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EDITED BY RICHARD T. JAMES JR. MD

400 AVINGER LANE, SUITE 203

DAVIDSON NC 28036 US

www.practicalpointers.org rjames6556@aol.com

JULY 2003 HIGHLIGHTS AND EDITORIAL COMMENTS

7-1 DIAGNOSING STREP THROAT IN THE ADULT PATIENT: DO CLINICAL CRITERIA REALLY SUFFICE?

Recently the American College of Physicians recommended an algorithm which may be used to diagnose group A strep pharyngitis on clinical grounds alone, eschewing microbiological testing.

Tonsillar exudates

Tender anterior cervical adenopathy

Fever

Absence of cough.

The ACP guidelines allow empirical antibiotic treatment for patients who meet 3 or 4 of the criteria, and non-treatment for all others.

Other prestigious organizations recommend rapid antigen testing or culture before treatment is begun.

Most primary care clinicians would likely chose to treat with penicillin on clinical grounds.

7-2 ACUTE UNCOMPLICATED URINARY TRACT INFECTION IN WOMEN.

Trimethoprim-sulfamethoxazole (**TM-S)** for 3 days remains the therapy of choice. Telephone consultation and treatment is safe. For recurrent episodes of infection and for prophylaxis, self treatment is a reasonable clinical approach.

7-3 STRUCTURAL AND SYMPTOMATIC EFFICACY OF GLUCOSAMINE AND CHONDROITIN IN KNEE OSTEOARTHRITIS

Evidence that glucosamine benefits symptoms and slows joint deterioration.

The purity and dose of these over-the-counter preparations are not regulated by the FDA.

Primary care clinicians may be willing to prescribe it despite regulation by the FDA.

7-4 MORTALITY RISK REDUCTION ASSOCIATED WITH SMOKING CESSATION IN PATIENTS WITH CORONARY DISEASE.

Smoking cessation has a greater effect on reducing the risk of mortality among patients who smoke than the effect of any other intervention. Risk of death was reduced by 36% in those who quit.

Ask your patients who smoke to read this article.

7-5 DIRECT OBSERVATION OF REQUESTS FOR CLINICAL SERVICES IN OFFICE PRACTICE.

Patient-requests for prescriptions are becoming more frequent as direct-to-the-public advertising by drug companies becomes more common. Patient-requests for consultations, and tests are also becoming more frequent as the public becomes more sophisticated.

Primary care clinicians will find it necessary to negotiate with patients about these requests. Physicians' role in educating patients about risks, benefits, and costs of new "miracle" drugs is becoming more important.

Primary care clinicians must increasingly understand patients' anxieties and what they really want to receive from the consultation. The patient negotiates from fear and uncertainty. The physician negotiates from a specialized knowledge. Meeting a common ground satisfactory to both requires patience and give-and-take.

7-6 THE METABOLIC SYNDROME

The close association of type 2 diabetes with cardiovascular disease **(CVD**) led to the hypothesis that the two arise from a common antecedent. This concept has been codified by the WHO and others as "the metabolic syndrome". This diagnosis might hold the promise for enhanced prevention of diabetes and CVD.

The metabolic syndrome: Obesity (especially central obesity); Dyslipidemia (especially high triglycerides and low HDL-cholesterol); Hyperglycemia; Hypertension

Is the risk associated with a cluster of all 4 traits likely to exceed the sum of the four traits? I believe. . . "The whole is greater than the sum of the parts"?

7-7 WOMEN NEED BETTER INFORMATION ABOUT ROUTINE MAMMOGRAPHY

The public should be told about all the outcomes of screening in terms it can understand. Surgical and psychological morbidities are important outcomes. Unnecessary treatments arise from overdiagnosis. This includes biopsies, segmental excisions, mastectomies, and even radiotherapy. "Until tools are developed that are capable of measuring a wide variety of outcomes, we cannot weigh the evidence satisfactorily."

"The age at which the trade-off between benefit and harm becomes acceptable is a subjective judgment that cannot be answered on scientific grounds." Most women who are screened have not been educated about the uncertainties.

7-8 NURSES' EXPERIENCES WITH HOSPICE PATIENTS WHO REFUSE FOOD AND FLUIDS TO HASTEN DEATH.

Voluntary refusal of food and fluids has been proposed as an alternative to physician-assisted suicide **(PAS)** for terminally ill patients who wish to hasten death. Oregon hospice nurses reported the quality of the process of dying for most of these patients was good.

But, "We don't know enough about it." "We have to get this out and talk about it, because this is happening."

7-9 CLINICAL AND ORGANIZATIONAL FACTORS ASSOCIATED WITH FEEDING TUBE USE AMONG NURSING HOME RESIDENTS WITH ADVANCED COGNITIVE IMPAIRMENT

A growing proportion of the approximately 4 million older US adults with Alzheimer's disease or other dementias are surviving to the advanced stages of their disease. Eating and swallowing problems typically develop during the terminal stages. Whether to initiate feeding tube use or to focus on comfort care is a challenging dilemma facing families, clinicians and institutions.

Growing empirical data and expert opinion indicates that feeding tubes has no demonstrable health benefits in this population, and may be associated with increased risks and discomfort.

The quality of care of cognitively impaired patients in nursing homes is inversely related to the numbers who have feeding tubes in place.

"Comprehensive implementation of advanced care planning is likely to reduce the use of feeding tubes."

7-10 COMPARISON OF CARVEDILOL AND METOPROLOL ON CLINICAL OUTCOMES IN PATIENTS WITH CHRONIC HEART FAILURE

Carvedilol extended survival compared with metoprolol.

However**,** the challenge in primary care is not so much which beta-blocker to choose, but judicious use of a beta-blocker in select patients with heart failure. They are underused in primary care practice for treatment of heart failure.

7-11 EFFECT OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ON RISK OF ALZHEIMER'S DESEASE

The study lends support to the hypothesis that NSAIDs may protect against the development of Alzheimer's disease. They are too toxic to be used for this purpose in large numbers of patients.

This is provocative study suggests that we may be on the way to developing safe preventive measures.

7-12 THE INFLUENCE OF FINASTERIDE ON DEVELOPMENT OF PROSTATE CANCER

Finasteride prevents or delays the appearance of PC at a risk of increasing incidence of high grade cancers.

Not yet ready for general use, but provocative. Preventive or delaying measures may be in the offing.

