—a 65% greater likelihood of spontaneous passage.
2. “With the low risk-profile of these drugs, and their wide therapeutic window, our results suggest that physicians should consider a new algorithm for the management of urolithiasis in which treatment begins with a course of medical therapy.”
3. The effects of calcium blockers and alpha blockers are mediated through receptors located in the ureter. Evidence suggests that relaxing the ureter and increasing hydrostatic pressure proximal to the stone facilitates passage.
4. Other studies have reported that these drugs shorten the time to passage, and reduce pain.
5. Both calcium blockers and alpha blockers are well tolerated. Costs of treatment are relatively low.
6. The investigators suggest that corticosteroids might provide additional benefits.

CONCLUSION

The meta-analysis suggests that medical therapy is an option for facilitation of urinary-stone passage for patients amenable to conservative management.

Lancet September 30, 2006; 368: 1171-79 Meta-analysis, first author John M Hollingsworth, University of Michigan, Ann Arbor.

POUNding Migraine is a Symptom Complex

9-4 DOES THIS PATIENT WITH HEADACHE HAVE MIGRAINE OR NEED NEUROIMAGING?

In assessing patients with headache (**HA**), clinicians are often faced with two important questions. Is the HA migraine.? Does the patient require neuroimaging?

Almost all persons have a HA within their lifetime. Despite the high prevalence of HA, physicians are often uncomfortable diagnosing specific HA disorders.

Ultimately, all forms of HA share a common final link in the perception of pain—nociceptive information transmitted via the nucleus of the trigeminal nerve. Mechanisms activated in secondary HA disorders (structural or metabolic) resemble those activated in primary HA disorders (migraine and tension-type). Diagnosis and differentiation can be difficult.

The Headache Society has developed a formal, comprehensive HA classification system which includes migraine with and without aura. The classification system may be too cumbersome for most primary care clinicians to use properly. Efforts have been made to produce short, practical, memorable, and effective screening tools.

Undifferentiated HA is usually of benign etiology. Neuroimaging rarely reveals significant intracranial pathology. However, a variety of intracranial lesions may be heralded by HA, and neuroimaging is required to make the diagnosis. Thus, there is a tension between knowing that benign HAs are overwhelmingly common, and the fear of missing an intracranial lesion. Neuroimaging resources may, as a result, be overused.

This systematic review assessed the performance characteristics of screening questions for diagnosing migraine, using the Headache Society diagnostic criteria as the reference standard. It also addressed the accuracy of the clinical examination in predicting the presence of underlying intracranial pathology, using neuroimaging as the reference standard.

It is written primarily for generalists and non-neurologists.

Does this patient have migraine?

When assessing the patient with HA, it is useful to rule in or rule out migraine as a diagnosis. “Fewer than half of patients with migraine are properly diagnosed, and only one third of affected patients receive migraine-specific drugs.”

This study determined the clinical features that distinguish patients with migraine without aura from those who have other types of HA.

Patients who present with classic visual aura—a slowly evolving scintillating scotoma that moves or passes through the visual field over roughly 30 minutes, then disappears, and is followed by the onset of unilateral disabling HA—constitute an easy diagnosis.

For patients with migraine *without* classical aura, the diagnosis is frequently missed. Migraine is a symptom complex. It is unlikely that any single feature (except classical visual auras) will be sufficient to rule in or rule out migraine.

These authors cite a 1993 study¹ which, in their opinion, had the fewest methodological deficiencies. The study represents patients with HA without aura that are similar to patients seen in primary care.

The study was based on 5 questions used as a screening tool:

- 1) Is the HA pulsating?
- 2) Does it last between 4 and 72 hours (without medication)?
- 3) Is it unilateral?
- 4) Is nausea present?
- 5) Is the HA disabling?

If the answer is “yes” to 4 or 5, the likelihood ratio of migraine is high (LR = 24: migraine vs not-migraine). If 3 are present, LR is 3.5. For 1 or 2, the LR is below 1.0

These authors have constructed a mnemonic based on these 5 criteria: POUNDing

P = PULSATING

hO = HOURS OF DURATION (4 to72)

U = UNILATERAL

N = NAUSEA OR VOMITING

D = DISABLING

Looking for a combination of symptoms is important in diagnosis of migraine.

Does this patient need neuroimaging?

This study also determined the clinical features which identify those who might require neuroimaging. In a primary care clinic, the prevalence of serious intracranial abnormalities for patients with HA is less than the 1%.

