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Pulmonary Medicine

Bioterrorism and Physicians: Tear-Out Sheet

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This issue, with the article, "Bioterrorism and Physicians," and the tear-out Table, is being sent to all physicians in the state, under a Bioterrorism Preparedness grant from the Centers for Disease Control and Prevention.

On Being Told I'm Disgusting: The Hateful Family



Most patients and families approach their physician with a large amount of good will, sometimes investing the doctor with a degree of sagacity and knowledge that may be unrealistic if not fanciful. Yet most patients and families know the medical miracles they see on television won't necessarily translate into reality for them. It is always jarring, however, when the doctor falls badly short of family expectations and the family holds the doctor responsible for a poor outcome. And, of course, some families, like some patients, are just plain difficult to deal with for any number of reasons.

My example: waiting to board a boat, I was standing on a dock with my 12 year-old son. I was approached by a man, saying, "Hi, Doc." I put out my hand to shake his, which he took and said, "You don't remember me, do you?"

"Sorry, I can't place you."

"You took care of my father, Fred Jones (not the real name)."

"Oh yes, I remember him."

"He died."

"Yes, I know. That was several months ago. I'm sorry."

"What you did was disgusting. You sent him to Dr. S. He shouldn't be a doctor. He's disgusting. All you doctors disgust me. When I saw my father, who used to be a lawyer, and what Dr. S. did to him at that hospital, it was a crime. Dr. S. didn't care. And I called you and you weren't there."

"I sent your father to Dr. S. because I thought he was the best person to help your father. I had and still have complete confidence in him even to the point of sending my patient to another hospital so Dr. S. could care for him. And I'm sorry but I don't take calls all day, every day. There is always a neurologist covering for me though."

"Well, Dr. S. is terrible and so are you."

The conversation didn't stop there although the content did. For about ten minutes I was harangued, luckily in normal conversational tones, about Dr. S.'s incompetence and my own inferior practices and judgment. My son, much to his credit, wandered off out of earshot after the first few sentences. "Who's Dr. S.?", was his first comment. "Why was that guy so angry?" was his second.

The patient himself was a very pleasant man who became physically and mentally disabled in his late 70s as a result of Parkinson's disease. At Dr. S.'s hospital, his son, my accuser, had been forcibly removed by security agents because he interfered with nursing care. The rest of the family was only mildly more tractable. They forced a transfer from Dr. S.'s care back to mine and the patient remained under my care until he was deemed terminally ill and qualified for hospice.

What made them so angry? The first question is whether their anger was justified. Perhaps they received shoddy care and perceived a lack of interest and poor communication. Certainly there was no shortage of communication, and equally certain, the patient did not do well initially. But this is not so uncommon for sick patients, especially the elderly. And although there was a lot of time spent communicating, little, apparently, was communicated.

In my particular experience the social inappropriateness of the harangue in a public setting with my child in attendance suggests a personality disorder in the patient's son. But why so angry? Did I fail the patient? Did he fail his father? Did he, when the roles of caregiver and dependent were reversed, fail to live up to expectations (his own or his perceived expectations)? Did he feel that he let down his family? His mother was frequently overwhelmed by her husband's

disorder and had trouble coping. Was his failure to compensate translated into anger at his father's doctors because he perceived I had failed him?

He acted as if he was betrayed. I was the expert, presumably the doctor with the "magic;" and the magic failed (to materialize). No cure, little benefit, no magic bullet, then no hope. Was it the loss of hope? I could have said, before the referral to Dr. S.'s hospital, "I'm sorry, there's nothing I can do. Let's just make him comfortable and let nature take its course." I will never know what the family's response would have been. My guess is, "How can you say that?" Maybe you're just not smart enough. "We'll go elsewhere," which, in retrospect might have worked out better for all of us; but I believed there was a reasonable chance to help Mr. Jones.

On reflection, I did nothing that I think was wrong. I had even spent enough time with the patient and his wife that I had a good rapport. I had explained that hospitalization for his ailment occurred only under extreme circumstances. Although they understood this on an intellectual level it was never fully processed.

Hateful families may be more difficult to understand than hateful patients, but are generally less challenging. The physician's obligation is to the patient, not the family and one can often "finesse" the interaction. When the patient is incompetent, there is less room for avoiding confrontation. I can only recommend trying to avoid fueling any fires. Sympathize with their complaints and with any bad outcome. You can't mollify but you can make a bad situation worse. Never argue. Never raise your voice. Never show anger. Never admit to a mistake you didn't commit.

— Joseph H. Friedman, MD

Smallpox Visits the White House



It was an undistinguished rural community, settled in 1740, with a population which never exceeded 5,000. And were it not for a decisive battle fought within its township limits, the name Gettysburg would never have achieved its special measure of immortality.

In the early days of June, 1863, Lee's Army of Northern Virginia advanced into southern Pennsylvania and confronted the Union troops led by Meade. A bloody battle persisted for three July days, culminating in the charge of Pickett's division, perhaps the turning point of the Civil War, with military casualties exceeding 53,000 in killed, wounded and missing. With this tragic measure of shed blood, it was only fitting that the fertile valley of Gettysburg be transformed into a consecrated burial ground for those who had fallen on its fields. Its dedication was scheduled for a November afternoon, 1863.