7-13 INTERACTION OF SPIRINOLACTONE WITH ACE INHIBITORS OR ANGIOTENSIN-RECEPTOR BLOCKERS

Spirinolactone and ACE inhibitors act synergistically or additively to increase plasma potassium levels. Toxic and even lethal concentrations may result. Spirinolactone is established as an important additive in therapy for patients with severe heart failure. The dose should not exceed 25 mg daily, and in some patients should be less.

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Still Some Debate—Treat On Clinical Grounds Alone Or Require Confirmation Of The Infection ?

7-1 DIAGNOSING STREP THROAT IN THE ADULT PATIENT: DO CLINICAL CRITERIA REALLY SUFFICE?

Even after years of study, considerable debate remains about the most appropriate method of diagnosis and treatment of group A beta-hemolytic streptococcus **(GAS)** infections.

Most cases of pharyngitis seen in primary care are viral. GAS is *the only* commonly occurring cause of sore throat for which antimicrobial therapy is indicated.

The signs and symptoms of GAS pharyngitis and viral pharyngitis overlap so broadly that precise diagnosis on clinical grounds is difficult. A revised guideline from the Infectious Disease Society of America now advocates use of the rapid antigen test alone to confirm the diagnosis.[1] This is simpler than culture and yields results that allow rapid treatment decisions. More sensitive rapid tests such as optical immunoassay (OIA) have appeared on the market.

Recently the American College of Physicians recommended an algorithm which may be used to diagnose GAS on clinical grounds alone [1], eschewing microbiological testing. The CDC and the American College of Family Physicians have also approved this recommendation. The algorithm was developed by Centor and published in 1981. It relates the probability of GAS pharyngitis to 4 clinical findings:

Tonsillar exudates

Tender anterior cervical adenopathy

Fever

Absence of cough.

The ACP guidelines allow empirical antibiotic treatment for patients who meet 3 or 4 of the criteria, and non-treatment for all others. In the Centor study, only 10% of adult patients presenting to an urban emergency department met all 4 criteria. Throat cultures were positive in 56% of this group. In the 20% of patients meeting 3 criteria, the probability of a positive culture was 30%. The positive predictive values associated with meeting 3 or 4 clinical criteria would be approximately 40%. This means that 60% of the patients treated empirically would have a negative culture or rapid antigen test.

"Use of the Centor algorithm does indeed identify patients whose risk of GAS infection is so low that microbiological testing or antibiotic treatment is unnecessary." [1]

The stated goal is to reduce excess antibiotic use. The editorialist comments—"I think it is unlikely that clinicians will perform cultures or rapid tests when a practice guideline endorsed by so many prestigious organizations states that clinical criteria suffice".

Millions of patients visit primary care offices each year with symptoms of sore throat. Issues of appropriate diagnosis and treatment present a major public health concern. In the general population of adult patients with sore throat, only about 10% are estimated to have a GAS infection. The risk factor most feared is rheumatic fever. But it is rare. The risk of preventable suppurative or non-suppurative complications in adults with GAS pharyngitis is small. Antibiotic therapy may truncate the illness, but only if started early in the illness, and may only be a day or two. "Given this limited benefit, the main purpose of any diagnostic strategy for adults should be to minimize unnecessary antimicrobial therapy."

National data indicate that the more expensive, broader spectrum antibiotics are prescribed for about three quarters of adults who consult community primary care physicians because of a sore throat. The rapid antigen test has a generally high specificity (few false positives). This should minimize over-prescription of antibiotics. Penicillin is still the drug of choice. (Erythromycin for allergic individuals.) "Penicillin-resistant group A beta-hemolytic streptococci have never been recovered for any clinical source."

In some subsets of patients such as parents of school-age children and school teachers, clinicians should raise their index of suspicion. Rapid antigen testing may be warranted in these groups.

The editorialist concludes—"I do not believe it is prudent to rely exclusively on clinical criteria for diagnosis and management of GAS pharyngitis." [1]

Annals Int Med July 15, 2003; 139: 150-151 Editorial by Alan L Bisno, University of Miami School of Medicine, Miami, FL www.archinternmed.com

1 The editorialist's conclusions conflict with some recommendations in the text. Doubt about the best course to take remains. I would add 2 other criteria which will help determine the prescription of penicillin: 1) Does the patient look sick, and 2) What is the patient's (and parent's) personal preference and degree of anxiety? I believe most primary care clinicians would prescribe penicillin on clinical grounds alone. RTJ

Treating Acute Uncomplicated Lower Urinary Tract Infection in Women by Telephone Consultation Appears Safe And Effective

7-2 ACUTE UNCOMPLICATED URINARY TRACT INFECTION IN WOMEN.

This "Clinical Practice" review article discusses a case of a young woman with dysuria and urgency for 3 days. She had several previous episodes. She does not have fever, chills, vaginal discharge, or flank pain. How should she be evaluated and treated?

Most lower urinary tract infections (**LUTI**; acute bacterial cystitis) in women are uncomplicated. They are not associated with signs or symptoms of upper UTI or structural abnormalities of the urinary tract. Recurrences are common. Most are caused by *E coli*. Staphylococcus accounts for most of the remainder. Klebsiella and Proteus are isolated causes.

A history of dysuria and frequency without vaginal discharge or irritation raises the probability of acute cystitis to more than 90%. Women with previous cystitis who have symptoms suggesting a recurrence have a 90% chance that infection is present.

Risk factors:

Sexual activity, especially within 48 hours. (Celibate women rarely have cystitis.)

Use of spermicidal agents.

Impaired voiding and poor perineal hygiene in older women. (Neurological disease and dementia.)

Estrogen deficiency.

Diabetes.

Cystocele and incontinence.

Diagnostic tests.

Pyuria on urinalysis (about 5% false negatives; 30% false positives.)

Dipstick testing has largely supplanted microscopy and culture. It is most accurate when the presence of nitrite or leukocyte esterase is considered a positive result. This yields a sensitivity of 75% (25% false negatives) and a specificity of 82% (18% false positives). Defined in this fashion, a positive dipstick results in a 25% higher post-test probability of infection than the pre-test probability. .

"Most patients with consistent symptoms and a positive dipstick can be treated without the need to obtain a culture." A negative dipstick cannot rule out an infection when the pretest likelihood is high. Here it is advisable to culture.

The accuracy of findings on a culture of a midstream "clean catch" specimen depends on how a positive culture is defined. When a positive is defined by the traditional 100 000 bacteria per milliliter, there will be few false positives, but many false negatives. (High specificity; sensitivity only about 50%.)