The pre-test probability of intracranial pathology is highly variable. It depends on initial presentation, which ranges from 1% in chronic HA to 43% in thunderclap HA.

With a pre-test probability of 1%, a further decrease in probability would *not* likely change clinical management. “Does it truly help a clinician to know that a particular feature on history or physical examination lowers the pretest probability from 1% to 0.5%?”

When the pretest probability of having significant pathology is high enough (43%), the absence of other abnormal findings is unlikely to provide enough reassurance to forego further investigation. The only significant pathology among patients with thunderclap HA is subarachnoid hemorrhage. These patients should undergo investigation regardless of associated clinical features.

An abnormal neurological examination is the most robust finding indicating intracranial pathology. “If a patient presents with a chronic headache, and abnormal findings on neurological examination, the probability of a significant abnormality is high enough to warrant a neuroimaging study.”

Findings such as altered mental status, HIV, and cancer should raise suspicion of serious intracranial pathology in patients with new-onset HA.

Patients with HA and atypical aura (other than recurrent episodes of classical visual aura of migraine) have increased likelihood of intracranial pathology. Patients with sensory or motor aura, aura that has changed in character, or aura that cannot be clearly described as typical should undergo imaging.

JAMA September 13, 2006;m 296: 1274-83 Original investigation, first author Michael E Detsky, University of Toronto, Canada.

1 “Diagnostic Screen for Assessment of the IHS Criteria for Migraine by General Practitioners” Cephalalgia, 1993; 13 (supl) 54-59

Testing HbA_{1c} More Often Than Every Several Months May be Misleading

9-5 GLYCATED HAEMOGLOBIN (HbA_{1c}) MONITORING

HbA_{1c} has become the monitoring test of choice to assess medium term control of diabetes. It is a key parameter on which to base changes in management of patients.

This article discusses some of the physiology of HbA_{1c} and some common situations in which it may be misleading. With increasing emphasis on achieving lower HbA_{1c} values, clinicians need to understand its limitations.

Glycation of hemoglobin is non-linear over time. Formation of HbA_{1c} occurs over the lifespan of the red cells (~ 120 days). Approximately 50% is present in older cells (aged 90-120 days—the end of lifespan). The other 50% occurs in younger cells (aged 1 -90 days). Thus, HbA_{1c} represents a weighted average of blood glucose over the previous 3 to 4 months. A greater percentage is present in older cells.

Several situations illustrate how HbA_{1c} may be misleading, and may lead to inappropriate changes in diabetic control:

1) If the average red cell lifespan is shorter than normal, HbA_{1c} will be lower than would be expected for the degree of chronic hyperglycemia. (Because of less time to complete glycation.) This might occur in the presence of anemia due to chronic blood loss, or due to hemolysis. A reduced (falsely normal) HbA_{1c} in these circumstances might indicate (incorrectly) that glucose control is adequate. If blood loss is sufficient to shorten the average lifespan, HbA_{1c} concentration could theoretically be halved, and could give a false impression that glucose control is exemplary.

2) If the HbA_{1c} is measured shortly after treatment of diabetes is begun, and time is insufficient to allow it to fall, therapy may be inappropriately intensified despite a more favorable plasma glucose, and the patient may risk hypoglycemia in response to an inappropriate increase in drug therapy.

3) Persistent fetal hemoglobin, hemoglobin variants, hemoglobin changes due to uremia also cause potentially clinically misleading HbA_{1c}. Newer methods to resolve interferences are available. The laboratory should be able to advise.

Testing HbA_{1c} more often than every several months may potentially cause clinically misleading results.

Results of two consecutive determinations of HbA_{1c} may vary up to 0.6% or more, depending on method. Trends are more valuable than small absolute differences between two values.

Organizations setting standards for HbA_{1c} levels recommend:

For type 1 diabetes < 6.5%

For type 2 diabetes < 7.0%

Standards should be individualized, noting the life expectancy, age, incidence of hypoglycemia, comorbid conditions, and the considerable inter-individual differences in mean blood glucose and HbA_{1c} concentrations.

The change in risk of complications of diabetes corresponding to a change in HbA_{1c} is non-linear. In a population study in which HbA_{1c} was reduced from 9% to 7%, approximately 50% of the decrease in events occurred at a mean HbA_{1c} of 8.6%. Small improvements can give large benefits.

HbA_{1c} should *not* be used to diagnose diabetes. Plasma glucose cut-offs should be used. If local point of care plasma glucose levels indicate possible diabetes, it may be reasonable to request an HbA_{1c}. Indiscriminate use of HbA_{1c} risks incorrect classification. Some patients whose HbA_{1c} is above the population upper reference interval, may not meet the formal criteria for diabetes. Implications of an incorrect diagnosis for an individual patient are considerable.

