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

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Correspondence to:

Practical Pointers, Inc.
c/o Richard James, Publisher
400 Avinger Lane #203
Davidson NC 28036

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HIGHLIGHTS AND *EDITORIAL COMMENTS* FEBRUARY 2005

2-1 DOES THIS PATIENT HAVE INFLUENZA?

This systematic review deals chiefly with precision and accuracy of diagnosis of flu by symptoms and signs. It leads to other publications by the CDC which are helpful in diagnosis, treatment, and prophylaxis of flu

Diagnosis by signs and symptoms: "Fever, headache, myalgias and cough are the classic symptoms that physicians associate with influenza. Unfortunately, these symptoms are frequently seen in patients presenting with other infections during influenza season, making the clinical diagnosis of influenza a challenge to the primary care physician."

Epidemiology ; Clinician's knowledge of the current epidemiological status of flu in the community is basic to accurately estimate the probability of influenza in a given patient.

Laboratory diagnosis: Rapid diagnostic tests are now available for office use. Results are available within 30 minutes: The tests require swabs of the nasopharynx. The sensitivity (% of patients with flu who have a positive test) and specificity (the % of patients who do not have flu who have a negative test.) vary. Two commercial tests have waivers from the Clinical Laboratory Improvement Amendments, and can be used in office settings.

Treatment: Four drugs are approved for early treatment—oseltamivir (*Tamiflu*); zanamivir (*Relenza*); amantadine (*Symmetrel*; Generic); and rimantadine (*Flumadine*; generic). Tamiflu is effective against both A and B, and can be given by mouth.

Test and treat or treat empirically without testing: Depending on the acuity of the illness, vaccination status, and presence of co-morbid conditions, some physicians might choose to treat empirically with an antiviral drug. Empirical treatment may be favored because the test may be a false negative.

Decision must be based on epidemiologic estimates of the likelihood of the infection in the community. The decision is sensitive to prior vaccination status.

Physicians who were provided with rapid test results prescribed fewer antibiotics, ordered fewer lab studies and chest X-rays, and kept the patient in the emergency department for shorter periods of time and generated fewer charges.

Chemoprophylaxis: Three drugs are approved—amantadine, rimantadine, and oseltamivir.

CDC has, in the past, encouraged use of amantadine and rimanatadine for chemoprophylaxis. Oseltamivir (Tamiflu) may be a better choice since it covers both A and B. It is well tolerated. Less than 1% of patients experience nausea and vomiting which leads to withdrawal. The UK is stockpiling the drug in anticipation of a pandemic of the Asian bird flu.

Prophylaxis is indicated for persons at high risk of serious complications and immunosuppressed patients including those in institutions. <u>Vaccinated</u> as well as unvaccinated immunosuppressed residents in institutions where an outbreak occurs should receive chemoprophylaxis for the duration of the outbreak.

If non-immunosuppressed patients can be vaccinated, the prophylaxis may be continued for 2 weeks until immunity develops.

"Almost No Pattern of Drinking (Even Low-To-Moderate) is Entirely Risk Free."

2-2 ALCOHOL AND PUBLIC HEALTH

Over the past 30 years, advances in our understanding of drinking problems have been substantial.

This review considers 3 subtopics: 1) the epidemiology of alcohol's role in health and illness, 2) treatment of alcohol use disorders as part of public health, and 3) prevention and policy research.

Alcohol is causally linked to more than 60 different medical conditions—most, but not all, detrimental.

For most diseases there is a dose-response relationship. Not only the volume of consumption, but patterns of drinking (especially binge drinking) determine the burden of disease. Almost no pattern of drinking (even low-to-moderate) is entirely risk free.

*Breast cancer (**BC**):*

Meta-analyses have shown a linear increase in risk of BC associated with increasing average consumption of alcohol.

*Coronary heart disease (**CHD**):*

*C*omprehensive meta-analyses reiterate the protective effect of low-to-moderate alcohol intake—a J-shaped curve.

Injury (violence)

Several pharmacological effects are likely to increase probability of aggressive behavior.

Alcohol accounts for about as much of the burden of disease globally as tobacco. Its burden is surpassed only by unsafe sex, high blood pressure, and malnutrition.

Among heavy drinkers who have no evidence of severe alcohol dependence, an intervention in primary care aimed at reduction of drinking to moderate levels may benefit. Evidence suggests that clinically significant effects on drinking behavior can follow a brief intervention—but not in alcohol-dependent persons.

Overall, a discouraging report. Primary care clinicians may have some place in prevention of alcohol dependence by early assessment and intervention.

Many experts have urged screening, especially for patients who are hospitalized for any reason.

AUDIT and CAGE questionnaires available on Google. Screening in itself may broach the subject and lead patients to self-examination.

The relation between breast cancer and alcohol has not been well publicized. I believe it prudent to inform women at high risk (family history; breast cancer genes) about the risk.

No level of alcohol consumption is known to be safe in pregnancy.

Cessation is Difficult to Achieve. When Successful, it Saves Lives.

2-3 THE EFFECTS OF A SMOKING CESSATION INTERVENTION ON 14.5-YEAR MORTALITY: A Randomized Trial

The Lung Health Study entered over 5500 community-dwelling adult volunteers. All were heavy smokers (mean of 31 cigarettes daily and a history of 40 pack-years). At baseline, all had modestly impaired FEV1 and FVC, but were asymptomatic. None considered themselves to be ill.

Randomized to: 1) Intervention group received an intensive 10-week smoking cessation program consisting of a strong physician message and 12 two-hour group sessions using behavior modification and nicotine gum and 2) Usual care group.

At 5 years, 22% of the special intervention group had stopped smoking *vs* 5% of the usual care patients.

Mortality rates per 1000 person-years at 14 years:

	Sustained quitters	Intermittent quitters	Continuing smoker
Cardiovascular disease	1.0	1.5	2.9
Lung cancer	1.5	3.0	3.6

The most prominent difference between groups was observed in the youngest participants. "It could be argued that smoking cessation was more effective in preventing truly premature death."

This type of intervention would not be feasible in primary care practice.

The discouraging (yet realistic) outcome of this all-out effort—78% of heavy smokers failed to achieve cessation even though they received an all-out intervention, and were aware of a beginning disability from smoking.

This would tilt efforts to intervene much earlier in life, particularly to prevent smoking in the first place.

Cessation benefits all ages. Younger patients can be told their risk of dying at a relatively young age (35-44) is high as a result of smoking. This might deter a few.

Rate Control of AF Appears to be at Least Equivalent to Rhythm Control.

2-4 RATE VS RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

Patients with AF have a 4- to 5-fold increase in risk of stroke and a 2-fold increase in risk of death. Because of the frequency of AF at present, and its increasing incidence as the population ages, there are enormous implications regarding AF-associated stroke, and its prevention.

The two fundamental approaches to management are 1) reestablishment and maintenance of sinus rhythm (rhythm control), and 2) control of ventricular rate by intraventricular node blocking agents (rate control).