President Abraham Lincoln was asked to address the audience gathered for the dedication of the battlefield cemetery. He left the White House at noon, November 18, boarding the train to Gettysburg. His 10 year-old son Tad, who had taken ill the day before with what had been incorrectly called scarlatina, was unable to accompany him.

The speech, hallowed by history as the Gettysburg Address, was given on the afternoon of November 19. One observer described the President as "sad, mournful, almost haggard." Lincoln returned to his railroad car weary, uncharacteristically silent, and suffering from a severe headache. On the train ride back to the capitol, aided by William Johnson, his personal valet, Lincoln bathed his head in cold water in an attempt to lessen the severity of the head and neck ache.

Lincoln cancelled his appointments for November 20 and confined himself to bed. His private physician recorded some high fever, headache, backache and general malaise and considered a diagnosis of bilious fever. By the morning of November 23, the President now exhibited a diffuse rash and his physician altered the diagnosis to scarlatina. There were, at this time, many cases of smallpox in the city of Washington; and it was felt that news of Lincoln's smallpox might increase the level of local anxiety. By the next morning, when there were typical vesicular lesions over Lincoln's body, finally the news had to be shared concerning the nature of the President's ailment. The disclosure, however, declared that Lincoln was the victim of a mild varioloid disorder, thus using the Latin name for smallpox [variola] as a euphemism while avoiding the commonly used term, smallpox.

Lincoln's sole visitor during the first week of acute illness was his personal secretary, John Hay [Class of 1858, Brown University], who conveyed Lincoln's wishes to members of his Cabinet. The fever subsided by November 27 and the skin lesions began to diminish, replaced by much generalized peeling and itching. Lincoln's health and spirits improved. By December he was well enough to attend a session of the Cabinet and later to receive a Congressional delegation, where he assured them of his complete recovery.

Lincoln now resumed his custom of hearing citizens appealing for one thing or another. Carl Sandburg, the Lincoln biographer, quotes Lincoln [aware that he might still be infectious] as saying: "I now have something I can give to everybody."

Lincoln's smallpox was mild, leaving at most a few more facial blemishes on a face not known for its pristine complexion. But Lincoln's valet and friend, William Johnson, was not as fortunate. He developed smallpox a few days after the onset of Lincoln's illness and died shortly thereafter. He was buried in Arlington at Lincoln's expense.

African-Americans were especially vulnerable to the renewed spread of smallpox within the Washington region. Despite the Emancipation Proclamation of 1862, blacks with smallpox were not admitted to the various fever hospitals and thus endured their illness in makeshift tents set up in the black neighborhoods of the Capitol. The case fatality rate for blacks with smallpox was substantially greater than for whites in Washington, partially because of this discriminatory policy of exclusion but partially, too, because blacks were more genetically susceptible to the virus of smallpox.

It is unlikely that Lincoln had ever been vaccinated during his childhood. The first documented vaccination against smallpox had been undertaken by Edward Jenner in 1796 in Gloucester, England. News of the new procedure reached these shores in 1799, when Harvard's first professor of medicine, Benjamin Waterhouse, read the results in letters from his friend the London physician Lettsom. Waterhouse then requested some of the precious cowpox serum, the basis for the vaccination procedure. Lettsom sent some to Waterhouse and gradually, over the next few years, an increasing number of Americans received the protection conferred by this vaccine. Most of the vaccination programs in the early decades of the 19th Century, however, were confined to the East coast. There is no evidence that Abraham Lincoln, born in rural Kentucky, had ever received a vaccination.

Despite the introduction of vaccination in the early years of the 19th Century, smallpox continued its ravages amongst the great majority who remained unvaccinated. There was a major pandemic affecting Europe from 1837 to 1840; major epidemics in India from 1849 to 1850; and a devastating epidemic sweeping the southern regions of Africa from 1864 to 1865. At no time during the middle decades of the 19th Century was the United States free of smallpox, particularly amongst the many impoverished immigrants seeking asylum in America.

Following the Franco-German War, smallpox swept through western Europe, killing an estimated 500,000 people. Germany was the first nation to mandate vaccination for both its military and civilian personnel. And whatever Germany's motivation for this enlightened policy might have been, its dramatic reduction in smallpox morbidity/mortality prompted other western nations to adopt similar policies.

Lincoln was not the only national leader to be affected by smallpox in the 19th Century. The emperors of both China and Japan succumbed to the disease in the same decade. Lincoln's bout of smallpox, however, proved quite mild and had little effect upon the American affairs of state. But the awesome responsibilities of leadership which weighed so heavily on Lincoln prompted him to seek relief by frequently attending evening performances at Ford's Theater, including, tragically, the performance on the evening of April 14, 1865.