How frequently should HbA_{1c} be determined?

These commentators suggest:

Two measurements a year in patients who are meeting goals of treatment and who have stable control.

A maximum of 4 to 6 a year in patients whose treatment has changed, or who are not meeting treatment goals.

Don't test HbA_{1c} too frequently, this may mislead. No data exists for assessing rate of change of HbA_{1c} over short periods.

“As situations of increased hemoglobin turnover are often not stable, if the values of HbA_{1c} are interpreted at all, they should logically be combined with home glucose measurement as an indicator of day to day control.”

BMJ September 16, 2006; 333: 586-88 “Cases in Primary Care Laboratory Medicine”, review article first author Timothy M Reynolds, Queen's Hospital, Burton upon Trent, UK

What would changes in HbA_{1c} be after a severe acute hemorrhage? If my assessment is correct, HbA_{1c} would remain essentially the same for a few days or weeks after the event. As time goes on, and, as more young red cells enter the pool, the HbA_{1c} will decrease. This might lead to a false assurance of good control.

=====

“The Diagnosis Is Primarily A Clinical One”

9-6 ACUTE APPENDICITIS: A Refresher Course of Clinical Points

- The lifetime risk of acute appendicitis in the U.S. is about 9% for males and 7% for females. The diagnosis is primarily a clinical one.
- The classical presentation is a colicky peri-umbilical pain manifesting during the first 24 hours, then becoming constant and sharp, and migrating to the right iliac fossa. However, this may be present in only 50% of patients.
- The initial pain represents a referred pain resulting from the visceral innervation of the midgut.

The localized pain is caused by involvement of the parietal peritoneum after progression of the inflammatory process.

- Movement and cough may exacerbate the pain and often localize it to the right iliac fossa. Loss of appetite, nausea, and constipation are often present. Rebound tenderness is present, but should not be elicited to avoid distressing the patient.
- The classical presentation can be influenced by age. Acute appendicitis in the elderly and the very young can present diagnostic difficulty because of a non-specific presentation, often with subtle clinical signs. Infants and children often seem withdrawn. Elderly people may present with confusion. A high index of suspicion is required in such patients. These groups may experience increased mortality from appendicitis.
- In patients with a pelvic appendix, tenderness to the right on rectal or vaginal examination may be suggestive of acute appendicitis.
- Urinalysis reveals abnormalities in up to 40%. Predominant leukocytosis (neutrophils > 75%) is present. Pregnancy test should be done to exclude pregnancy.
- CT scan is more diagnostic than ultrasound, but should be done only when a diagnosis cannot be made. It may identify abnormalities such as peri-appendiceal inflammation and a calcified appendicolith. Consider the risk of excessive exposure to radiation associated with CT.
- There is no good evidence that analgesia should be withheld on the grounds that it may cloud the clinical picture.
- All patients should receive broad spectrum antibiotics (intravenous, one to three doses). They decrease the incidence of postoperative wound infection and intra-abdominal abscess.
- Risk of perforation is between 16% and 36% after the first 36 hours after onset of symptoms. It increases 5% for every 12 hour period thereafter.
- Laparoscopic appendectomy in adults reduces wound infections, postoperative pain, length of hospital stay and time taken to return to work. The number of intra-abdominal abscesses may be higher. An added advantage of laparoscopy is the ability to do diagnostic laparoscopy initially. This may discover alternative pathology.

- Pregnancy is a special consideration. Appendicitis is the most common non-obstetric emergency needing surgery in pregnant women. Displacement of the appendix by the gravid uterus often makes the presentation atypical. Localized tenderness can be present anywhere on the right side of the abdomen.

BMJ September 9, 2006; 333: 530-34 Clinical Review, first author D J Humes, University Hospital

=====

Should These Drugs Be Removed From General Use?

9-7 ROLE OF CHOLINESTERASE INHIBITORS IN DEMENTIA: *Needs Rethinking*

Since 2001, the UK National Institute for Health and Clinical Excellence (**NICE**) has recommended that three licensed cholinesterase inhibitors donepezil (*Aricept*) rivastigmine (*Exelon*) and galantamine (*Razadyne*) should be made available for treatment of patients with mild to moderate Alzheimer's disease.