Treatment

Acute uncomplicated LUTI:

Trimethoprim-sulfamethoxazole (**TM-S**--*Generic; Bactrim; Septra*)

A 3-day course of TM-S (double strength; 160/800 twice a day) results in bacteriological cure in about 95% of women. Longer courses are not more effective. Single-dose treatment is less effective, eradicating infection in about 87%, but is associated with a lower rate of adverse effects.

Trimethoprim alone is just as effective and can be prescribed for patients allergic to sulfa. Watch for resistance to TM-S. It is becoming common in some communities. However, many women with resistant organisms are still cured by TM-S.

Fluoroquinolones (ofloxcin [*Floxin*]; ciprofloxacin[*Cipro*])

Given for 3 days are effective, but are second-line agents because of cost and concerns about development of resistant organisms.

Nitrofurantoin (*Generic; Macrodantin*)

Is less active against gram negative rods other than *E coli.*

Beta-lactams (ampicillin; amoxicillin)

Should be avoided because of frequent bacterial resistance and low cure rates.

Phenazopyridine (*Pyridium*; *generic*--over-the-counter) for one or two days may be helpful in women with severe dysuria.

Telephone consultations:

Acute uncomplicated LUTI treated by telephone consultation appears safe and effective.

Recurrent LUTI:

Continuous prophylaxis

Half tablet of TM-S (single strength 80/400) every night or three times weekly for 6 months, up to 5 years.

Postcoital regimen

TM-S half tablet or one tablet (80/400) once.

Intermittent self-treatment

Beginning at onset of symptoms TM-s double-strength (160/800) twice daily for 3 days.

Cranberry juice

For prevention. Contains proanthocyanidins that appear to inhibit attachment of pathogens to the uroepithelium. 200 to 750 mL daily has been reported to reduce risk of symptomatic recurrent LUTI. The amount of actual cranberry varies considerably.

Postcoital voiding:

Several studies report no benefit.

Topical estrogen

In postmenopausal women topical estriol cream may reduce episodes of recurrent LUTI

Oral estrogens are not effective.

Vaginal spermicides

Should be avoided in women who have frequent episodes of LUTI.

NEJM July 17, 2003; 349: 259-66 Review article "Clinical Practice", by Stephan D Fihn, University of Washington, Seattle. www.nejm.org

Comment:

Much of this review is "old hat" to primary care clinicians. I felt the reminder about self-treatment, telephone consultations, and the 3 day TM-S therapy would be helpful. RTJ

7-3 STRUCTURAL AND SYMPTOMATIC EFFICACY OF GLUCOSAMINE AND CHONDROITIN IN KNEE OSTEOARTHRITIS

Drugs for treatment of osteoarthritis are classified as either symptom-modifying (lessening pain and improving function) or structure-modifying (benefiting the joint-space).

Chondroitin and glucosamine are natural compounds found in healthy cartilage. Their efficacy has been debated over 20 years.

This meta-analysis brings evidence of efficacy up to date.

Conclusion: Both compounds reduced symptoms. Glucosamine slowed the narrowing of the joint space.

STUDY

1. Systematic search of randomized, placebo-controlled trials up to 2002 assessed the efficacy of oral glucosamine or chondroitin.
2. Determined effects on joint space by X-ray; and joint pain, stiffness, and mobility by several different questionnaires

RESULTS

1. Fifteen studies met inclusion criteria. Oral glucosamine was used in 1020 patients; oral chondroitin in 755. Both were compared with placebo. Mean patient age = 62

2. Glucosamine dose was usually 1500 mg daily; chondroitin dose 800 mg to 2000 mg daily.
Duration of therapy varied from one month to three years for glucosamine; 90 days to 1 year for chondroitin.
3. The quality of glucosamine trials was significantly higher than the chondroitin trials.
4. Compared with placebo, glucosamine was associated with less narrowing of the joint space. The benefit was rated as low to medium, with about 0.3 mm mean difference in the width of the space after 3 years.
(*Glucosamine has a disease-modifying effect as well as a symptom-benefiting effect. RTJ)*
No structural improvement was adequately documented in the chondroitin group.
5. Effect of symptoms for both drugs was uniformly favorable as compared with placebo. The minimal time to onset of improvement was 2 weeks. Pain, stiffness, and joint mobility were all improved.
6. The absolute difference of benefit compared to placebo was 20%. The number needed to treat to benefit one patient = 5.
7. Adverse effects were infrequent and similar to placebo. "The safety profile of glucosamine and chondroitin can be considered excellent."

DISCUSSION

1. The inclusion criteria of this study led to selection of randomized trials representative of the pragmatic effects of the drugs (ie, the efficacy on osteoarthritis in a self-administered long-term treatment). No studies of intra-articular or intravenous administration were included. (*Also no studies of the 2 drugs combined. RTJ*)
2. Data suggests that glucosamine efficiently prevents the long-term progression of osteoarthritis. "The structural efficacy of glucosamine is highly significant and ranges from low to medium."
3. All trials allowed NSAIDs as rescue medication. The favorable symptomatic effects of glucosamine and chondroitin led to lower cumulative doses of NSAIDs.
4. "In accordance with our results, it can be definitely stated that the oral administration of glucosamine or chondroitin decreases the symptoms of osteoarthritis. The tolerance of the 2 compounds is excellent."

CONCLUSION

Both compounds led to symptomatic improvement. Glucosamine had a low-to-moderate benefit on joint structure.

Archives Int Med July 14, 2003; 163: 1514-1522 Original investigation, first author Florent Richy, University of Liege, Belgium. www.archinternmed.com

Comment:

There is a serious problem with these compounds—they are not under supervision of the FDA.

Are the "compounds" pure? Are all brands and manufacturing batches standardized? Probably not.

Many patients may be willing to give the compounds a try. I would favor glucosamine alone. Data on the two compounds combined were not studied.

COST: One pharmacy web site quotes glucosamine 500 mg at $0.36 each--$30 a month at three times daily.

There are many brands and doses. Most quote the combination of glucosamine and chondroitin. These over-the-counter compounds are frequently on sale—at times buy one, get one free. Shop around. RTJ

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"A Greater Effect On Reducing The Risk Of Mortality Among Patients Who Smoke Than The Effect Of Any Other Intervention."

7-4 MORTALITY RISK REDUCTION ASSOCIATED WITH SMOKING CESSATION IN PATIENTS WITH CORONARY DISEASE.

Smokers have an estimated 1.5 to 3 times the risk of developing coronary heart disease as non-smokers. (*And at an earlier age*.)