— Stanley M. Aronson, MD, MPH

Pulmonary Medicine – Introduction

Allan Erickson, MD

This issue of *Medicine & Health/Rhode Island* contains articles dealing with several topics in Pulmonary Medicine. When the American Review of Tuberculosis began in 1917, as the principal subspecialty journal of the field, its title told the story: pulmonary medicine began with tuberculosis. That journal is now titled the *American Journal of Respiratory and Critical Care Medicine* and the field now includes diverse areas of interest, which are sampled in this issue. The first article focuses on a very sophisticated and current topic in tuberculosis; i.e., its elimination. An important topic for all primary care givers, TB elimination stresses the identification and treatment of latent TB infection. The second paper deals with a controversial issue in the treatment of a common disease, COPD. The last 2 papers deal with topics that are relatively new to the field of Pulmonary Medicine. The first deals with the common and underdiagnosed condition of obstructive sleep apnea. Studies demonstrate that general-

ists as well as internists and even pulmonologists fail to screen patients adequately for this treatable condition. Finally, the ethics of the Intensive Care Unit and death and dying are topics important to all physicians, regardless of their areas of interest. I hope that these updates will be informative, helpful in your practices, and make interesting reading as the field of Pulmonary Medicine continues to mature.

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Tuberculosis – Elimination in the Third Millennium?

E. Jane Carter, MD

Tuberculosis (TB) remains the leading cause of death from an infectious agent as well as a leading cause of disability in the world. The resurgence of TB in the early 1990s reinvigorated TB control in the United States. The epidemiologic upswing as well as the public health response to it occurred in a parallel fashion in Rhode Island. Over the last decade improvements in mycobacterial lab expertise, improved surveillance, expanded clinical services and availability of expert consultation have reduced incidence rates within Rhode Island.¹

The incidence of TB in Rhode Island was reported at 5.4/100,000 for the year 2000.² A majority (61%) of the state's active cases occur in foreign-born individuals, a phenomenon that again parallels national data. In Rhode Island TB is spread evenly throughout the ethnic/racial reporting groups: nonHispanic whites (30%), nonHispanic blacks (22%), Hispanic (20%) and Asian/Pacific Islander (22%). TB diagnosed in children, the sentinel marker of ongoing community-based transmission, has declined in Rhode Island; children under

age 15 represented only 6% of the cases diagnosed in 2000.

Two important communications on TB were published in 2000: the Institute of Medicine's report, *Ending Neglect: Elimination of TB in the United States*³ and the ATS/CDC guidelines, *Targeted Screening and Treatment of Latent TB Infection*.⁴

IOM REPORT

The major contributor to the resurgence of tuberculosis within the United States in the late 1990s was the deterioration of the public health infrastructure essential for the control of TB. The major contributor was not the rise in AIDS. As case rates decline in the US again, the risk rises that concern over this disease will wane and infrastructure for TB control will again be allowed to crumble. This phenomenon has been described as the U shaped curve of concern - as the incidence of a disease rises so does the public concern over that disease with concomitant dedication of resources; when the disease rate falls, so falls public concern, interest and often dedicated resources.

To achieve TB elimination in the United States, the IOM identifies 5 steps: 1) Maintaining control of TB while adapting to the declining incidence and changing systems of health care financing/management. 2) Speeding the decline of TB by increasing efforts related to targeted testing and treatment of latent TB infection (LTBI). 3) Research and development of new tools such as improved diagnostic tests for infection, new drugs to shorten the course of treatment, and an effective vaccine. 4) Increase United States involvement in global efforts for TB control. 5) Mobilize support for elimination.

It is in the realm of screening for LTBI and its treatment that the cooperative efforts of all physicians will be necessary. The ATS/CDC guidelines⁴ for screening and treatment published in May 2000 will be the backbone for that effort.

LTBI SCREENING

Screening for LTBI is performed to identify individuals who are infected with tuberculosis and who would benefit from

Figure 1.
Groups for Targeted Testing for LTBI

Persons at high risk for recent infection

Individuals residing in or visiting in high incidence countries for significant amounts of time:

Central and South America, Caribbean, Central and South east Asia, Indian Subcontinent, Africa, Russia, Selected portions of Eastern Europe.

Recent Immigrants (within the last 5 years) from high incidence countries

Residents and employees of high risk congregate settings:

prisons, jails, hospitals, nursing homes and other long term care facilities, homeless shelters, AIDS hospices.

Mycobacteriology Lab Personnel

Persons With Medical Conditions That Increase the Risk of Reactivation

Diabetes

Silicosis

Chronic renal failure/hemodialysis

Immunosuppression due to steroid use (greater than 15 mg for 1 month)

Solid organ transplantation

Weight below standard

HIV

IVDA

treatment to reduce the 10% lifetime risk of reactivation. It is recommended that screening be targeted on high risk populations; i.e., individuals who are either at high risk for having been exposed to tuberculosis or individuals who, if infected, are at high risk for progressing to active disease. (Figure 1)

Screening for TB infection is a two step process: 1) application and measurement of a tuberculin skin test and 2) risk stratification to allow interpretation of the skin test measurement. The preferred skin test is the intradermal or Mantoux skin test. Multipuncture tests, such as the Tine test, are not accurate due to the inability to deliver a standard antigen dose. Use of multipuncture tests is therefore discouraged. The Mantoux skin test is administered by injecting 0.1 ml of 5 tuberculin units (TU) into the ventral surface of the forearm. Measurement of the transverse diameter of resultant induration in millimeters is recorded at 48-72 hours.