Meta-analyses show quite consistently that these drugs have modest beneficial effects compared with placebo—at six months, a mean difference of 2 to 3 points on the Alzheimer's disease assessment scale (range 0 to 70); of 2.4 points on the assessment of activities of daily living on the progressive deterioration scale (range 0 to 100); and a difference of 2.5 points on the neuropsychiatric inventory scale (range 12 to 120). Caregivers often reported improvements in behavioral disturbances and activities of daily living in patients taking the drugs. But also when their relative-patient was taking a placebo.

Within one year, 9% of Alzheimer's patients who were taking the drugs were admitted to care homes vs 14% of those on placebo. At three years, the numbers were almost identical—42% vs 44%.

The health-economic analyses are more controversial. NICE is reviewing the original recommendations favoring these drugs, and is considering revising the guidelines because the drugs do not provide value for money, and because their benefits are, by any criteria, modest. Also, because after the drugs were approved, multidisciplinary memory clinics were established organized around prescriptions of cholinesterase inhibitors and monitoring their effects. NICE considers that this diverts resources from high-quality integrated care.

This proposed action has met with a hostile reception from some segments of the public. Caregivers have voiced moving accounts of marked improvements in their affected relatives, and dismay that a source of help is being taken away. NICE has been unfairly accused of ageism and stigmatization of people with dementia. A frequent argument is that the new recommendations are wrong because the medicines are all that the doctors have to offer.

It has been claimed that the adoption of the revised guidelines would be devastating for patients and carers. "The tragedy is that the only currently licensed medicines for a cruel illness have turned out to be of marginal benefit."

"These medicines should no longer be allowed to have such influence on services for patients with Alzheimer's disease and their families."

Look For Iron Deficiency

9-8 RESTLESS LEG SYNDROME

Restless leg syndrome (**RLS**) has probably been known for over 3 centuries. It remains underdiagnosed. Recently, there have been new treatment options and advances in its patho-physiology.

RLS has a prevalence of 10% to 15% in white adults. It occurs in children and adolescents as well as adults. In over 1/3 of patients symptoms start before age 10. Most are not diagnosed until middle or late adult life. One study has asked whether "growing pains" in children may be a manifestation.

RLS is characterized by unpleasant "creepy crawly" sensations in the lower limbs. They occur mainly in the evenings when the person is seated, or at night in bed. Symptoms are temporarily relieved by moving the legs. This causes the patient to move relentlessly, often pacing about in an attempt to gain relief.

The International Restless Legs Syndrome Study Group suggests 4 criteria for diagnosis:

- 1) The desire to move the extremities, often associated with paresthesias or dysesthesias
- 2) Motor restlessness
- 3) Aggravation of symptoms by rest, and at least temporary relief by activity
- 4) Worsening of symptoms in the evening or night.

RLS is commonly associated with periodic leg movement in sleep (limb jerking).

It may be idiopathic, or it may indicate a diverse range of disorders: e.g., Parkinson's disease, uremia, iron deficiency. It may be aggravated by pregnancy. About 40% of patients have a family history of RLS.

Iron deficiency is present in about 1/4 of patients, particularly in older people. The severity of symptoms is proportional to the reduction in iron. Symptom severity increases as serum ferritin levels become lower. Reduction of iron in parts of the CNS (shown by MRI) and reduced ferritin in the cerebrospinal fluid suggest that iron deficiency may have a role in pathophysiology. The possibility of iron deficiency needs to be investigated and treated. Treatment may reduce symptoms.

Drug treatment may be offered to patients with particularly troublesome symptoms or lack of sleep. Dopamine agonists (receptor stimulating drugs often prescribed for Parkinson's disease) are first line treatment. They are effective, alleviating symptoms in 70-90% of patients. They are well tolerated. Ropinirole, (*Requip*) a dopamine agonist is approved by the FDA for treatment of RLS in the USA. Others may be just as effective.

Little information is available about treatment in pregnancy. All drugs are best avoided.

“A Distinguishable Subset Within The Broad Diagnostic Category Of Chronic Fatigue Syndrome.”

9-9 POST-INFECTIVE AND CHRONIC FATIGUE SYNDROMES PRECIPITATED BY VIRAL AND NON-VIRAL PATHOGENS.

Post-infective fatigue states have been linked to a diverse spectrum of severe infections, although associations between the syndrome and infections are not consistent.

This prospective population-based cohort study delineated the risk factors, symptom patterns, and longitudinal course of prolonged illnesses after a variety of acute infections.

Conclusion: A relatively uniform post-infective fatigue syndrome persists for a limited period (6 months or more) in a minority of patients after 3 severe infections.