"The results of our meta-analysis suggest that in most patient populations with persistent AF, or at high risk of recurrent AF, a strategy of maintaining rhythm control does not translate into significant benefit on survival compared with a strategy of rate control in combination with anticoagulation…"

Indeed, the suggestion is that rhythm control may actually be inferior in regard to survival.

Compared to patients in normal sinus rhythm (NSR) , patients with AF have more heart-related symptoms and less efficient ventricular function, decreased exercise tolerance, higher risk of stroke, lesser quality of life, a requirement for anticoagulation, and shorter survival. If restoration and maintenance of NSR, could be accomplished easily and safely and could be constantly maintained, outcomes would be more favorable than among patients with persistent AF. The problem is that NSR may be difficult to achieve and maintain, and the drug therapy required is toxic and often has to be withdrawn.

Many patients for whom rhythm control is attempted revert to AF and are later crossed over to rate control. If anticoagulation is adequate in the AF patients, risk of stroke is low.

Practical Pointers has previously abstracted two studies which arrived at the same conclusion—rate control is not inferior to rhythm control. I thought the point deserved emphasis. See www.practicalpointers.org December 2002 [12-2]

Should Beta-Lactams be the Antibiotics of Initial Choice in Adults with Community-Acquired Pneumonia?

2-5 EFFECTIVENESS OF BETA-LACTAM ANTIBIOTICS COMPARED WITH ANTIBIOTICS AGAINST ATYPICAL PATHOGENS IN NON-SEVERE COMMUNITY ACQUIRED PNEUMONIA.

One of the barriers to better define treatment of community-acquired pneumonia (**C-AP)** is the inability to accurately determine which organisms might be the cause. *Streptococcus pneumoniae* has long been considered a common pathogen. It is now apparent that other organisms are causative—*Mycoplasma pneumoniae, Chlamydia pneumoniae,* and Legionella species. Their major distinguishing feature is a lack of response to beta-lactam antibiotics.

This meta-analysis compared the efficacy of beta-lactam antibiotics (eg. penicillin; amoxicillin) with antibiotics active against atypical pathogens in adults with C-AP: 7 different fluoroquinolones (eg, levofloxacin); 2 macrolides (eg, erythromycin; azithromycin).

The study assessed only the necessity for coverage of atypical pathogens in the *initial* management of community-acquired pneumonia.

"Data from our analysis do not support the need for antibiotics that possess specific activity against atypical pathogens in the *initial* managements of adults with mild-to-moderate community-acquired pneumonia."

"We suggest that the role of *M pneumoniae* and *C pneumoniae* in community-acquired pneumonia may have been overplayed." There was no evidence that specific therapy is required for *M pneumoniae and C pneumoniae.* Legionella infections do require specific therapy.

Antibiotic treatment should always be reassessed in any patient who shows signs of deterioration or failure to improve.

"Beta-lactams should remain the antibiotics of *initial* choice in adults with community-acquired pneumonia."

This approach to therapy reflects the British view. It remains controversial. When I was abstracting the study, I wondered if beta-lactam therapy would be generally acceptable in the USA. I believe amoxicillin would often be prescribed initially in out patients with suspected pneumonia. The study gives some assurance that it is not a bad choice. However, as the study states, careful follow-up is required to judge if the patient's illness is improving or deteriorating.

The article did not mention the increasing resistance of S pneumoniae to beta-lactams (as well as many other antibiotics including erythromycin). Primary care clinicians should be aware of the likelihood of penicillin resistance in their community. There are now reports that some strains of S pneumoniae are susceptible only to vancomycin.

Usually Self-Limited and Typically Heal Without Medical Intervention

2-6 BITES OF BROWN RECLUSE SPIDERS AND SUSPECTED NECROTIC ARACHNIDISM

"Among both physicians and the general public the perceived threat of spider bites far exceeds the actual risk." Loxosceles spider bites are the only proven medically important cause of necrotic arachnidism in North America. The brown recluse spider (*Loxosceles reclusa)* is most commonly blamed. Diagnosis is made by collection and proper identification of the spider. This is rarely possible.

Bites occur much less commonly than as perceived by physicians and patients. The misdiagnosis of spider bites is given to a wide spectrum of dermatologic conditions, some of which are far more dangerous than a spider bite. (*See the long list p. 703*)

"Since many diseases mimic loxoscelism, and since documented bites are rare, any diagnosis of loxoscelism should be considered highly suspect."

Treatment remains controversial. Initial care should include routine first aid: elevation and immobilization; application of ice; local wound care; and tetanus prophylaxis. A wide range of other interventions has been reported, none with consensus regarding efficacy. Many are costly, painful, and potentially toxic.

"Because the injury from the bite of a brown recluse spider is usually self-limited and typically heals without medical intervention, controlled trials would be essential to justify treatment before advocating any particular therapy." There is no therapy with proven efficacy.

Even severe necrosis is rarely life-threatening. The bite is typically self-limiting and self-healing.

Patients often overemphasize spider involvement in idiopathic wounds, a tendency that can misdirect physicians toward an erroneous diagnosis. "Physicians should be skeptical of any undocumented history of spider bite and should entertain a broad differential diagnosis before attributing a skin ulcer as loxoscelism."

Conservative use of simple first aid and local wound care may be the best approach.

This sensible report may save some patients considerable discomfort.

Potentially A Less Intimidating Alternative to Warfarin. Concerns about Hepatotoxicity

2-7 XIMELAGATRAN—Promises and Concerns

Melagatran is a highly-specific direct thrombin inhibitor, an analogue of hirudin, the thrombin inhibitor found in the medicinal leech. It is a small dipeptide which binds reversibly to the active site of thrombin. It inhibits clot-bound thrombin as well as free thrombin. Ximelagatran is a prodrug form of melagatran. It is rapidly absorbed from the GI tract. When given orally it is rapidly converted to melagatran. Its antithrombin activity is immediate. Peak blood levels are attained in 3 hours. It is cleared entirely by renal excretion in 12 hours.

Since the effect is predictable at a fixed dose, monitoring is not necessary.

This is not yet a practical point for primary care since the drug is not yet approved by the FDA. Many attributes of the drug make it a very attractive anticoagulant: immediate action when given orally; a fixed dose without need for monitoring; rapid renal clearance; no food or drug interactions; active against clot-bound as well as free thrombin; reversible binding to thrombin.

If the risk of hepatotoxicity can be controlled by monitoring, I believe it will be a major therapeutic advance.

ABSTRACTS FEBRUARY 2005

2-1 DOES THIS PATIENT HAVE INFLUENZA?

(JAMA February 23, 2005; 293: 987-97 "The Rational Clinical Examination", first author Stephanie A Call, University of Louisville KY.)