Cessation reduces risk of subsequent mortality and cardiac events by as much as 50%. "Stopping smoking therefore may have a greater effect on reducing the risk of mortality among patients who smoke than the effect of any other intervention."

This systematic review determined the magnitude of risk reduction achieved by smoking cessation in patients with CHD.

Conclusion: Cessation is associated with a substantial reduction in all-cause mortality among patients with CHD.

STUDY

1. Systematic search up to April 2003 selected prospective cohorts of patients with CHD which reported all-cause mortality and had at least 2 years of follow-up.
2. Twenty studies were included which calculated the relative risk of mortality among smokers with CHD who quit with those who did not quit. Most of the studies had a follow-up between 3 and 7 years.

RESULTS

1. There was a 36% reduction in risk of death among those who quit compared with those who continued to smoke.
2. Results from individual studies did not vary greatly despite many differences in patient characteristics, such as age, sex, and type of CHD.
3. Pooled risks:

	Ceased smoking			Continued smoking		
	Patients	Deaths	%	Patients	Deaths	%
	5659	1044	18	6944	1884	27

(Absolute difference = 9% Number needed to stop smoking to prevent one death = 11)

4. Non-fatal infarcts were also reduced in those who quit. (Relative risk = 0.68)

DISCUSSION

1. The reduction in risk of total mortality associated with cessation of smoking is at least as great

as other secondary prevention therapies such as use of statin drugs, aspirin, beta-blockers, and ACE inhibitors.

2. The risk reduction occurs quickly after cessation, as early as 2 years.

3. Most smokers who quit do so quickly after their CHD diagnosis.

CONCLUSION

Quitting smoking is associated with a substantial reduction in risk of all-cause mortality among patients with CHD.

JAMA July 2, 2003; 290: 86-97 Original investigation, first author Julia A Critchley, University of Liverpool, UK

Comment: www.jama.com

Show this article to your patients who smoke. RTJ

"A Strong, Independent Predictor Of Referral And Prescribing"

7-5 DIRECT OBSERVATION OF REQUESTS FOR CLINICAL SERVICES IN OFFICE PRACTICE.

"Consumer empowerment in health care is increasingly accepted as inevitable, right, and potentially beneficial."

Patient requests can influence the conduct and content of the medical visit.

This observational study surveyed the frequency of requests and their influence on physician's prescribing.

Conclusion: Patient's requests were persuasive and influenced physician's prescribing.

STUDY

1. Observational study audiotaped over 500 patient-physician encounters.

2. All patients presented a new problem or a significant health concern.

3. Main outcome measures included prevalence of requests for physician action: requests for laboratory, imaging, or other diagnostic tests; for a new medication; for referral to a physician specialist; for all or part of a physical examination; for refill or renewal of a medication; for a therapeutic procedure or a lifestyle prescription; for referral to non-physician.

RESULTS

1. Twenty three percent of patients made a request for at least one diagnostic test, speciality referral, or a new prescription.

2. Requests were more common among patients experiencing greater health- related distress.

3. Requests were associated with higher likelihood of receiving specialty referrals (odds ratio = 4), and a prescription for a new medication (odds ratio = 3).

4. Physicians reported that visits during which patients requested diagnostic tests were more demanding than visits in which no requests were made.

5. Patients whose physician failed to fulfill one or more requests reported significantly less visit satisfaction.

DISCUSSION

1. Patients of primary care physicians frequently made direct requests for clinical interventions.
2. Primary care clinicians are troubled by direct-to consumer advertising which provokes patient requests.
3. This implies that primary care clinicians should develop a protocol for responding to patient's requests.
4. Some requests by patients are veiled, not direct. The patient may suggest a candidate diagnosis, may describe symptoms characteristic of a particular diagnosis, emphasize severity of symptoms, appeal to a certain life circumstance, and share stories of previous drug efficacy.
5. Patient requests are a strong, independent predictor of referral and prescribing.
6. One implication is that programs for containing health costs must address the patient as well as the physician. "It is perhaps unrealistic to expect that physicians will refuse to provide clinical services to patients whose requests are sufficiently strident."

Archives Int Med July28, 2003; 163: 1673-81 Original investigation, first author Richard L Kravitz, University of California, Sacramento www.archinternmed.com

Comment:

I believe requests for a new "miracle" drug the patient learns about in the lay press or on TV will become more common. Direct-to-the-public advertising of expensive new drugs is an effective means by which pharmaceutical companies increase their "market share". Primary care clinicians should be able to advise patients about the absolute benefits of an advertised drug as compared with an old, standard, less costly drug. One way is to explain the number of patients needed to treat for how long to benefit one. This can be added to advice about any new adverse effects, and especially about increased costs compared with old standard drugs, often generics..

I believe primary care clinicians will more readily honor a request for a consultation and a request for a specific test. Testing can be a valuable means of reassurance. (Eg, ordering an EKG for a patient with chest pain, even though the clinician knows it is highly unlikely to be cardiac in origin.)

This article touches an important point in the art of practicing medicine. Physicians must increasingly be able to understand patient's anxieties and what each one really wants to receive from the consultation. The patient negotiates from fear and uncertainty. The physician negotiates from a specialized knowledge. Meeting a common ground satisfactory to both requires patience and give-and-take.

Primary care medicine is the most difficult specialty. RTJ

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The Individual Traits Of The Syndrome Cluster Together To A Notably Greater Degree Than Expected By Chance Alone.

7-6 THE METABOLIC SYNDROME

The close association of type 2 diabetes with cardiovascular disease **(CVD**) led to the hypothesis that the two arise from a common antecedent. This concept has been codified by the WHO and others as "the metabolic syndrome". This diagnosis might hold the promise for enhanced prevention of diabetes and CVD.

Substantial uncertainties remain about the clinical definition of the syndrome. Is it a discrete, unifying disorder? Will diagnosing the syndrome confer any benefit beyond risk assessments and treatment strategies associated with diagnosing and treating the syndrome's component traits?

The metabolic syndrome:

Obesity (especially central obesity)

Dyslipidemia (especially high triglycerides and low HDL-cholesterol)

Hyperglycemia

Hypertension

As yet, no consensus exists for specific thresholds for establishing the diagnosis of each of these traits as components of the syndrome. Inclusion of insulin resistance as a diagnostic component is controversial. The individual traits of the syndrome cluster together to a notably greater degree than expected by chance alone. This lends support to the existence of a discrete disorder.