STUDY

1. This study, in a rural area of Australia, was based on patients with IgM positive serological results indicating acute Epstein-Barr virus, Q fever, or Ross-River virus infections.
2. Of the subjects (n = 253; age range 17-63), none had symptoms of the infection for over 6 weeks. None reported pre-existing medical disorders or drug abuse likely to be associated with prolonged fatigue.
3. Used a self-reported questionnaire assessing 6 symptom domains: acute illness; irritability; fatigue; neurocognitive disturbance; musculoskeletal pain; and mood disturbance.
4. Classified participants as provisional cases of post-infective fatigue syndrome (n = 28) if their somatic symptom scores exceeded the threshold of 3 out of a possible 12 at 3 months.
5. Invited these participants and matched participants (who had recovered promptly from the same infection) for physical, laboratory, and psychiatric follow-up.
6. A physician and psychiatrist diagnosed chronic fatigue syndrome at 6 months after the onset of symptoms.
7. Follow-up for 1 year.

RESULTS

1. The case rate for provisional post-infective fatigue syndrome (%):

Six weeks	35
Three months	27
Six months	12
Twelve months	9
2. Compared with subjects who recovered more promptly (n = 224), the 28 subjects considered to have the post infective fatigue syndrome reported higher scores for the fatigue factor.
3. Fatigue (of the 6 symptom domains) had the strongest and most consistent correlation

with functional impairment (“days out of role in the past month”).

4. This post-infective syndrome was stereotyped, and occurred at similar incidence after each of the 3 infections.
5. The syndrome was predicted largely by the severity of the acute illness, rather than by demographic, psychological, or microbiological factors.
6. “If the same pathophysiological underpinned all the clinical aspects of the acute infective illness, and the post-infective fatigue state, we would predict that, in the 28 patients, the individual symptomatic factors (n = 6) would resolve in a uniform manner across time.”
7. Actually, there were substantial variations. The scores on the acute illness, and the irritability factors showed the greatest initial speed of reductions. Compared with the other patients, scores of fatigue fell much more slowly, and remained high at 6 and 12 months. Neuro-cognitive disturbances also remained high.

DISCUSSION

1. Prolonged fatigue states after infections are common and disabling. They may persist for 12 months or longer.
2. The severity of the acute illness, not the demographic or psychological factors was predictive of the post-infective fatigue syndrome.
3. This “provides strong evidence for a causative role of these infections in triggering chronic fatigue syndrome detected at six months”. And “also confirm that chronic fatigue syndrome is a relatively common sequel of several different infections—now documented to include Epstein-Barr virus, Ross River virus, and Q fever—but not minor upper respiratory tract or gastrointestinal infections”.
4. Premorbid and intercurrent mood disorders were not associated with increased likelihood of the syndrome.
5. “Patients with post-infective fatigue syndrome constitute a distinguishable subset within the broad diagnostic category of chronic fatigue syndrome.”

BMJ September 16, 2006; 333: 575-78 Original investigation by the Dubbo Infection Outcomes Study Group, first author Ian Hickie, Sydney University, Sydney, Australia

=====

Is This A Good Application For Primary Care Practice?

9-10 EFFECTS OF ROSIGLITAZONE ON THE FREQUENCY OF DIABETES IN PATIENT WITH IMPAIRED GLUCOSE TOLERANCE OR IMPAIRED FASTING GLUCOSE

Acarbose (*Precose*) and metformin (*Generic*) reduce incident type 2 diabetes (**DM2**) by 25%. Lifestyle interventions that target diet and physical activity reduce it by more than 50%.

Rosiglitazone (*Avandia*) reduces insulin resistance (increases hepatic and peripheral insulin sensitivity), and preserves insulin secretion. It is approved for treatment of DM2.

This study assessed prospectively whether rosiglitazone would reduce the frequency of development of DM2 in patients with impaired fasting glucose, impaired glucose tolerance, or both.

Conclusion: Rosiglitazone reduced incident DM2 and increased likelihood of regression to normoglycemia.