This article begins by describing a 45-year-old schoolteacher seen in the office with a 24-hour illness. Her temperature was 101.5^0. She had a dry cough, sore throat, myalgias and malaise. Her physical examination was not remarkable except for mild pharyngeal erythema. She had chosen not to receive the flu vaccine.

A number of her students have been absent from school due to similar symptoms. Does she have the "Flu"? What to do?

This systematic review deals chiefly with precision and accuracy of diagnosis of flu by symptoms and signs. It leads to other publications by the CDC which are helpful in diagnosis, treatment, and prophylaxis of flu.

DIAGNOSIS BY SIGNS AND SYMPTOMS.

This MEDLINE search study attempted to determine if any symptom or sign, or group of symptoms and signs, could lead to a more reliable clinical diagnosis of influenza. The authors found 6 prospective, randomized controlled trials which were conducted during flu seasons, and included clinical signs and symptoms as predictors of influenza. Several "gold standards" for the diagnosis of flu were used. (Eg, culture; antibody determination; PCR). This allowed comparison of patients who truly had influenza from those who had an influenza-like-illness.

The authors then compared the likelihood that a symptom or group of symptoms would separate those having influenza from those who did not.

Symptoms considered included; fever; cough; myalgia; malaise; headache; sore throat.

Results: In general, these symptoms were more common in patients who had the flu, compared with those who did not have the flu. But the odds ratios were not very high. Overall, the likelihood of a symptom being present in a patient with flu was only about twice that of controls. No single clinical finding consistently had a positive likelihood ratio high enough to clinically "rule in" influenza, nor did any single finding have a negative likelihood ratio low enough to clinically "rule out" influenza. There were several clues, however. The absence of fever and absence of cough reduced the likelihood of flu to below 50%. Feverishness, myalgia, malaise, sore throat and sneezing each had a likelihood ratio indistinguishable from 1.0 (flu vs non-flu). Thus these symptoms were of no diagnostic value. The strongest predictor of influenza was the acute onset of both fever and cough in patients age 60 and over.

"Fever, headache, myalgias and cough are the classic symptoms that physicians associate with influenza. Unfortunately, these symptoms are frequently seen in patients presenting with other infections during influenza season, making the clinical diagnosis of influenza a challenge to the primary care physician."

(Primary care clinicians are quite aware that the clinical diagnosis of flu depends much more on the epidemiological picture than on symptoms.)

EPIDEMIOLOGY

(www.cdc.gov/flu/weekly/fluactivity.htm).

During the flu season, many persons develop influenza-like-illness **(ILI),** defined by the CDC as fever > 100^0, plus either cough or sore throat. The CDC has set up a surveillance system throughout the country to monitor the prevalence of ILI. The frequency of infections attributable to various viral agents that cause ILI varies geographically from week to week throughout the flu season. A variety of nonspecific symptoms also accompany other respiratory infections. (Eg, adenovirus, rhinovirus, parainfluenza.) In addition, bacterial agents may be linked to ILI.

Ten to twenty percent of US residents contract flu each year. Given the antigenic shift, the virus has the capability to cause epidemics and global pandemics.

US Sentinel Providers Surveillance Network (sponsored by the CDC) gathers data on ILI across the country. Reports are available weekly. They provide a synopsis of epidemiological information, including laboratory surveillance data, ILI frequency, and regional variability of outbreaks. State and local health departments also provide information on local conditions.

Based on sentinel data, patient visits to primary care for ILI peak at 3% to 7% during the flu season. At times, up to 1 of every 14 primary care visits in the US is because of ILI.

The majority of laboratory samples from patients with ILI test *negative* for influenzae. The implication is that these patients have other viral illnesses.

Clinician's knowledge of the current epidemiological status of flu in the community is basic to accurately estimate the probability of influenza in a given patient.

LABORATORY DIAGNOSIS

(http://www.cdc.gov/professionals/labdiagnosis.htm)

Surveillance and diagnostic testing can aid clinical judgment and help guide therapy. Early diagnosis can reduce the inappropriate use of antibiotics and provide the option to use antiviral drugs. "As with any diagnostic test, results should be evaluated in the context of other clinical information." Both the sensitivity and specificity of rapid tests are lower than for viral culture and vary by test. Interpretation should be guided by the context of the level of influenza activity in the community.

Rapid diagnostic tests are now available for office use. Results are available within 30 minutes: The tests require swabs of the nasopharynx. The sensitivity (% of patients with flu who have a positive test) and specificity (the % of patients who do not have flu who have a negative test.) vary. Two commercial tests have waivers from the Clinical Laboratory Improvement Amendments, and can be used in office settings:

1. QuickVue A+B: Distinguishes between influenza A and B.
2. ZstatFlu: Detects both A and B, but does not distinguish between them.

Since the symptoms of flu are non-specific and similar to other infections, clinical diagnosis is difficult. Rapid tests can help. Samples should be collected within the first 4 days of illness. Most tests done in the office (when compared with the "gold standard" of culture) are approximately 70% sensitive for detecting flu (30% false negatives); and about 90% specific (only about 10% false positives). [Ie, a negative test performs well in ruling out flu.]

Tests do not need to be done on all patients. When an epidemic is present in the community, rapid testing may *not* be helpful. If a rapid test is negative, this does not conclusively rule out flu; if positive, does not conclusively rule in flu. If the patient is test-negative, he likely does not have flu, but there are exceptions. Under many circumstances (eg, when likelihood of flu in the community is low), the test may not be cost effective. Primary care clinicians may tilt toward testing patients who have not been vaccinated.

<u>TREATMENT</u> OF EARLY INFECTION WITH ANTIVIRALS

(http://www.cdc.gov/flu/professionals/antiviralback.htm)

(http://www.cdc.gov/flu/professionals/treatment/0405antiviralguide.htm)

There are 4 specific antiviral agents available to treat flu:

1. **Amantadine** (*Symmetrel*; *Generic* – an old drug used for treatment of Parkinsonism) Effective against type A only. Affects a membrane ion channel protein, decreasing viral replication and shedding.
   Use within the first 2 days of illness reduces duration of illness by 1 to 2 days. But use for *treatment* is discouraged because the flu virus may develop resistance.
   Dose in adults = 100 mg twice daily for 5 days. (In the elderly, 100 mg once daily for 5 days.)
   Cost: Relatively inexpensive—about $3.00 for a 5-day treatment.
   Adverse effects in about 10% of recipients, mainly on the central nervous system.
2. **Rimantadine** (*Flumadine*; *Generic*) similar to amatadine. *Note possible confusion with ranitidine, a histamine blocker. Use the trade name.*
   Very similar to amantadine. Active against type A only. Dose is the same.
   Cost is considerably higher—about $3 for one 100 mg tablet of Flumadine. Slightly less for generic rimanatadine.
   Adverse effects and withdrawals are reported to be about half that of amantadine.