Evidence is accumulating that people with the metabolic syndrome are at increased risk of incident diabetes and CVD relative to people without the syndrome. The question is—does the metabolic syndrome increase adverse outcomes to a greater degree than predicted by the presence of its individual components? More definitive data on outcomes and effects of interventions are required.

The goal of identifying metabolic risk factors is to prevent morbidity and mortality due to type 2 diabetes and CVD. Relatively modest lifestyle changes can reduce risk for type 2 diabetes in mildly hyperglycemic persons. Control of raised BP and lipids reduces risk. Although insulin sensitization in itself may be beneficial in preventing type 2 diabetes, we do not know if this strategy will ameliorate all the metabolic disturbances of the syndrome or prevent CVD.

Prevention of obesity is the most direct route to prevention of the metabolic syndrome.

BMJ July 12, 2003; 327: 61-62 Editorial by James B Meigs, Harvard Medical School, Boston, Mass.
www.bmj.com/cgi/content/full/327/7406/61

Comment:

Is the risk associated with a cluster of all 4 traits likely to exceed the risk of the sum of the four traits. Is . . . "The whole greater than the sum of the parts." I believe it is RTJ

"The Age At Which The Trade-Off Between Benefit And Harm Becomes Acceptable Is A Subjective Judgment That Cannot Be Answered On Scientific Grounds." Most Women Who Are Screened Have Not Been Educated About The Uncertainties.

7-7 WOMEN NEED BETTER INFORMATION ABOUT ROUTINE MAMMOGRAPHY

There is controversy about mammography. Most of the controversy seems to miss the point. The question of whether the benefits of screening outweigh the harms is essentially a value judgment. "The problem is that, up to now, this judgment has been made by paternalistic agents of the state rather than by women supported by their general practitioners." In order to make an informed choice about screening, women need to be aware of the range of uncertainties for both the benefits and the harms.

Evidence of effectiveness

Public health programs aim to reduce mortality from breast cancer **(BC**) by offering routine mammography for healthy individuals. The public receives highly conflicting messages about the effect of screening. Every new published estimate is hotly debated in the media. Results are usually couched in terms that most people will misunderstand. A recent newspaper headline reported. . . "A 44% reduction in breast cancer mortality in women aged 40-69." And . . ."Screening halves breast cancer death rate." Not mentioned was that mortality also fell in those who were not screened (likely due to improvements in treatment). The percentage reduction in mortality remains unknown and incalculable.

The public needs to be told about all the outcomes of screening in terms it can understand. Surgical and psychological morbidities are equally important outcomes. Unnecessary treatments arise from overdiagnosis. This includes biopsies, segmental excisions, mastectomies, and even radiotherapy. "Until tools are developed that are capable of measuring a wide variety of outcomes, we cannot weigh the evidence satisfactorily."

Evaluating harm

Harms are often dismissed as a price worth paying for the perceived general good. Individual women may suffer physical, psychological, emotional, social, and financial harm. The result may be temporary or life-long. It is important that women understand the potential harms and make an informed choice for which they are willing to take responsibility.

Almost all pamphlets used in BC screening programs use relative risk information about benefits in preference to absolute risk reductions. Framing information as an absolute benefit is highly persuasive. Evidence shows that, when people are offered more detailed information about their personal risks, they are less likely to opt for tests.

Assessment of benefit

Screening contributes to the rise in incidence of BC. Invitations to screening use this rise to justify screening. The invitations do not mention ductal carcinoma in situ **(DCIS)** which accounts for about 20% of cancers detected by screening. DCIS has an uncertain natural course. It is an early stage of disease. It results in 40% mastectomy rate. "The consequences of diagnosis of this enigmatic, little understood disease are serious."

Women are not told the number needed to screen to prevent one death, The US Preventive Task Force found it was necessary to screen 1224 women age 40-74 for 14 years to prevent one death from BC. They concluded that "The age at which the trade-off between benefit and harm becomes acceptable is a subjective judgment that cannot be answered on scientific grounds."

Improving understanding

We need to demystify the statistics about relative and absolute risk, risk of mortality and morbidity, lifetime risk, 10-year risk, and age-related risk.

There are 5 common misconceptions about screening:

Screening tests are meant for patients with known symptoms

Screening reduces the incidence of BC

Early detection implies reduced mortality

All breast cancers progress

Early detection is always a benefit.

Most women who are screened have not been educated about the uncertainties, harms, and limitations of screening, or the importance of finding pathology of uncertain importance.

The focus of research into screening programs should be to develop flexible decision aids to meet women's desires for balanced information. A cultural change is necessary to improve the experience of citizens and enable them to take responsibility for their decisions.

"It is unacceptable that women taking tests continue to suffer morbidity and regret because they found out the harms of screening."

BMJ July 12, 2003; 327: 101-03 "Education and Debate", commentary, first author Hazel Thornton, University of Leicester, UK. www.bmj.com/cgi/vontent/full/327/7406/101

The authors cite a web page which informs about *prostate* cancer screening. www.cancerscreening.nhs.uk/prostate/index.html This also leads to information about screening for breast cancer, cervical cancer, and colo-rectal cancer.

"Suffering Less And Being More At Peace."

7-8 NURSES' EXPERIENCES WITH HOSPICE PATIENTS WHO REFUSE FOOD AND FLUIDS TO HASTEN DEATH.

Voluntary refusal of food and fluids has been proposed as an alternative to physician-assisted suicide **(PAS)** for terminally ill patients who wish to hasten death.

A small proportion of terminally ill patients choose PAS or euthanasia for reasons of hopelessness, depression, feeling unappreciated, a sense of meaninglessness of continued existence, readiness to die, and fear of loss of independence and control.

Unlike PAS , the choice to stop eating and drinking is legal throughout the USA, available to competent patients, and does not necessarily require participation of a physician. Some physicians assert that the moral basis for this choice is stronger than that for PAS or euthanasia. Others challenge that assertion by asking whether this behavior is different from suicide, with or without a physician's assistance. Some believe that physician-collaboration with a patient who intends to hasten death is morally impermissible.

This study asked hospice nurses in the state of Oregon about their perceptions of patients who chose to stop eating and drinking in order to hasten death. They compared these patients with those who hastened death by means of legalized PAS.

Conclusion: Hospice nurses reported that terminal patients who voluntarily chose to reuse food and fluids usually died a "good" death within 2 weeks.