STUDY

1. Multicenter, multicountry randomized, placebo controlled trial followed 5000 adults (all over age 30; mean age = 55)
2. Baseline characteristics:

A. History of hypertension	44 %
B. Tobacco use	44 %
C. Sedentary	27 %
D. BMI (mean)	31
Waist men / women (mean)	102/96 (cm) 40/38 (inches)
BP (mean)	136/83
3. Many were taking a variety of drugs—antiplatelets, and drugs for hypertension and lipid disorders..
4. All underwent a 75 g oral glucose tolerance test. All had impaired glucose tolerance or impaired fasting glucose (or both).
 - A. Impaired fasting glucose (57%)

Fasting plasma glucose equal to, or greater than 100 mg/dL; and less than 126 mg/dL.
 - B. Impaired glucose tolerance (14%)

2-h plasma glucose greater than 140 and less than 200
 - C. Both (29%)

(To convert to mmol/L multiply by 0.0555)
5. None had a history of diabetes (except gestational) or cardiovascular disease.
6. Randomized to: 1) rosiglitazone 8 mg daily [n = 2600] or 2) placebo [n = 2604]
7. All participants (including placebo recipients) received advice about healthy diets and lifestyle.
8. Primary outcome = composite of incident diabetes or death. Follow-up = median of 3 years.

Analysis by intention to treat.

RESULTS

1.	Composite outcome*	Became normoglycemic**	
	Rosiglitazone	11.6%	38.6%
	Placebo	26%	20.5%***

* The composite outcome (development of DM2 or death) contained mainly subjects who developed diabetes. Deaths were infrequent; slightly over 1% in both groups.

** Regression of fasting plasma glucose to less than 100 mg/dL

*** Note that about 1/5 of subjects taking placebo became normoglycemic.¹

2. Absolute difference = 15.4% (NNT for 3 years to prevent one composite outcome) = 6; NNT to achieve normoglycemia in one subject = 5)
3. Cardiovascular events were much the same in both groups, except for incidence of heart failure [rosiglitazone 0.5% vs placebo 0.2%]
4. About ¼ of subjects stopped taking the assigned treatment during the study.
5. Weight gain was higher in the rosiglitazone group by 5 pounds.
6. The effect of rosiglitazone was much the same in all countries, in both sexes, and across all ages.
7. The median fasting glucose was lower in the rosiglitazone group by 9 mg/dL; and the 2-h glucose was 29 mg/dL lower.
8. Mean BP in the rosiglitazone group was 1.7/1.4 mm Hg lower.
9. Mean hepatic ALT concentrations were lower in the rosiglitazone group by 4.2 U/L.

DISCUSSION

1. “This large prospective, blinded, international clinical trial shows that 8 mg of rosiglitazone, together with lifestyle recommendations, substantially reduces the risk of diabetes . . . by 60% in individuals at high risk for diabetes.”²
2. This reduction in risk is the same magnitude as the reduction achieved with lifestyle approaches or acarbose. And greater than the reductions reported with metformin.³
3. A higher reduction in risk was achieved by in the subgroup of subjects with the highest BMI and waist circumference.
4. Rosiglitazone was associated with a higher risk of edema and fluid retention (an effect of the drug on the kidney). The higher risk of heart failure may be related to this factor.
5. “Balancing both the benefits and risks suggests that for every 1000 people treated with

rosiglitazone for 3 years, about 144 cases of diabetes will be prevented with an excess of four to five cases of congestive heart failure.”

CONCLUSION

Rosiglitazone substantially reduced incident DM2 and increased the likelihood of regression to normoglycemia in adults with impaired fasting glucose or impaired glucose tolerance, or both (prediabetes).

Lancet September 23, 2006; 368: Original investigation by the Diabetes REduction Assessment with ramipril⁴ and rosiglitazone Medication (DREAM) Trial investigators Reported by the Population Health Research Institute, Hamilton, Ontario, Canada.

Study supported by the Canadian Institutes of Health Research; and by Sanofi-Aventis, Glaxco, and King Pharmaceuticals.

- 1 I believe this is an important point. Why did about 1/5 of patients on placebo revert to normoglycemia? Could it have been due entirely to changes in lifestyle resulting from the original advice they received about diet and lifestyle? Note also that the rosiglitazone group also received lifestyle advice.
- 2 Authors and journal editors continue to report relative risk reductions (which are misleading). I predict that the advertisements will state “Avandia reduces risk of developing diabetes by 60%”. Actually the drug benefits only 1 in 6 over 3 years. (Absolute reduction less than 20%.)
- 3 A trial from the Diabetes Prevention Program Research Group NEJM February 7, 2002; 346: 393-403 reported that, in a group with pre-diabetes metformin reduced progression to DM2.
Incidence of DM2 per 100 person-years of treatment:
Placebo –11
Metformin—7.8
Lifestyle—4.8
Considering the difference in cost, some patients may prefer metformin to rosiglitazone.
- 4 Previous studies suggested a role for the ACE inhibitor ramipril (*Altace*) in lowering risk of diabetes in subjects with impaired fasting glucose or impaired glucose tolerance. The outcome of this branch of the trial was disappointing—no significant benefit in reducing risk of progression of prediabetes to DM2. “Effect of Ramipril on the Incidence of Diabetes” NEJM October 12, 2006; 355: 1551-62

=====

“More Than One In Eight People Aged 75 and Older Have A Moderate Or Severe Valve Disease.”