*3. **Oseltamivir** (*Tamiflu)* . Effective against A and B.
   A neuraminidase inhibitor. Blocks the active site of the enzyme, resulting in viral aggregation at the host cell surface, reducing the number of viruses released from the cell.
   Given by mouth within 48 hours of onset of flu reduces duration of symptoms (compared with placebo) by about 1 day. It also significantly reduces lower respiratory tract complications, antibiotic use, and hospitalizations. Tilt use toward patients at high risk (elderly, heart and lung disease, diabetes) and to unvaccinated patients.
   Adverse effects: Nausea and vomiting the most common. Fewer than 1% withdrew.
   Dose: 75 mg twice daily for 5 days.
   Cost: $66 for ten 75 mg tablets
   Limited data on development of antiviral resistance. No cross resistance to amantadine.

*4. **Zanamivir** (*Relenza*) Similar to *Tamiflu*. Effective against A and B.
   A neuraminidase inhibitor. Given by inhalation. Not for patients with underlying lung disease.

CDC encourages use of oseltamivir and zanamivir for *treatment*.

All 4 drugs reduce the duration of clinical illness if instituted within 48 hours of onset. Because of costs and adverse effects, they should be used only when the likelihood of infection and the expected benefit are both high. The drugs also lessen chance of contagion and may lessen complications.

TEST AND TREAT OR TREAT EMPIRICALY WITHOUT TESTING.

When a sick patient presents during the flu season, clinicians may have to decide to base therapy on rapid tests, or treat empirically without testing.

Depending on the acuity of the illness, vaccination status, and presence of co-morbid conditions, some physicians might choose to treat empirically with an antiviral drug. Empirical treatment may be favored because the test may be a false negative.

Again, decision must be based on epidemiologic estimates of the likelihood of the infection in the community. The decision is sensitive to prior vaccination status. The estimated reduction in serologically confirmed cases of flu was reported to be about 60%.

If one can estimate the probability of flu to be greater than 30%, rapid diagnostic testing does not add to the overall cost-effectiveness of treatments. Clinicians must develop a pre-test probability based on clinical signs and symptoms, vaccination history, and epidemiology. (http://www.cdc.gov/weekly/fluactivity.htm)

In a patient with clinical flu, a positive rapid test increases the odds of infection almost 5-fold. A negative rapid test lowers the probability of flu but will not rule it out if the prior probability of flu is high.

Physicians who were provided with rapid test results prescribed fewer antibiotics, ordered fewer lab studies and chest X-rays, and kept the patient in the emergency department for shorter periods of time and generated fewer charges.

How does the primary care clinician decide to do a rapid-test? Much depends on the current epidemiology, the patient's preference, applicability and effectiveness of antiviral therapy following a positive test, and whether a positive diagnosis would lessen family and community infection.

1. If during a high flu season a sick patient presents early in the illness with compatible symptoms, I believe many clinicians would treat with antivirals without testing. Even if the test were negative, many clinicians would opt for empirical antiviral therapy.

2. If the patient insists on being tested, I would go ahead and test, explaining that the test is not perfect.

3. If the patient has a close family with older susceptible members, I would test with the idea of treating the patient, and applying "ring prophylaxis" to the family. This may help break a cycle of a local epidemic.

<u>CHEMOPROPHYLAXIS</u> WITH ANTIVIRAL DRUGS AFTER EXPOSURE OR SUSPECTED EXPOSURE

CDC recommends 3 drugs for prophylaxis. The inhaled drug zanamivir (*Relenza*) is not recommended.

Chemoprophylaxis is usually not recommended for patients who have received flu vaccine.

1. **Amantadine** (*Symmetrel*)

   70% to 90% effective chemoprophylaxis against type A.

   High risk patients should be given priority.

   Dose: As above.

   Duration of therapy: Usual family prophylaxis = 7 days.

For protection of high risk patients and unvaccinated health-care workers who are continually exposed, may be given for 6-8 weeks.

Adverse effects—CNS and GI

2. **Rimanatadine** *(Flumadine)*

As for amantadine

Again reported to be associated with fewer adverse effects, but costs more.

3. **Oseltamivir** (*Tamiflu*)

Effective prophylaxis for both A and B.

Dose = 75 mg daily for 7 days in the family setting. Up to 6 weeks in elderly in nursing homes, and health care workers continuously exposed.

In the recent past, CDC encouraged use of amantadine and rimanatadine for chemoprophylaxis. Tamiflu is approved for prophylaxis. It is likely the preferred drug. The UK is stockpiling it for use in case of a pandemic.

Prophylaxis is indicated for persons at high risk of serious complications and immunosuppressed patients including those in institutions. Vaccinated as well as unvaccinated immunosuppressed residents in institutions where an outbreak occurs should receive chemoprophylaxis for the duration of the outbreak.

If non-immunosuppressed patients can be vaccinated, the prophylaxis may be continued for 2 weeks until immunity develops.

REVIEW OF INFLUENZA-RELATED ARTICLES ABSTRACTED BY *PRACTICAL POINTERS* 1999-2004

Because of the clinical importance of this disease, the inevitability of infection each year, the possibility of pandemics, and new developments in diagnosis and treatment, I recall the articles I have abstracted over the past 5 years. The full abstract may be accessed through the web site (www.practicalpointers.org) RTJ

Dose-Sparing With Intradermal Injections Of Influenza Vaccine November 2004 [11-3]

Evidence that low-dose intradermal injections elicits an immune response similar to intramuscular vaccine. Of clinical importance during vaccine shortages.

Structure of the 1918 Flu Virus February 2004 [2-17]

A crucial change in the hemagglutinin molecule, which protrudes from the virus, enabled an avian virus to lock on to human cells and to be transmitted from human to human. A billion people were infected. Some authorities predict a repeat pandemic is inevitable. (*The emergence of a new avian flu in Asia is scary. RTJ)*

Tackling the Next Influenza Pandemic. June 2004 [6-13]

Suggests that “ring prophylaxis” (short-term post-exposure administration of close contacts with a neuraminidase inhibitor) may break the cycle of contagion while awaiting the protection of a vaccine.

Influenza Vaccination and Reductions in Hospitalizations for Cardiac Disese and Stoke in the Elderly March 2003 [3-1]

Vaccination is associated with a large reduction in hospitalizations due to heart disease and stroke as well as pneumonia.

Effectiveness of Neuraminidase Inhibitors in Treatment and Prevention of Influenza A and B June 2003 [6-12]

They are effective, but no substitute for vaccination. Choosing individuals for whom the drugs are indicated is a clinical judgment call.

Contribution of Influenza and Respiratory Syncitial Virus to Community Cases of Influenza-Like-Illness October 2001 [10-12]

RSV is a common cause of ILI.

The Safety of Inactivated Influenza Vaccine in Adults and Children with Asthma November 2001 [11-7]

Vaccine does not worsen asthma. No more adverse effects than with placebo.

Effects of Influenza Vaccination of Health-care Workers on Mortality of Elderly People in Long-term Care January 2000 [1-13]

Vaccination of health-care workers was associated with substantial decrease in mortality among frail elderly patients. Vaccination protects not only the health-care worker, but the patients they serve.

Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir (*Tamiflu*) in Treating Acute Influenza. February 2000 [2-1]

Is effective and safe. *Tamiflu* may be especially indicated when an epidemic occurs for which vaccine may be ineffective due to appearance of an antigenically novel virus.

Effectiveness of Live, Attenuated Intranasal Influenza Vaccine in Healthy, Working Adults July 1999 [7-4]

Safe, and reduced severity of illness and absenteeism among adults even though the correlation between the strain used and the strain which appeared during the flu season was poor.

Intranasal Influenza Vaccine: Adding to the Armamentarium for Influenza Control July 1999 [7-5]

Is easily self-administered and can be administered when convenient to the patient. "The Institute of Medicine has placed the administration of influenza vaccines to the general population on its list of most beneficial vaccines and strategies for the 21st century."

New Options for Prevention and Control of Influenza July 1999 [7-7]

Even when there is a close match between vaccine and epidemic strains, vaccine effectiveness is typically in the range of 30% to 50%. Large gaps in immunity must be filled by other means.

New Recommendations for Adult Immunization December 1999 [12-8]

The Advisory Committee on Immunization Practices recommends the age for receiving vaccine be lowered from 65 to 50. (Morbidity and mortality begins to risk at age 50.)

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Almost No Pattern of Drinking (Even Low-To-Moderate) is Entirely Risk Free.

2-2 ALCOHOL AND PUBLIC HEALTH

After collapse of "prohibition" in the US, a new compromise was reached—alcohol was no longer viewed as a threat to all, but rather to a small subclass of people who are alcohol dependent.

Over the past 30 years, advances in our understanding of drinking problems have been substantial. This review considers 3 subtopics: 1) the epidemiology of alcohol's role in health and illness, 2) treatment of alcohol use disorders as part of public health, and 3) prevention and policy research. Medical approaches are appropriate in health care settings. Population based public health interventions address broader dimensions of alcohol problems.

Epidemiology:

Alcohol is causally linked to more than 60 different medical condition—most, but not all, detrimental. For most diseases there is a dose-response relationship. Not only the volume of consumption, but patterns of drinking (especially binge drinking) determine the burden of disease. Almost no pattern of drinking (even low-to-moderate) is entirely risk free.

The burden of alcohol is substantial, accounting on a net basis for 7% of the total burden of disease in developed countries. Alcohol accounts for about as much of the burden of disease globally as tobacco. Its burden is surpassed only by unsafe sex, high blood pressure, and malnutrition.

The article focuses on relations between alcohol and for 3 important disease categories: breast cancer; cardiovascular disease, and intentional injury.

*Breast cancer (**BC**):*

Meta-analyses have shown a linear increase in risk of BC with increasing average consumption of alcohol. Consumption of 10 g (1 drink) daily of pure alcohol increases risk of BC by 9% compared with abstainers; 30-60 g daily increases risk by 41%. Combining alcohol with postmenopausal estrogen replacement therapy magnifies the risk.

*Coronary heart disease (**CHD**):*

Comprehensive meta-analyses reiterate the protective effect of low-to-moderate alcohol intake—a J-shaped curve. The lowest risk was at 20 g per day (2 drinks). After this, the risk reverses. Consumption of 70 g per day is associated with the greatest risk compared with abstainers.

Drinking with meals also seems to have a protective role.

The effect on lipids and hemostatic factors may explain the benefit of low-to-moderate drinking. This applies only to people who have a pattern of regular drinking, without episodes of heavy drinking. Episodic heavy drinkers have increased risk. (Even though the average daily intake may be in the low-to-moderate range.)

An irregular pattern of heavy drinking increases risk of stroke and sudden cardiac death.

Intentional injury (violence):

Alcohol is consistently associated with violent crime. There is a small to moderate effect size in the overall relation between consumption and aggression. Several pharmacological effects are likely to increase probability of aggressive behavior. A benzodiazepine-like action may reduce fear and anxiety related to the social, physical, and legal consequences of drinking. Increase in risk-taking and aggressive behavior results.

Alcohol also affects cognitive functioning, leading to impaired problem solving in conflict situations.

Of course, alcohol is associated with occurrence of unintentional injury, to innocent bystanders and family members as well as to the drinker. 29% of the alcohol-attributable deaths in the UK are related to injuries.

Treatment:

Brief intervention:

Among heavy drinkers who have no evidence of severe alcohol dependence, an intervention in primary care aimed at the reduction of drinking to moderate levels may benefit. Alcohol-dependent drinkers are likely to require specialized interventions.

Approaches to management have been divided into 3 general categories: 1) brief intervention, 2) specialized programs, and 3) mutual help groups.

Individuals in the low positive range of the Alcohol Use Disorders Identification Test (AUDIT; 8-15) should receive a brief intervention. This is intended to provide prophylactic treatment before or soon after the onset of problems with hazardous drinking rather than with dependence. It is typically designed to moderate alcohol consumption, rather than promote total abstinence. Evidence suggests that clinically significant effects on drinking behavior can follow a brief intervention—but not in alcohol-dependent persons.

Pharmacotherapy:

Although benzodiazepines have played a key role in treatment of withdrawal, and disulfram (*Antabuse*) has been in clinical use since 1940, pharmacotherapy has not yet had a demonstrable impact on alcohol dependence.

Now, consistent with neurobiological research, drugs to treat excessive drinking have focused on agents which have selective effects on endogenous opioids, serotonin, and dopamine. Naltrexone (an opioid antagonist) has been shown to reduce rate of relapse, although the effects are small. Acamprosate (an amino acid derivative) has an effect on neurotransmission of both gamma amino benzoic acid and glutamate. Studies in Europe have shown an advantage over placebo. The drug seems to hold substantial value for treatment of alcohol dependence.

Lack of compliance is the problem.

Implications for practice:

Individuals who obtain help for a drinking problem, especially in a timely manner, have better outcomes. The type of help they receive (self-help or formal treatment) makes little difference in the long-term.

Medically-based inpatient treatment is not demonstrably more effective than non-medical residential or outpatient treatment.

The authors go on to discuss several societal methods of attempting to reduce alcohol consumption by governments. Some have demonstrated a benefit: increasing taxes on alcohol; reducing the blood-alcohol level defining drinking-under-the-influence (Sweden has reduced it to 0.02%--one drink); increasing surveillance of drivers; restricting the hours bars are open, and holding the bar-keeper responsible for problems related to patrons who were served after they became intoxicated.

As with the food and tobacco industries, the alcohol industry has resisted policy changes.

Lancet February 5, 2005; 365: 519-30 Review article, first author Robin Room, Stockholm University, Sweden.

"Low Level Alcohol Consumption and the Fetus", an editorial in BMJ February 19, 2005: 375-56, first author Raja A S Mukherjee, St George's Hospital Medical School, London, UK comments on the fetal alcohol syndrome.