Based on the sensitivity and specificity of the tuberculin skin test and the prevalence of TB in various groups, three cut-off levels are utilized to define a positive skin test : greater than or equal to 5mm, greater than or equal to 10mm, or greater than or equal to 15 mm. (Fig-

ure 2) Risk stratification takes into account both the risk of having been infected in the past as well as the risk of reactivation if the patient is infected. Thus, interpretation of a positive skin test cannot be accurately made without an epidemiologic risk history having been taken. It is not a test that can be inter-

preted within a vacuum. In addition if the patient's health status changes from year to year, the interpretation of the same size skin test in the same individual may change. For example, an 8 mm skin test would be considered a negative skin test in a US born individual with no medical history and no known recent exposure to a documented, contagious case. However, the same skin test in the same individual would be considered positive if the patient were found to be infected with HIV or to undergo organ transplantation.

An issue that often arises is the question of whether tuberculin skin testing may be performed in individuals who have been previously vaccinated with BCG. BCG is the vaccination used in countries with a high incidence of TB disease. Children infected with TB prior to the age of 5 years do not have a sufficiently developed immune system to contain the initial infection. Dissemination occurs rapidly with a resultant risk of TB meningitis. TB meningitis has a high mortality rate even when identified and treated early in its course. BCG has been shown to reduce dramatically, if not ablate, the risk of TB meningitis in children. BCG has a more variable, and unpredictable, protection factor in adults. A meta-analysis of published BCG stud-

Figure 2
Criteria for Positive Tuberculin Skin Test, Statified by Risk Group

Reaction Greater than or equal to 5 mm

- HIV
- Recent contacts of tuberculosis case patients
- Fibrotic changes on the chest x-ray consistent with prior TB
- Patients with solid organ transplants
- Patients receiving immunosuppressive drugs (equivalent to 15 mg prednisone/day for greater than 1 month)

Reaction Greater than or equal to 10 mm

- Recent immigrants (within 5 years) from high incident countries or areas
- IVDA users
- Residents or employees of high risk congregate settings
- Mycobacteriology lab personnel
- Persons with medical conditions which increase the risk of reactivation*
- Children younger than 4 years
- Infants, children and adolescents exposed to adults at high risk

Reaction Greater than or equal to 15 mm

- Persons with no risk factors for TB

* diabetes, chronic renal failure, weight loss of greater than 10% of IBW, silicosis, some hematologic malignancies such as leukemia and lymphoma, gastrectomy or jejunooileala bypass, some other malignancies such as head and neck or lung.

Figure 3.
Recommended Drug Regimens for Treatment of LTBI

Drug	Interval/Duration	Rating *	
		HIV -	HIV+
Isoniazid	Daily for 9 months	A (II)	A (II)
	2 x/week for 9 months	B (II)	B (II)
Isonizid	Daily for 6 months	B (I)	C (I)
	2 x/week for 6 months	B (II)	C (I)
Rifampin and Pyrazinamide	Daily for 2 months	B (II)	A (I)
	2 x/week for 2-3 months	C (II)	C (I)
Rifampin	Daily for 4 months	B (II)	B (III)

*USPHS rating system

A=preferred B=acceptable alternative C=offer when A or B unacceptable

I= randomized control trial

II= data from clinical trial that are not randomized or are conducted in a different population

III=expert opinion

All figures adapted from reference #4.

ies reveal marked variability in vaccine efficacy, ranging from an 80% protective factor to a detrimental factor in one study (patients receiving vaccine were more likely to develop documented TB disease).⁵ Thus, BCG is a reasonable childhood vaccine (almost always given within the first few weeks of life) to reduce the risk of TB meningitis in children in high incidence areas, but it should not be counted on to remove the risk of TB disease in infected adults. In addition, it should be noted that in no individual does BCG prevent inhalation of the organism nor infection by the TB organism; rather, it modulates TB disease of childhood.

BCG does not uniformly convey a positive Mantoux skin test even when skin testing follows shortly after vaccination. Amongst recipients of BCG 15% to 90% will become reactive to tuberculin. However, in the majority of individuals this reactivity wanes with time.⁶ Thus, tuberculin skin testing is not contraindicated in individuals who have been previously vaccinated with BCG. The standard cutoffs may be utilized to define tuberculin positivity in vaccinated adults. A positive Mantoux skin test in a BCG vaccinated individual denotes infection with *M. tuberculosis* when the person tested meets the published guidelines for the definition of a positive skin test, i.e. the person is at increased risk for recent infection or the person tested is

...BCG is a reasonable childhood vaccine (almost always given within the first few weeks of life) to reduce the risk of TB meningitis in children in high incidence areas, but it should not be counted on to remove the risk of TB disease in infected adults.



at increased risk for development of disease by the presence of concomitant medical problems. (Figure 2)

Tuberculin skin testing requires experience and expertise in both administering and interpreting the test. Therefore, self-reading of the test with resultant interpretation by the patient is not recommended.

Screening for LTBI should be coupled with treatment for LTBI. The only absolute contraindication to treatment of LTBI (where single drug therapy is utilized) is the presence of active TB disease. Screening for active disease is carried out by the combined use of a chest

radiograph and a history and physical exam targeted for signs, symptoms and findings to suggest TB disease. An abnormal chest radiograph or symptoms or physical findings suggestive of TB disease should prompt further diagnostic evaluations, such as sputum examinations. A normal chest radiograph does not rule out the presence of extrapulmonary TB. The history and physical examination are necessary for this purpose. Single drug therapy should never be instituted for LTBI until active disease is ruled out. Single drug therapy may be postponed or multidrug therapy can be started until active disease is reliably ruled out. Use of a single agent in the face of unrecognized active disease leads to the development of drug resistance rather than to cure.