9-11 BURDEN OF VALVULAR HEART DISEASE

Since the incidence of rheumatic fever has fallen dramatically in developed countries, valvular heart disease (**VHD**) is not usually regarded as a major problem. VHD is now mostly degenerative. It is related to the increasing age of the population. Availability of echocardiography has led to an increase in diagnosis.

This study reassessed the prevalence of VHD in the population, and its effect on overall survival.

Conclusion: Moderate or severe VHD is common. It increases markedly with age and is associated with increased mortality.

STUDY

1. Assessed the prevalence of VHD by two methods:

- 1) Meta-analysis of 3 large general population based studies.
- 2) A community-based group of patients referred for echocardiography. ¹

2. The meta-analysis obtained data from 3 epidemiological studies sponsored by the NHLBI.

The studies used strictly defined criteria for diagnosis of VHD in over 11 500 community dwelling adults. They were considered to represent a randomized sample of the general US population.

3. Echocardiographs were obtained in a large number of subjects of different age groups

Age	18-30	n = 4315	
	45-64	n = 2435	
	65 an older	n = 5125	Total = 11 875

4. Judicious, comprehensive assessment was applied to ensure that all clinically significant valve diseases were noted. Valvular stenosis of moderate to high severity was judged to be present if leaflet motion was obviously limited, or if increased blood flow velocity across the valve suggested such a diagnosis. Regurgitation was detected by standard color Doppler criteria for aortic and mitral regurgitation.

RESULTS

1. Moderate or severe (left sided) valve disease was detected in 615 individuals (5.2%)
2. Prevalence increased markedly with age—from 0.7% in the young group; to 13.3% in the 75 and older group. Prevalence began to increase at age 65.
3. The US national prevalence of VHD is calculated to be 2.5%.
4. No difference in prevalence between males and females. Men had a higher prevalence of aortic stenosis.
5. Mitral regurgitation the most common VHD, increasing from 0.5% in the young to 9.3% in

the aged; mitral stenosis the least common.

6. Predominant cardiac chamber remodeling was characteristic of volume and pressure overload:

Mitral regurgitation Left ventricular enlargement without hypertrophy.

Mitral stenosis Left atrial enlargement without left ventricular alteration.

Aortic stenosis Left ventricular hypertrophy without enlargement. (Aortic stenosis
has poor clinical tolerance.)

Aortic regurgitation Left ventricular hypertrophy

7. Over 10 years after diagnosis, mortality rates were increased in those with VHD—adjusted risk ratio = 1.36 (valve disease vs no valve disease). Risk of death increased each year. (*By my calculation from their graph (figure 2A; page 1008), over 10 years, survival was 80% in those without VHD, and 64% in those with VHD.*)

DISCUSSION

1. “The population burden of clinically noteworthy valvular heart disease is considerable in the US population.” “More than one in eight people aged 75 and older have a moderate or severe valve disease.”
2. The estimate of prevalence of VHD in the USA corresponds to a burden in the year 2000 of 4 to 5 million adults.
3. Older age is an independent determinant of all forms of VHD. The burden will likely increase with time.
4. VHD is not benign; it has profound consequences in cardiac remodeling and mortality. This emphasizes the importance of early diagnosis. The appropriateness of surgical correction may lessen as the patient ages and develops more co-morbidity.

Lancet September 16, 2006; 368: 1005-11 Original investigation, first author Vuyisile T Nkomo, Mayo Clinic. Rochester MN.

1 The community study was performed in Olmsted county MN, the home of the Mayo Clinic.

I omitted this portion of the study because it largely duplicated the findings of the meta-analysis. It differed in that the cohort studied consisted of patients referred for a clinical indication. VHD was diagnosed in 1.8% of the cohort, and increased from 0.3% in young patients, to 11.7% in those over age 75. Risk ratio of mortality associated with VHD (compared with no-VHD) was 1.75 over 10 years.