The neurocognitive deficits in the fetal alcohol syndrome are pervasive.

Over the past 30 years the opinions of professionals have changed. Previously fetal alcohol syndrome was considered to be a possible consequence of chronic alcohol consumption occurring in specific high risk populations. Behavioral changes may be seen even at low doses of alcohol consumption. No level of alcohol consumption is known to be safe in pregnancy.

"The only safe message in pregnancy is abstinence from alcohol."

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Cessation is Difficult to Achieve. When Successful, it Saves Lives.

2-3 THE EFFECTS OF A SMOKING CESSATION INTERVENTION ON 14.5-YEAR MORTALITY: A Randomized Trial

Smoking cessation almost certainly has beneficial effects on subsequent mortality. This is the first trial assessing the long-term effect on mortality of a randomly applied smoking cessation program.

Conclusion: Cessation intervention programs can reduce subsequent mortality, even when successful in only a minority of participants.

STUDY

1. The Lung Health Study entered over 5500 community-dwelling adult volunteers (mean age 48). All were heavy smokers (mean of 31 cigarettes daily and a history of 40 pack-years). At baseline, all had modestly impaired FEV1 and FVC, but were asymptomatic. None considered themselves to be ill.
2. Randomized to: 1) Intervention group received an intensive 10-week smoking cessation program consisting of a strong physician message and 12 two-hour group sessions using behavior modification and nicotine gum. 2) Usual care group.
3. About 75% of the original participants were followed continuously for a mean of 14 years.
4. Determined mortality rates and specific causes of death.

RESULTS

1. At 5 years, 22% of the special intervention group had stopped smoking *vs* 5% of the usual care patients. (The authors state that smoking status determined at 5 years changed relatively little over the following years.)
2. Over 14 years 731 died. All-cause mortality was lower in the intervention group—8.8 per 1000 person-years vs 10.4. The mortality benefit was greatest among subjects who actually managed to quit.
3. Mortality rates per 1000 person-years at 14 years (*Figure 3 p 237*):

	Sustained quitters	Intermittent quitters	Continuing smoker
Cardiovascular disease	1.0	1.5	2.9
Lung cancer	1.5	3.0	3.6

4. The hazard ratio for death (usual care *vs* intervention) was greatest in the 35 to 44 year-old subset. (HR = 1.9)

DISCUSSION

1. "The striking feature of our findings is the statistically significant difference in all-cause mortality in the intention-to-treat analysis." Mortality was higher in the usual care group than in the special intervention group even though cessation was successful in only a minority of participants.
2. The authors emphasize that the results of the study apply only to heavy smokers who already have evidence of some airway obstruction.
3. The most prominent difference between groups was observed in the youngest participants. "It could be argued that smoking cessation was more effective in preventing truly premature death." The mechanisms by which cessation induces coronary events are apparently reversible to some extent in the short term. Benefits in reduction of lung cancer are usually not evident for 5 years.
4. There was no difference in lung cancer mortality between men and women.
5. The authors estimate the cost of the program for each individual was about $2000.

CONCLUSION

An intensive smoking-cessation program followed by 5 years of reinforcement led to a reduction in all-cause mortality in a group of heavy smokers.

Annals Int Med February 15, 2005; 142: 233-39 original investigation by the Lung Health Study, first author Nicholas R Anthonisen, University of Manitoba, Winnipeg, Canada.

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Rate Control of AF Appears to be at Least Equivalent to Rhythm Control.

2-4 RATE VS RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

Patients with AF have a 4- to 5-fold increase in risk of stroke and a 2-fold increase in risk of death. Because of the frequency of AF at present, and its increasing incidence as the population ages, there are enormous implications regarding AF-associated stroke, and its prevention.

The two fundamental approaches to management are 1) reestablishment and maintenance of sinus rhythm (rhythm control), and 2) control of ventricular rate by intraventricular node blocking agents (rate control).

In 1), electrical or pharmacological cardioversions is followed by antiarrhythmic agents. In 2), anticoagulation to prevent thromboembolic events is combined with A-V nodal blocking agents.

Maintaining normal sinus rhythm **(NSR)** has several theoretical advantages over rate control: more efficient left ventricular function, decrease in symptoms, reduced risk of thromboembolic events, reduced need for anticoagulation, and a reduced risk of death. But antiarrhythmic drugs have risks: they are proarrhythmic, and have significant non-cardiac effects.

This meta-analysis was conducted to add precision to the relative merits of the 2 approaches.

Conclusion: Rate control appears to be at least equivalent to rhythm control.

STUDY

1. Literature search identified 5 randomized (not blinded) trials (over 5000 patients; mean age = 69) comparing pharmacologic rhythm control with rate control + anticoagulation as first-line therapy. About 2/3 had a history of hypertension; 28% a history of heart failure.
2. All patients had persistent AF or AF that was considered likely to be recurrent.
3. Amiodarone was the most frequently used drug for the rhythm control group. The choice of A-V nodal blocking agents varied between trials—beta-blockers, digoxin, calcium blockers.
4. Follow-up ranged from 1 to 3.5 years.

RESULTS

1. Many patients in the rhythm control group failed to maintain NSR. Some in the rate control group regained NSR
2. Mortality and stroke: A trend in favor of rate control, but no statistical difference in all-cause mortality and stroke between groups. In absolute terms:

	Rate control (%)	Rhythm control (%)
Death	13	14.5
Stroke (ischemic)	3.5	3.9

DISCUSSION

1. "The results of our meta-analysis suggest that in most patient populations with persistent AF, or at high risk of recurrent AF, a strategy of maintaining rhythm control does *not* translate into significant benefit on survival compared with a strategy of rate control in combination with anticoagulation..."
2. Indeed, the suggestion is that rhythm control may actually be inferior in regard to survival.
3. The rate of torsades de points and cardiac arrest due to bradycardia and pulseless electrical activity was significantly higher in the rhythm control group. This was despite the frequent use of amiodarone which is considered to have a low risk of proarrhythmia, but significant risk of non-cardiac toxicities.
4. Another reason for lack of benefit in the rhythm control group is the difficulty of maintaining sinus rhythm.
5. Appropriate use of anticoagulation is the key feature in preventing embolic events in patients with AF. *(In the real world of practice, control of the INR may be less precise and rate of bleeding may be higher than in controlled trials. I do not believe, however, that this would tilt toward rhythm control in primary care. RTJ)*

CONCLUSION

In patients with AF, a strategy of rate control in combination with anticoagulation appears to be at least equivalent to a strategy of attempting to maintain sinus rhythm in preventing clinical outcomes.

Archives Int Med February 14, 2005; 165: 258-62 "Review Article", first author Simon de Denus, University of Montreal Canada.

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Should Beta-Lactams be the Antibiotics of Initial Choice in Adults with Community-Acquired Pneumonia?