An oft-encountered question is the safety of Mantoux skin testing during pregnancy. Tuberculin skin testing is an important aspect of prenatal screening in high risk populations. TB disease in the mother conveys the risk of intrauterine growth retardation as well as the risk for progressive and/or congenital TB in the baby. In the pregnant patient, Mantoux skin testing is safely performed, is a reliable reflection of the immune status, and is interpreted in the same manner as in a nonpregnant patient. Pregnant patients with a positive skin test or who are recent contacts to persons with contagious TB should have a chest radiograph with appropriate shielding as soon as possible, even in the first trimester. Treatment of TB disease during pregnancy is an unquestioned necessity. Treatment of LTBI during pregnancy is controversial due to a suggestion in the literature of increased drug toxicity in the form of hepatitis. Experts agree that documented recent infection with TB or LTBI with co-infection with HIV convey increased risk of progression during pregnancy and therefore should be treated (benefits outweigh risks). The majority of experts defer treatment of LTBI to the postpartum period in all other women.

Four regimen options are recommended for treatment of LTBI. (Figure 3) The regimen should be individualized to the needs and situation of the individual patient. Considerations in the determination of which regimen to uti-

lize include ability to monitor for side effects, ability to comply over time, concomitant medication use, and co-morbid conditions. All intermittent regimens, i.e. twice weekly regimens, should be given under DOT (**directly observed**) conditions.

Treatment of LTBI under any of the regimens requires clinical monitoring and evaluation. Adherence to the regimens is critical. There is, in fact, no test at the end of therapy to document completion or cure. The Mantoux skin test is not influenced by therapy; it serves only as a marker of infection. Thus, it is the health care provider's assessment of adherence that serves as the surrogate marker to ensure cure. All patients treated for LTBI should be given documentation for their personal records as to tuberculin skin test status, chest radiographic findings, regimen utilized for treatment, and adequacy of adherence. This documentation aids in avoiding duplicative testing or screening that may be required for work, school or change in health care provider.

Isoniazid (INH) is the most commonly utilized antituberculous agent. It has been in clinical use the longest. Its utility in decreasing risk of reactivation has been demonstrated in prospective, randomized trials. Its advantages include simplicity (once daily dosing of a single agent), few drug-drug interactions, and safety. A prospective cohort study of INH therapy for LTBI in a public health clinic revealed that the rate of INH hepatitis during clinically monitored therapy was very low.⁷ 0.1% of all patients starting and 0.15% of all patients completing therapy had hepatotoxic reactions to INH, all of whom recovered with cessation of the drug. This rate of INH induced hepatitis is lower than the rate of hepatitis reported for other commonly utilized drugs such as lovastatin (1.9% incidence of hepatitis at 1 year).⁸

The short course dual agent regimen for LTBI pairs rifampin and pyrazinamide together for a 60 day regimen. In prospective randomized trials of LTBI in HIV infected individuals this two drug regimen revealed similar efficacy and safety compared to a 12 month INH monotherapy regimen. However, there have been recent reports of 3 deaths due to hepatitis caused by this combination.⁹

Clearly clinical, and possibly biochemical monitoring, of patients on this regimen is indicated. The final caveat of the short course regimen of rifampin and pyrazinamide in the treatment of LTBI involves the issue of drug-drug interactions. Rifampin interferes with the metabolism of multiple other drugs through its effects on the P450 cytochrome system of the liver. Metabolism of multiple other drugs is increased dramatically. Oral contraceptives and injectable contraceptives in the form of Depoprovera are metabolized more quickly. Therefore, all women of child bearing age treated with a rifampin based regimen must be informed to use an alternative form of birth control during therapy.

Similar considerations of drug-drug interactions must occur in HIV-infected individuals. Rifampin is contraindicated when **protease inhibitors (PI)** or **non-nucleoside reverse transcriptase inhibitors (NNRTI)** are utilized. Rifabutin may be substituted for rifampin when HIV infected patients are already on PIs or NNRTIs (except in the case of hard-gel saquinavir or delavirdine or soft gel saquinavir or nevirapine – in the first instance rifabutin is contraindicated, in the second instance few data are available). The substitution of rifabutin for rifampin is based on expert opinion, not clinical trial data.

Efficacy of any of the regimens for LTBI is clearly related to number of doses of medications taken, not on duration of therapy alone. Thus, the 9-month regimen of INH should include 270 doses of INH at a minimum, taken over at most 12 months, allowing for short, intermittent lapses in adherence. The 6 month regimen of INH should consist of 180 doses in at most 9 months. The 2 month Rifampin-Pyrazinamide regimen should consist of 60 doses in 3 months. It should be noted that dosages of all antituberculous drugs are based on weight. Not to correct for weight in small adults predisposes to side effects of the drugs.

CONCLUSIONS

TB case rates in the United States are at their lowest ever. Elimination of tuberculosis is now the goal, through strategies such as screening for latent TB infection tied to treatment of the same.