STUDY

1. Over 300 hospice nurses responded to questionnaires regarding terminally ill patients who voluntarily and

deliberately refused all food and fluid with the primary intention of hastening death. This did not include those stopping food and fluids for other reasons such as loss of appetite or inability to eat or drink because of disease.

2. Nurses rated possible reasons why patients refused food and fluid to hasten death; patients' overall peacefulness and suffering, and quality of the process of dying.
3. They were asked almost identical questions about patients who had died after ingestion of a prescribed lethal medication. (PAS)

RESULTS

1. Of the 307 nurses who responded to the questionnaire, 41% reported that in the previous 4 years, they had cared for a patient who deliberately chose to stop eating and drinking.
2. This action was taken by the patients because they were ready to die, saw continued existence as pointless, considered their quality of life poor, wished to control the manner of death, and wished to die at home.
3. Stopping drinking and eating did hasten death; 85% of the patients died within 15 days.
4. Sixteen patients subsequently resumed eating and drinking--some because families encouraged the patient to eat.
5. On a scale from 0 (very bad death) to 9 (very good death) , the median score for quality of these deaths was rated by the nurses as 8. Most nurses rated the last 2 weeks of life as peaceful, with low levels of pain and suffering. A few patients, however, had "bad" deaths with significantly higher scores of pain and suffering. As compared with patients who died by PAS, those who stopped eating and drinking were rated as suffering less and being more at peace.
6. Patients who stopped eating and drinking were older than patients who died by PAS. (74 vs 64 years).
7. Few of these patients were evaluated by a mental health professional .
8. Three nurses believed that allowing a hospice patient to hasten death deliberately in this manner was unethical. But none reported that they would actively oppose a patient's choice.
9. A high percentage of nurses reported that most or all family members accepted the patient's decision. The family members were more prepared for, and more accepting of, the ill person's death than were family members of other hospice patients.

DISCUSSION

1. One third of hospice nurses in Oregon reported that at least one patient they had cared for in the previous 4 years had deliberately hastened death by stopping food and fluids.
2. Even though physician-assisted suicide is legal in Oregon, almost twice as many patients chose to stop food and fluids as died as a result of PAS.
3. Voluntary refusal of food and fluid is not common. (Only a few among 40 000 Oregon deaths.) The authors propose, however, that this choice may occur often enough to be of clinical relevance in hospice care.

4. Most deaths were peaceful, within 15 days, and with little suffering. Anorexia, which occurs in some dying patients, may facilitate the choice of stopping eating and drinking.
5. In Oregon, health care workers may suggest refusal of food and fluids as an option when patients request PAS.

CONCLUSION

Oregon nurses reported that some hospice patients chose to hasten death by stopping food and fluids, even though PAS is legal in that state. The quality of the process of dying for most patients was good.

NEJM July 24, 2003; 349: 359-65 Original investigation, first author Linda Ganzini, Oregon Health and Science University, Portland. www.nejm.org

An accompanying editorial (pp 325-26) by Sandra Jacobs comments:

A primary complaint, dry mouth, can be treated with ice chips and swabbing.

The process of guiding patients through this option has remained uncomfortable, and largely unknown, for most physicians. Complicity (ie, giving permission) may indeed be uncomfortable for hospice, family, and physician. "The most important thing is to insure comfort and stay involved." In some cases, the quality of death may be poor. These patients may need comfort support with morphine. Good palliative care is essential.

The first author of the study was worried about thoughts of thousands of depressed, elderly people going on hunger strikes, and physicians being too quick to offer this alternative. "We don't know enough about it." "We have to get this out and talk about it, because this is happening."

Comment:

I believe many physicians would be reluctant to recommend refusal of food and fluid to their dying patients on moral grounds, although they may have no qualms about a decision that the patient makes voluntarily.

We do need more experience and discussion. As the article suggests, the question about diagnosis and treatment of depression in these terminally ill patients is not at all clear. RTJ

"A Challenging Dilemma Facing Families, Clinicians And Institutions."

7-9 CLINICAL AND ORGANIZATIONAL FACTORS ASSOCIATED WITH FEEDING TUBE USE AMONG NURSING HOME RESIDENTS WITH ADVANCED COGNITIVE IMPAIRMENT

A growing proportion of the approximately 4 million older US adults with Alzheimer's disease or other dementias are surviving to the advanced stages of their disease. Eating and swallowing problems typically develop during the terminal stages. Whether to initiate feeding tube use or to focus on comfort care is a challenging dilemma facing families, clinicians and institutions.

Growing empirical data and expert opinion indicates that feeding tubes have no demonstrable health benefits in this population, and may be associated with increased risks and discomfort.

The prevalence of feeding tube use varies considerably (a 10-fold variation) among nursing home residents with advanced dementia who are living in different facilities, states, and countries.

This study identified characteristics of institutions and patients related to feeding tube use.

Conclusion: More than one third of severely cognitively impaired residents in nursing homes in the USA have feeding tubes. Use varies with the residents' clinical characteristics and the nursing homes' fiscal and organizational features.

STUDY

1. Nation-wide, cross-sectional study of all residents in Medicare or Medicaid certified nursing homes who had advanced cognitive impairment. (n = over 186 000)
2. Determined the resident and nursing home factors which independently influenced feeding tube use.

RESULTS

1. Thirty four percent of residents with advanced cognitive impairment had feeding tubes in place.
2. Resident characteristics associated with greater likelihood of use:
   Younger age; non-white race; male sex; divorced marital status; lack of advance directives; a recent decline in functional status; no diagnosis of Alzheimer's disease.
3. Institutional associations with increased use:
   For profit homes; homes located in urban areas; having more than 100 beds; lacking a special dementia unit; and lacking a nurse practitioner or physician on the staff.

DISCUSSION

1. "Among the most notable observations in the study is the increased likelihood of feeding tube use among residents living in for-profit nursing homes."
2. The lay and scientific press has put forward the notion that feeding tubes are likely to be used in nursing homes as a means of cost-saving. The staff's time required for feeding residents by hand is expensive. In addition, Medicaid reimbursement schemes in many states pay higher per diem rates for tube-fed residents. However, "While the potential for financial incentives to favor use of feeding tubes exists, this association remains to be proven."
3. Previous studies have shown that "Do Not Resuscitate" orders strongly influence feeding tube use. "This study underscores the important role of DNR orders at the nursing home level."
4. Facilities with a greater overall rate of DNR orders may be more proficient at engaging surrogates in discussions that lead to decisions not to use a feeding tube,
5. Nonwhites may have different cultural attitudes toward death and dying and be apprehensive about the medical system and have poor communication about advanced directives.
6. "Comprehensive implementation of advanced care planning is likely to reduce the use of feeding tubes."