2-5 EFFECTIVENESS OF BETA-LACTAM ANTIBIOTICS COMPARED WITH ANTIBIOTICS AGAINST ATYPICAL PATHOGENS IN NON-SEVERE COMMUNITY ACQUIRED PNEUMONIA.

One of the barriers to better define treatment of community-acquired pneumonia (**C-AP)** is the inability to accurately determine which organisms might be the cause. *Streptococcus pneumoniae* has long been considered a common pathogen. It is now apparent that other organisms are causative—*Mycoplasma pneumoniae, Chlamydia pneumoniae,* and Legionella species. Their major distinguishing feature is a lack of response to beta-lactam antibiotics. The part that atypical organisms play, and the need to provide specific antibiotic coverage for them in C-AP is contentious.

This meta-analysis compared the efficacy of beta-lactam antibiotics with antibiotics active against atypical pathogens in adults with C-AP.

Conclusion: There is *no* evidence that clinical outcomes are improved by using antibiotics active against atypical pathogens in *all-cause non-severe, community-acquired pneumonia*. (Except for legionella infections which are rare.)

STUDY

1. This systematic review compared beta-lactam antibiotics with antibiotics active against atypical pathogens in *initial* treatment of non-severe, C-AP in out-patients.
2. The meta-analysis included 18 double-blind, randomized, controlled monotherapy trials comparing any beta lactam therapy (usually amoxicillin or amoxicillin-clavulanate[a]) *vs* antibiotics effective against atypical pathogens. (Nine different fluoroquinolones, two macrolides, and one ketolide.) All beta-lactams lacked activity against the atypical pathogens.

   (**a** *The authors state that beta-lactamase producing bacteria (including H influenzae) are an uncommon cause of mild out-patient pneumonia. Addition of the beta-lactamase inhibitor, clavulanate, increases likelihood of adverse effects. RTJ*)
3. Over 6700 patients were identified. None had a requirement for parenteral antibiotics at study entry. None had hospital-acquired or aspiration pneumonia, were immunosuppressed, or had major kidney or liver dysfunction. The specific inclusion and exclusion criteria resulted in participants who were younger and with a better prognostic risk profile than observational pneumonia cohorts. (Ie, considered to be mild-to-moderate C-AP.)
4. Primary outcome = failure to achieve improvement or clinical cure.

RESULTS

1. Number failing to achieve cure or improvement was 18% is each group.
2. There was no significant difference in outcomes between treatments in any study.
3. There was no significant heterogeneity between studies.
4. No significant difference in all-cause mortality.

5. No significant difference in treatment effect in patients with *M pneumoniae*, or *C pneumoniae* [b]

(**b** *This was despite the lack of response of both these organisms to amoxicillin. Why then was response to amoxicillin equal to that of specific antibiotics? Infections caused by these organisms tend to be mild and self-limiting. Definitive diagnosis is difficult. The classification of these infections in the study may have been suspect. Perhaps the numbers of patients included in the trials was insufficient to detect any statistical difference. RTJ)*

6. Antibiotics effective against legionella in patients who actually had legionella infections resulted in better outcomes.

DISCUSSION

1. "Data from our analysis do not support the need for antibiotics that possess specific activity against atypical pathogens in the *initial* managements of adults with mild-to-moderate community-acquired pneumonia." (Ie, less severe cases.)
2. "Our results are valuable in guiding the management of many adults with community-acquired pneumonia."
3. The three antibiotics active against atypical pathogens have excellent in vitro activity against each of the atypical organisms considered to cause community-acquired pneumonia. Most also have good coverage for *S pneumoniae.*
4. All the beta-lactams considered lacked activity against atypical pathogens.
5. Only for patients with legionella infections was there a statistically significant improvement in those receiving antibiotics active against atypical organisms. But, legionella is uncommon in patients with non-severe pneumonia. (*This small subset of patients must be detected early and treated aggressively RTJ*)
6. "We suggest that the role of *M pneumoniae* and *C pneumoniae* in community-acquired pneumonia may have been overplayed." There was no evidence that specific therapy is required for *M pneumoniae and C pneumoniae.* Legionella infections do require specific therapy.
7. These findings agree with the British Thoracic Society guidelines. They are at variance with the American Thoracic Society guidelines. The authors of the study suggest that their study provides good evidence contrary to the American guidelines.
8. The study assessed only the necessity for coverage of atypical pathogens in the *initial* management of community-acquired pneumonia. Antibiotic treatment should always be reassessed in any patient who shows signs of deterioration or failure to improve.

CONCLUSION

"Evidence is lacking that clinical outcomes are improved by using antibiotics against atypical organisms in all-cause, non-severe, community-acquired pneumonia."

"Beta-lactams should remain the antibiotics of *initial* choice in adults with community-acquired pneumonia. "

BJM February 26, 2005; 330: 456-60 "Primary Care", original investigation (a meta-analysis), first author Graham D Mills, Waikato Hospital, Hamilton, New Zealand.

An editorial in this issue of BMJ (p 460), first author Mark Woodhead, Manchester Royal Infirmary, Manchester, UK comments:

> This study "should reassure all heath professionals who routinely manage non-severe, community-acquired pneumonia that therapy using oral beta-lactam antibiotics, macrolides, or fluoroquinolones is equally effective when judged by clinical cure and mortality."
>
> "Beta-lactams should remain the preferred therapy for these patients."
>
> One situation in which a beta-lactam would not be first choice is when legionella infection is suspected. Such infections are rare in the community.
>
> In many patients with community-acquired pneumonia cared for by primary care clinicians, confirmation by radiography is not carried out. Detection of community-acquired pneumonia by clinical means is neither sensitive nor specific. Nevertheless, it "would seem reasonable to apply these research findings to patients with suspected (rather than confirmed) community-acquired pneumonia on the basis of specific features such as focal chest signs, dyspnea or tachypnea, or prolonged fever. "Use of beta-lactams in patients with suspected community-acquired pneumonia will pose only a limited—and thus acceptable—risk for development of bacterial resistance."

www.hopkins-abxguide.org presents a helpful wide range of infections and recommended antibiotics. John G Bartlett, the author of *Pneumonia, community-acquired* does not recommend amoxicillin. His first choices for empiric therapy of C-AP are doxycycline and azithromycin. The US FDA does, however, consider amoxicillin (among many others) indicated for lower respiratory infections.