=====

“All Patients Should Be Screened Regardless Of Whether They Seem To Be At Risk”

9-12 CDC RECOMMENDS OPPORTUNISTIC HIV TESTING

The CDC has issued new recommendations designed to make voluntary HIV screening on an opportunistic basis a routine part of medical care for all patients aged 13 to 64. The objective is to increase early diagnosis among the estimated 250 000 Americans who are HIV positive, but are not aware of it.

The recommendations apply only to health-care settings, not to non-clinical outreach programs or community centers.

No special consent is required to conduct the test.

The main recommendations:

- 1) All patients should be screened regardless of whether they seem to be at risk.
- 2) Patients should be able to opt out of screening.
- 3) The need for special consent should be eliminated, and be replaced by a standard requirement for consent.
- 4) Counseling on HIV before and after the test is advisable, but not mandatory.

The goal is to ensure that all patients who receive medical care also have the opportunity to learn if they are infected. Making the test a normal part of care is an important step toward removing the stigma associated with testing.

All pregnant women especially should be tested. (Some state laws require this.)

The majority of patients now detected with HIV have a CD4 count under 200. Screening will detect HIV at an earlier stage, when CD4 counts are higher, making treatment more effective.

BMJ September 30, 2006; 333: 669 “News”. Reported by Bob Roehr, Washington DC
www.cdc.gov

A recent “Analysis and Comment” on Health Policy” (BMJ April 29, 2006; 332: 1027-30; Practical Pointers April 2006) commented that “All screening programs do harm. Some do good as well”. The report cites 9 criteria for efficient screening. Among them are:

- 1) Clinical management of the condition, and patient outcomes should be optimized before screening is offered. What arrangement will be made routinely all over the country for those testing positive? (Country-wide systems to treat positive patients must be in place in primary care and be acceptable to patients. Without this, screening may be associated with increased costs and little benefit.)
- 2) High quality randomized, controlled trials should provide evidence that the screening program effectively reduces morbidity.
- 3) The screening program should be clinically, socially, and ethically acceptable.

4) The benefit should outweigh the harm.

5) The cost could be economically balanced in relation to the expenditure.

=====

“Now, More Than Ever, HIV Care Is Primary Care.”

9-13 THE CHANGING FACE OF HIV CARE

Management of HIV infections has advanced dramatically. Related morbidity and mortality has declined—attributed to improved prophylaxis against opportunistic infections, and the introduction of a potent combination of antiretroviral therapies (HAART; highly active antiretroviral therapy).

Some authorities have reported that the life expectancy of patients with HIV is approximating that of the general population. “HIV is becoming a chronic disease.” This has shifted the delivery of care in several ways:

1) Now there is emphasis on vaccination against pneumococcus and hepatitis. Before this, vaccination was not recommended because patients were not likely to survive long enough to benefit.

2) The physician of choice has changed. Earlier, infectious disease experts, oncologists, and palliative care specialists treated most patients. Now, as patients with HIV live much longer, they are developing non-HIV conditions (hypertension, cancer, diabetes, and coronary heart disease). In addition, anti-retroviral drugs are associated with dyslipidemia, diabetes, and neuropathies. As life expectancy and state of health improves, and life is extended, HIV patients may eat more and become overweight, with the same consequences.

As a result of these developments, more patients are being referred back to primary care.

An article in this issue of *Annals*¹ reports that, among HIV patients in New York City, the percentage of deaths due to non-HIV conditions has increased. Cardiovascular disease and age-appropriate malignancies are now more common, especially in persons over age 55.

However, despite advances, many patients with HIV still present in the late stages of the disease, and experience significant morbidity and mortality. In an effort to diagnose patients earlier, when CD4 levels are higher, the CDC recommends widespread screening. (*See previous abstract*)

Many problems remain. HIV is related to poverty. The infection rate is higher in intravenous drug users. Intravenous drug abuse is related to higher risk of death from HIV as well as higher risk of death secondary to the drug abuse itself.

Both primary care clinicians and HIV-specialists must develop practice routines to assure a high standard of care for all HIV patients. This includes educating persons how to avoid the infection and how to avoid spreading it; more screening for HIV; and aggressive treatment of chronic diseases. We will have to deal with interactions between HIV drugs and medication for chronic disease.

“Now, more than ever, HIV care is primary care.”

Annals Int Med September 19, 2006; 145: 463-65. Editorial by Judith A Aberg, New York University, New York.

1 “Causes of Death among Persons with AIDS in the Era of Highly Active Antiretroviral Therapy: New York City” Annals Int Med September 19, 2006; 145: 397-406, first author Judith E Sackoff, New York City Department of Health.

=====