CONCLUSION

More than one third of severely cognitively impaired residents in US nursing homes have feeding tubes. Use is independently associated with both the residents' clinical characteristics and the nursing homes' fiscal, organizational, and demographic features.

JAMA July 2, 2003; 290: 73-80 Original investigation, first author Susan L Mitchell, Harvard Medical School, Boston. www.jama.com

Comment:

The quality of care in nursing homes is inversely related to the numbers of feeding tubes in place. RTJ

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Carvedilol Extended Survival Compared With Metoprolol.

7-10 COMPARISON OF CARVEDILOL AND METOPROLOL ON CLINICAL OUTCOMES IN PATIENTS WITH CHRONIC HEART FAILURE

Beta-blockers reduce mortality in patients with chronic heart failure **(HF)** due to systolic dysfunction when added to diuretics and ACE inhibitors.

This study compared effects of two beta-blockers—carvedilol and metoprolol.

Conclusion: Carvedilol was superior.

STUDY

1. Randomized, double-blind trial entered over 3000 patients with chronic HF. (NYHA class II (48%); III (48%); IV (3%). Mean age = 62) All had a previous admission for a cardiac condition, an ejection less than 0.35 (mean = 0.26) , and were treated optimally with diuretics and ACE inhibitors
2. Randomized to: 1) carvedilol - target dose 25 mg twice daily, and 2) metoprolol - target dose 50 mg twice daily.
3. Primary endpoints = all-cause mortality and the composite of all-cause mortality and all-cause admission.
4. Follow-up = mean of 58 months

RESULTS

1. Outcomes	Carvedilol (n = 1511)	Metoprolol (n = 1518)	NNT*
All cause mortality	512 (34%)	600 (40%)	17
Composite endpoint	1116 (74%)	1160 (76%)	50
Cardiovascular deaths	438 (29%)	534 (35%)	17

(* Number of patients needed to treat for 5 years to benefit one by taking carvedilol rather than metoprolol.)

2. "Incidence of side-effects and drug withdrawals did not differ by much between the two studies groups."

3. Resting heart rate at each visit was similar in both groups, decreasing from about 82 to 68.

4. Carvedilol extended median survival by 1.4 years as compared with metoprolol.

DISCUSSION

1. Metoprolol has a high specificity for the beta-1 adrenergic receptor. Carvedilol blocks beta-1, beta-2, and alpha-1 receptors.

2. Carvedilol has other effects that might be advantageous in HF, including increasing insulin sensitivity. (Metoprolol has the opposite effect).

CONCLUSION

Carvedilol extended survival compared with metoprolol.

Lancet July 5, 2003; 362: 7-13 Original investigations, first author Philip A Poole-Wilson, Imperial College, London, for the Carvedilol Or Metoprolol European Trial (COMET) www.thelancet.com

Comment:

The challenge in primary care is not so much which beta-blocker to choose, but judicious use of a beta blocker in select patients with heart failure. They are underused in primary care practice for treatment of heart failure. RTJ

Provocative, Not Clinically Applicable.

7-11 EFFECT OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ON RISK OF ALZHEIMER'S DESEASE: ***Systematic Review and Meta-analysis of Observational Studies.***

Observational studies suggest that NSAIDs may protect against Alzheimer's disease **(AD).** The benefit may be due to their anti-inflammatory properties.

This meta-analysis quantified the risk of AD in NSAID users, as well as aspirin users, on potential prevention of AD.

Conclusion: NSAIDs offer some protection.

STUDY

1. Systematic review and meta-analysis of observational studies published between 1966 and 2002 examined the role of NSAID use in preventing AD.

2. Nine studies looked at NSAIDs and aspirin in adults over age 55. Six were cohort studies (over 13 000 patients); 3 were case-control (over 1400).

RESULTS

1. Pooled relative risks of Alzheimer's disease users vs non-users:

NSAIDs	0.72
Aspirin	0.87

2. Risk related to duration of use of NSAIDs:

Less than 24 months	0.83
Over 24 months	0.27

DISCUSSION

1. Benefit was greater with longer use.
2. Currently no data available on COX-2 selective inhibitors.

CONCLUSION

The study lends support to the hypothesis that NSAIDs may protect against the development of Alzheimer's disease.

BMJ July 19,2003; 327: 128-31 Original investigation, first author Mahyar Etminan, Royal Victoria Hospital, Montreal, Canada. www.bmj.com/cgi/content/full/321/7407/128

Comment:

This is not a clinically important practical point at this time. I abstracted the article for its provocative support of the hypothesis. Patients may be asking about it.

We have been grievously misled by observational studies before; it would take much more study to convince me. Should NSAIDs be used by primary care clinicians for this purpose? No. I believe the adverse effects of NSAIDs would overrule any hypothetical benefit.

I was not able to calculate absolute risk reductions from the limited data presented. RTJ

7-12 THE INFLUENCE OF FINASTERIDE ON DEVELOPMENT OF PROSTATE CANCER

Androgens are involved in the development of prostate cancer **(PC).**

Dihydro-testosterone **(DHT**)is the primary androgen in the prostate.

Testosterone is converted to DHT by a reductase. Finasteride inhibits this enzyme and lowers production of DHT.

This study asks—does inhibition of production of DHT by finasteride reduce risk of PC?

Conclusion: Finasteride reduced risk of PC. But increased risk of high grade PC.

STUDY

1. Entered over 18 000 men age 55 and older. All had a normal digital rectal examination and a prostate specific antigen **(PSA**) of 3.0 ng/mL or lower. Of these, about 9000 were followed to the end of the study.
2. Randomized to: 1) finasteride (*Proscar*) 5 mg daily, or 2) placebo
3. Prostate biopsy was recommended if the annual PSA, adjusted for the effect of Finasteride **[1],** exceeded 4.0 ng/mL, or if the digital examination was abnormal.

4. Follow-up = 7 years. It was estimated that 60% of participants would have PC diagnosed during the study, or would undergo a biopsy at the end of the study.
5. All men who had not been given a diagnosis of PC were offered a prostate biopsy at the end of the study.
6. Primary endpoint – prevalence of PC.

RESULTS

1. PC was detected:	Finasteride (n=4368)	Placebo (n = 4692)	Absolute difference	NNT*
	18.4%	24.4%	6%	17

(* Number needed to treat over 7 years to prevent one PC.)