Hopkins-abxguide comments:

1) *Mycoplasma pneumoniae*. Lower respiratory infection ("Walking pneumonia"). Often not severe, rather mild and self-limited. Dry cough. Minimal physical findings. Normal white count with clear chest on physical examination and pneumonia on chest X-ray. Diagnosis is problematic since culture difficult and serology insensitive at time pf presentation. Treatment is empiric. No response to beta-lactams since the organism lacks a cell wall. Erythromycin and doxycycline are first-choice antibiotics. Azithromycin and levofloxacin also effective.
2) *Chlamydia pneumoniae:* An obligate intracellular bacteria. Not responsive to amoxicillin. Erythromycin and doxycycline are first-line antibiotics. Rarely diagnosed clinically with certainty—treat empirically. Azithromycin and fluoroquinolones are effective.
3) *Legionella pneumoniae:* Not responsive to amoxicillin. Pneumonia severe and may be life-threatening. Culture difficult and requires 3 days on special media. Antigen in urine may aid diagnosis Fluoroquinolones (eg, levofloxacin) and azithromycin (*Zithromax*) often given i.v. because of severity of illness. The infection must be suspected early and treated aggressively.

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Usually Self-Limited and Typically Heal Without Medical Intervention

2-6 BITES OF BROWN RECLUSE SPIDERS AND SUSPECTED NECROTIC ARACHNIDISM

During the past 5 decades there has been a growing popular belief that spiders cause many cases of skin necrosis in the U. S. (Especially the brown recluse spider, *Loxosceles reclusa.*)

"Among both physicians and the general public the perceived threat of spider bites far exceeds the actual risk." The misdiagnosis of spider bites is given to a wide spectrum of dermatologic conditions, some of which are far more dangerous than a spider bite.

Therapeutic interventions continue without evidence-based justification.

Where Loxosceles spiders live

There are 11 species of loxosceles spiders in North America. The brown recluse spider *Loxosceles reclusa* is responsible for most cases of evenomation. Its native range is centered around south-central USA, from Texas and Oklahoma, north to parts of Iowa, Illinois and Indiana, and east to touch western Georgia, South Carolina and North Carolina. (*See map page 701*). Other species range across the Texas-Mexico border into California. Loxoscelism essentially does not occur beyond the spiders' usual habitat.

Loxosceles spider activity

The brown recluse is nocturnal. Human bites usually occur at night and when the spiders are threatened or trapped.

Spiders other than loxosceles have been reported to cause skin necrosis. The reports are questionable.

Diagnosis and misdiagnosis

Diagnosis is made by collection and proper identification of the spider. This is rarely possible.

A wide array of infectious and non-infectious conditions are frequently misdiagnosed as loxosceles bites. (*See the long list p. 703*)

"Since many diseases mimic loxoscelism, and since documented bites are rare, any diagnosis of loxoscelism should be considered highly suspect."

Treatment

Remains controversial. Initial care should include routine first aid: elevation and immobilization; application of ice; local wound care; and tetanus prophylaxis. A wide range of other interventions has been reported, none with consensus regarding efficacy. Many are costly, painful, and potentially toxic.

"Because the injury from the bite of a brown recluse spider is usually self-limited and typically heals without medical intervention, controlled trials would be essential to justify treatment before advocating any particular therapy."

Dapsone (a sulfone antibiotic which has been used to treat leprosy) has been advocated as treatment for loxoscelism. Many practitioners prescribe it. There is marginal evidence to support efficacy. The authors warn against its use because of major adverse effects, including hemolytic anemia.

Antivenom is not available in the U.S.

Conclusion

Loxosceles spider bites are the only proven medically important cause of necrotic arachnidism in North America. They occur much less commonly than as perceived by physicians and patients.

Accurate diagnosis can be made only if the spider is identified by an experienced arachnologist. An offending spider found outside the endemic area is likely not loxosceles, and necrosis is unlikely.

Even severe necrosis is rarely life-threatening. The bite is typically self-limiting and self-healing.

Patients often overemphasize spider involvement in idiopathic wounds, a tendency that can misdirect physicians toward an erroneous diagnosis. “Physicians should be skeptical of any undocumented history of spider bite and should entertain a broad differential diagnosis before attributing a skin ulcer to a spider bite.”

There is no therapy with proven efficacy.

Conservative use of simple first aid and local wound care may be the best approach.

NEJM February 17, 2005; 352: 700-07 “Review Article”, first author David L Swanson, Mayo Clinic, Scottsdale, Ariz.

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Potentially A Less Intimidating Alternative to Warfarin. Concerns about Hepatotoxicity

2-7 XIMELAGATRAN—Promises And Concerns

As the population ages and prevalence of obesity increases, the risk of atrial fibrillation and venous thromboembolism will increase.

Warfarin has been the mainstay of antithrombotic therapy. Its inherent problems are well known: delayed onset of action; narrow therapeutic index; unpredictable and variable pharmacological response; and need for mandatory regular laboratory monitoring. In addition, numerous drugs, some “dietary supplements”, alcohol, and some foods markedly influence the dose response. A higher level of diligence and reliability is required than for almost any other drug. Benefits of warfarin therapy are imperceptible. Harms (bleeding) are visible. (*Not knowing the benefits of a therapy, and being fully aware of its harms is a burden primary care clinicians often bear. RTJ*)

Clinical trials report an annual incidence of major bleeding of 1% to 4%. In the real world of practice, risk of bleeding will be higher. Bleeding from warfarin therapy is a leading iatrogenic cause of hospitalization.

Less complicated anticoagulation is needed—one that is available in both oral and parenteral forms; has a prompt onset of action; has a predictable dose response not requiring laboratory monitoring; and does not interact with other drugs. Might melagatran and ximelagatran meet these requirements?

Melagatran is a highly-specific direct thrombin inhibitor, an analogue of hirudin, the thrombin inhibitor found in the medicinal leech. It is a small dipeptide which binds reversibly to the active site of thrombin. It inhibits clot-bound thrombin as well as free thrombin. Ximelagatran is a prodrug form of melagatran. It is rapidly absorbed from the GI tract. When given orally it is rapidly converted to melagatran. Its antithrombin activity is immediate. Peak blood levels are attained in 3 hours. It is cleared entirely by renal excretion in 12 hours.

At therapeutic doses, ximelagatran induces prolongation of prothrombin time, partial thromboplastin time, and thrombin time. But since the effect is predictable at a fixed dose, monitoring in not necessary.

No specific food or drug interactions have been reported.

More than a dozen clinical studies comparing ximelagatran with low molecular weight heparin/warfarin have been conducted for 4 indications (orthopedic surgery, venous thromboembolism, myocardial infarction, and atrial fibrillation). In general, efficacy has been reported to be as great as with enoxaparin/warfarin. And major bleeding no more common. It has been pointed out that, in the real world of primary care, warfarin dose would not likely

be as well controlled as in trials, and the risks of bleeding in those receiving warfarin would be higher than in those receiving ximelagatran.

Given it is a less complicated, more use-friendly anticoagulant, it is potentially a less intimidating alternative to warfarin.

A rise in liver enzymes (ALT) has occurred in about 10% of patients, usually after several months. Hepatotoxicity remains a concern especially for long-term use. For this reason the FDA of the U.S. has not yet approved use. It is approved in Europe only for short-term use.

JAMA February 9, 2005; 293: 736-39 Editorial by Victor Gurewich, Beth Israel Deaconess Medical Center, Boston Mass.