Recent guidelines published in the US for screening and treatment emphasize targeted testing and treatment regardless of age with careful attention to adherence and side effect monitoring.

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Steroid Therapy in Chronic Obstructive Pulmonary Disease

Aidan O'Brien, MD, and Nicholas S. Ward, MD

Chronic obstructive pulmonary disease (COPD) has been defined clinically as a disease state characterized by the presence of airflow obstruction; the airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible.¹ The diagnosis of COPD usually includes elements of chronic bronchitis, and/or emphysema, however, some patients with asthma may go on to develop irreversible airflow obstruction, which can be indistinguishable from COPD.

Over 14 million people in the US are known to be afflicted with this disease, though many others remain undiagnosed. COPD is the fourth leading cause of death in the US. More disconcerting is the fact that the death rate due to COPD has increased by 11% in men between 1992-97 and by 28% in women over this same time period. This is due largely to the continued prevalence of smokers. (In 1997, 48 million adults Americans smoked). Pharmacologic therapies for COPD include anticholinergic agents, beta agonists, phosphodiesterase inhibitors, and corticosteroids. This article will discuss the evidence supporting the use of systemic and inhaled corticosteroids in the management of COPD.

Because COPD is now considered an inflammatory lung disorder, the use of corticosteroids in COPD would appear logical. Patients with this disease have evidence of bronchiolar obstruction due to fibrosis and infiltration of the bronchiolar walls by macrophages and lymphocytes. There is evidence of destruction of lung parenchyma, particularly in emphysema, with an increased number of macrophages and lymphocytes within the parenchyma.² Bronchoalveolar lavage fluid or induced sputum from patients with COPD contains increased number of macrophages, neutrophils, and eosinophils. There are also increased levels of inflammatory mediators such as leukotrienes (particularly

LTB-4), TNF-alpha, and IL-8 in patients' sputum. A negative correlation has been demonstrated between these markers of inflammation in sputum and **forced expiratory volume in one second (FEV1)** in patients with COPD. The severity of airflow limitation in smokers has also been found to be associated with the severity of airway inflammation as assessed by evaluating the number of subepithelial neutrophils, macrophages and natural killer cells in bronchial biopsies.³

Further support for the use of steroids in COPD is derived from the fact that there is evidence of airway reactivity in COPD. In one study, greater than two thirds of the COPD patients developed significant bronchospasm after inhaling methacholine.⁴ Mahler et al. found that 65% of patients with severe COPD had a positive bronchodilator response to inhaled albuterol (increase of ≥ 200 cc and/or $\geq 12\%$ improvement in FEV1).⁵ Thus, not only is there evidence of ongoing airway inflammation, but there is also evidence of airway reactivity with some reversibility of airways obstruction.

SYSTEMIC CORTICOSTEROIDS Stable COPD

An extensive literature describes the role of systemic corticosteroids in stable COPD.⁶⁻¹⁵ Studies evaluating the effects of short-term systemic steroids most often determined responsiveness by changes in spirometric indices alone. Defining a response to therapy as a 15-20% or greater increase in the baseline FEV1, patients with stable COPD treated with steroids have a clinically significant improvement in pulmonary function approximately 10-20% more often than similar patients who receive placebo.^{6,7} The addition of short-term systemic corticosteroids does not appear to lead to any further significant increases in FEV1 in those patients who respond to and are maintained on inhaled steroids.^{9,10} Because only a subset of patients with stable

COPD respond to systemic steroids, are there any good predictors of those who will most likely respond? Apart from those patients with an obvious asthmatic component to their disease, it appears that patients with a pretreatment positive bronchodilator test more often have a significant improvement in FEV1 in response to systemic steroids than those with a negative test.¹⁰

Long-term effects of systemic steroids in stable COPD have been evaluated. Patients taking oral prednisolone at a dose of more than 7.5mg per day were found to have a reduction in the long-term decline in FEV1.^{11,12} These effects were seen over a 14-20 year period. These studies had significant limitations in that they were retrospective and uncontrolled. In addition, a majority of the patients had positive bronchodilator responses, suggesting many subjects may have had underlying asthma.

Many studies have evaluated various clinical or laboratory parameters, in an attempt to identify predictive features of steroid responsiveness in patients with stable COPD. These included levels of **eosinophil cationic protein (ECP)**, immunoreactive neutrophil elastase-alpha1-protease inhibitor (NE-alpha1-PI) complex, IL-8, and inflammatory cells in induced sputum.¹³ Only the baseline eosinophil count in induced sputum has been shown to significantly correlate with reversibility of airflow obstruction following treatment with oral steroids.^{14,15} As mentioned above, another and more clinically useful predictor of steroid responsiveness is a positive bronchodilator response on routine spirometry.¹⁰

Acute exacerbations of COPD

The use of systemic corticosteroids in acute exacerbations of COPD has not been as well studied. Despite the widespread practice of using systemic steroids in acute exacerbations of COPD, the only well-designed study supporting their use up until 1996 was

that done by Albert et al. in 1980,¹⁶ which evaluated the benefit of intravenous methylprednisolone on bedside spirometry in patients admitted to hospital with a COPD exacerbation. Researchers found a greater improvement in both prebronchodilator and postbronchodilator FEV1 in the methylprednisolone treated group (approximately 15% increase). They found no significant difference in the FVC.