2. High grade tumors (Gleason 7,8,9,10) were more common in the finasteride group:
   Finasteride -- 6.4%; placebo -- 5.1%
   (Absolute increase in risk = 1.3%; one of 77 men.)
3. Finasteride has relatively little toxicity. Sexual side effects were more common in the finasteride group.[2] Urinary symptoms were less common.[3]

DISCUSSION

1. The lifetime risk of PC in the USA is 17%. About 29 000 men are expected to die of PC in 2003.
2. The high incidence and the unpredictable biology of PC make prevention an appealing option.
3. There is evidence that PCs that develop in men with low testosterone levels have higher Gleason scores and worse outcomes. However, it is possible that finasteride selectively inhibits low-grade tumors and selects for high grade tumors. The reason is not known.
4. "For a man considering using this medication, the greater absolute reduction in the risk of prostate cancer must be weighed against the smaller absolute increase in the risk of high-grade disease. "
5. The trade off between lower risk of prostate symptoms must also be weighed against the higher risk of sexual dysfunction. Individual preference is required.

CONCLUSION

Finasteride prevents or delays the appearance of PC at a risk of increasing incidence of high grade cancers.

NEJM July 17, 2003; 349: 215-24 Original investigation by the Prostate Cancer Prevention Trial, first author Ian M Thompson, University of Texas Health Science Center, San Antonio. www.nejm.org

Comment:

Proscar is approved by the FDA for treatment of benign prostate hyperplasia and male pattern baldness.

1 Finasteride lowers PSA by about ½. Thus the indication for biopsy in the finasteride group during the study was lowered to a PSA of 2 ng/mL or higher.

2 Erectile dysfunction and loss of libido about 66% in the finasteride group vs about 60% in the placebo group.

3 Benign prostate hyperplasia, urinary urgency and frequency, incontinence, retention, transurethral resection, and prostatitis about 2% to 3% lower.

Should primary care clinicians prescribe finasteride for prevention of PC. I would not, until more is known about risk of advanced PC. However, many men would likely accept treatment for symptomatic relief of BPH. Prevention of PC may be an added attraction for some. Because of the apparent risk of increase of high grade cancers, these patients should be monitored more closely. RTJ

An editorial in this issue of NEJM by Peter J Scardino comments:

Most of the PCs detected in the trial were low-grade or intermediate-grade and were found to be clinically localized. These cancers were detected early in their natural history and probably conferred a low risk of death. Improved survival is the goal of cancer prevention. The intermediate end point used in the trial—the histologic detection of PC—is not a proven surrogate. "On balance, finasteride does not seem to be an attractive agent for the chemoprophylaxis of prostate cancer." The cancers detected histologically were likely of little clinical significance.

A Lethal Combination

7-13 INTERACTION OF SPIRINOLACTONE WITH ACE INHIBITORS OR ANGIOTENSIN-RECEPTOR BLOCKERS

Low-dose spirinolactone (25 – 50 mg daily) added to standard treatments for severe congestive heart failure **(HF)** is associated with a substantial reduction in mortality Standard treatment includes ACE inhibitors **(ACE)** or angiotensin-II receptor blockers **(AT II RB).**

Spirinolactone, ACE inhibitors, and AT II RB all reduce renal excretion of potassium.

The higher the dose of spirinolactone, the greater the risk of *hyper*-kalemia. Many of the patients in this report were receiving doses larger than 50 mg/d. Doses ranged up to 100 mg, and even up to 200 mg.

This "Lesson of the Week" in BMJ reports 44 cases of severe hyper-kalemia in patients receiving combined therapy. These patients (mean age = 76) were admitted to a nephrology unit for treatment of life-threatening hyper-kalemia. All were receiving ACE or AT II RB in addition to spirinolactone. The great majority had type 2 diabetes.

Symptoms on admission included nausea and vomiting, diarrhea, muscle weakness and paralysis, arrhythmias, and severe dehydration. Five patients had to be resuscitated on admission. Mean plasma potassium was 7.7 mmol/L. *(See typical EKG of hyperkalemia p 149*) Mean serum creatinine concentration was 294 umol/L. Creatinine clearance was low. Dehydration was a common problem.

The majority were treated with hemodialysis. Seven were treated with conventional K lowering medical treatment: intravenous sodium bicarbonate, iv furosemide, iv glucose, and insulin. Six remained on chronic dialysis. Two died. Renal function recovered in the majority after closely monitoring volume administration.

Spirinolactone intake is reported to be the most common cause of secondary hyper-kalemic paralysis, which often mimics the Guillain-Barre syndrome. (Twenty six of the study patients had muscle weakness or paralysis.)

Advanced age, doses of spirinolactone > 25 mg, reduced renal function, and diabetes are associated with increased risk of the syndrome. Dose should not exceed 25 mg daily, or even every other day. Undetected hyper-kalemia may be suspected as a possible cause of sudden death in some patients with HF treated with spirinolactone. + ACE or AT II RB.

BMJ July 19, 2003; 327: 147-49 Original investigation, first author Eike Wrenger, Otto-von-Guericke University, Leipziger, Germany. www;bmj.com/cgi/content/full.327/7407/147

Comment:

Although this complicate would be very uncommonly seen in primary care practice, clinicians should be aware of it.

The combined drugs may lead to disaster.

This presents a good opportunity to review the renin-angiotensin-aldosterone system. I have to review it periodically, or I forget it.

Aldosterone is a hormone normally excreted by the adrenal. It is the "sodium-retaining, potassium-excreting" hormone.

Renin (produced by the kidney) converts

Angiotensinogen (inactive precursor produced by the liver) to

Angiotensin I (an inactive precursor protein) is converted by

Angiotensin-converting enzyme to

Angiotensin II (a highly active vasoconstrictor protein) which acts on the adrenal to produce

Aldosterone

*Angiotensin-converting enzyme inhibitors (**ACE** inhibitors)* block conversion of

Angiotensin I to

Angiotensin II, thus lowering levels of

Aldosterone, leading to

Sodium loss and potassium retention by the kidney. (As in Addison's disease)

Angiotensin II receptor blockers (**AT II RB**) act directly at the cellular level to block action of angiotensin II on the kidney, also resulting in sodium loss and potassium retention.

Spirinolactone is a direct aldosterone inhibitor. It increases excretion of sodium and impairs excretion of potassium.

The combination of spirinolactone with an ACE inhibitor or an AT II RB acts additively to decrease potassium excretion and may raise blood levels of potassium to lethal levels. RTJ