Another study looked at the effect of methylprednisolone given in the emergency department for acute exacerbations of COPD; that study found no improvement in FEV1 or FVC, and no difference in the rate of hospitalization after 5 hours.¹⁷ Of those patients who were discharged, there was no difference in the number who suffered a relapse and required unscheduled visits to the emergency department over the next 48 hours. In contrast, a more recent study with a similar design showed that the readmission rate was lower in the patients who received corticosteroids.¹⁸

Outpatient treatment of acute exacerbations of COPD with oral prednisone has also been evaluated. Thompson et al. showed that treatment led to a more rapid improvement in arterial PO₂, alveolar-arterial oxygen gradient, FEV1, and peak expiratory flow. Prednisone also resulted in fewer treatment failures and to a trend toward a more rapid improvement in dyspnea scale scores.¹⁹

In 1999, two studies were published in support of corticosteroids for acute exacerbations of COPD. The first investigated the effects of prednisolone 30mg once daily for 2 weeks versus placebo in patients admitted to hospital with COPD exacerbations.²⁰ After 5 days, there was a more rapid and greater increase in the FEV1, both pre- and post-bronchodilator, in the corticosteroid-treated group. Similar results were seen with the FVC. During the 1st week, significantly more patients in the placebo group than in the steroid-therapy group were likely to be withdrawn from the study. Hospital stays were significantly shorter in the steroid-therapy group (7 versus 9 days).

In the same year the Veterans Af-

fairs Cooperative Study Group published their results.²¹ They evaluated the effects of 2 and 8 weeks of steroid therapy versus placebo for patients hospitalized with acute exacerbations of COPD. Total patient enrollment was 271. Rates of treatment failure were significantly higher in the placebo group as compared to the steroid groups combined (33% vs 23% at 30 days, and 48% vs 37% at 90 days). Steroid therapy was associated with shorter initial hospital stays (8.5 vs 9.7 days), and with a greater FEV1 increase in the first 24 hours (100ml). At 6 months, there were no significant differences between the groups. There was also no difference between the 2 week and 8 week steroid groups in any outcome. There was a higher incidence of hyperglycemia requiring therapy in the steroid therapy groups as compared to the placebo group.

While inhaled corticosteroid therapy has established benefit in treatment of asthma, use of inhaled corticosteroids in patients with COPD is less well supported.



Thus, short courses of systemic steroids are indicated for COPD exacerbations. Only a minority of patients with stable COPD benefit from systemic steroids; good predictors of potentially responsive patients are those with a positive bronchodilator response, or a high eosinophil count in their sputum. Why this difference in responsiveness to steroids between acute exacerbations and stable COPD exists is not clear, though it has been postulated that there may be differences in the inflammatory response between these two disease states.

INHALED CORTICOSTEROIDS

While inhaled corticosteroid therapy has established benefit in treatment of asthma, use of inhaled corti-

costeroids in patients with COPD is less well supported. The safety of long-term, high-dose inhaled corticosteroids has not been well established. Inhaled steroids have been implicated in causing adrenal suppression,²² cataracts,²³ glaucoma,²⁴ and osteoporosis.²⁵

The guidelines on the use of inhaled steroids in COPD are somewhat vague, with discrepancies between published guidelines. The 1995 American Thoracic Society guidelines state: "The role of inhaled steroids in the treatment of COPD is less clear than in asthma. . . Benefits of aerosol steroids are insufficiently documented. . . Only 20-30% of COPD patients respond to oral steroids."²⁶ In contrast, the British Thoracic Society guidelines state: ". . . inhaled steroids should be given to patients who show an objective response to corticosteroids, either oral or inhaled. . . Those who do not respond should not continue on steroid therapy."²⁷

Despite the lack of consensus, the prevalence of inhaled steroid use in COPD patients is not only significant, but also increasing. In a recent study, a retrospective evaluation of baseline concomitant medication used by patients with COPD enrolled in 10 bronchodilator clinical trials from 1987-1995 was performed.²⁸ All these studies included only stable, moderate-to-severe COPD without evidence of asthma or atopy. They found that the percentage of these patients using inhaled steroids increased from 13% to 41% during this period.

In a recent retrospective study performed at the Providence VAMC,^{28a} we also evaluated the prevalence of inhaled steroid use in COPD patients. From a database of all patients on inhaled steroids (N = 661), we chose a random sample of 252 patients. We used a very liberal definition of asthma: positive bronchodilator test or methacholine challenge, eosinophilia, elevated IgE, documented responsiveness to systemic corticosteroid therapy, current oral steroid therapy. We found that 65% of our random sample met ≥ 1 criteria (56% asthma, 39% positive bronchodilator test). The remainder (35%) had COPD with irreversible airflow obstruction.

Many studies support the use of

inhaled steroids in patients with COPD which has an “asthmatic component,” most often selected based on having a positive bronchodilator test, but also if there is a personal or family history of asthma, or a history of exacerbation of symptoms by factors commonly implicated in precipitating asthma attacks.^{8,9} Studies evaluating short-term effectiveness of inhaled steroids in patients with irreversible airflow obstruction have provided conflicting results.^{10,29-33} In those studies where some benefit was demonstrated, those patients that responded frequently either had a positive bronchodilator test, an elevated serum IgE level, or an increased eosinophil count suggestive of an asthmatic component to their airflow obstruction.

The effect of inhaled steroids on the incidence of acute exacerbations in COPD patients has also been studied. Paggiaro et al. found no significant difference in the total number of COPD exacerbations with high-dose inhaled steroids when compared to placebo over a 6-month period; however, the exacerbations were less severe in the steroid-treated group.³⁴ These findings are in contrast to those of Bourbeau et al. who found no significant difference in the number or severity of COPD exacerbations between the treatment and placebo groups at 6 months.³⁵

The long-term efficacy of inhaled steroids in COPD is controversial. In a recent meta-analysis of previous inhaled steroid trials, with exclusion of the asthmatic patients in each trial, pre-bronchodilator FEV1 increased by 0.039L/year over a 2-year period of treatment with inhaled corticosteroid, as compared to placebo.³⁶ However, no benefit on the exacerbation rate of COPD was found. More recently, Pauwels et al. reported that subjects with mild COPD who continued smoking exhibited a small one-time improvement in lung function but the rate of decline in FEV1 over 3 years with long-term treatment with budesonide was not significantly different when compared to placebo.³³ Another recent report which also looked at the long-term effects of inhaled steroids in mild and moderate irreversible airways obstruction, came to the same negative conclusion, i.e. there

was no significant difference in the rate of decline of FEV1 compared to placebo during 3 years of treatment.³⁷ Of note, both of the latter studies involved patients with predominantly mild COPD. In contrast, both the ISOLDE trial from Britain³⁸ and the Lung Health Study³⁹ investigated the effects of chronic therapy with inhaled steroids in patients with moderate to severe COPD. Again, both demonstrated no significant difference in the rate of decline of FEV1 with chronic therapy; however, they did demonstrate benefits in other clinically relevant outcomes. The ISOLDE trial reported a reduction in the number of exacerbations, a decrease in the rate of decline in health status, and a decreased rate of withdrawal due to respiratory disease.³⁸ The Lung Health Study reported a reduction in respiratory symptoms, a decreased use of health care services, and improved airway reactivity.³⁹

Other supporting data for use of inhaled steroids in COPD includes that reported from the ISOLDE trial during the run-in phase.⁴⁰ Of the 272 patients enrolled, 160 were on inhaled steroids. As part of the run-in phase, they had their inhaled steroids stopped. Over the following 7 weeks, 38% of those who had been on inhaled corticosteroids suffered an exacerbation, versus 6% of those not previously on steroids. It is important to note that this was an observational study, and thus has many inherent limitations. Only the number of exacerbations was monitored. The authors did not assess lung function, quality of life, exercise capacity or dyspnea levels.

We have also investigated the effects of inhaled steroids in patients with “irreversible COPD”. In a prospective randomized cross-over trial, we evaluated the effects of withdrawal of inhaled steroids in this patient population over a 12-week period. All patients had severe COPD. Withdrawal of steroids led to a decrease in FEV1, increased number of exacerbations, and increased dyspnea with exercise (in press).

Are there any reliable factors that help determine which patients with COPD will respond to chronic inhaled steroid therapy? A response to a bron-

chodilator (as defined by the American Thoracic Society as a $\geq 12\%$ increase in either the FEV1 or FVC, with a minimum of at least 200cc of an increase),¹ is very frequently used to decide who should receive inhaled steroids.^{8,9} Other commonly used indicators of who may benefit from inhaled steroids include a personal or family history of asthma, seasonal or episodic dyspnea or wheezing, or atopy (history of allergy and positive skinprick test to common antigens). Distinguishing “reversible” from “irreversible” airways obstruction based on a bronchodilator test has many limitations. The reproducibility of the bronchodilator test is poor, and the percentage of patients with COPD who have a positive bronchodilator test increases with severity of airflow obstruction.⁴¹ In addition, there is a subgroup of patients with COPD, who despite having a negative bronchodilator test, respond to inhaled corticosteroids. It may be that this subgroup accounts for the conflicting results from the various studies looking at the benefits of inhaled steroids in patients with irreversible airways obstruction.

Response to a course of oral steroids has also been advocated. Wiener et al. found that approximately two thirds of patients who responded to a 6-week course of oral prednisone, also responded to a 6-week course of inhaled steroids.¹⁰ However, no relation between an oral steroid trial response and response to long-term inhaled steroids was found in the recent ISOLDE study.³⁸ Thus, it is clear that further investigation is warranted to help develop a more reliable method to help us identify these potential responders.

SUMMARY

COPD is a prevalent disease, with an increasing attributable mortality. Because inflammation plays a significant role in the pathogenesis of this disease, the use of anti-inflammatory therapies would appear indicated; hence the widespread use of corticosteroids in COPD. Although the majority of patients with stable COPD do not benefit from systemic steroids, there is good evidence supporting the use of short courses of systemic steroids

for COPD exacerbations. With respect to inhaled corticosteroids, the studies are conflicting. Those patients with an asthmatic component to their disease, or with a positive bronchodilator test, appear to benefit most from inhaled steroids. Those with irreversible disease do not benefit from short-term inhaled steroids. Long-term inhaled corticosteroids, though not having a significant effect on the rate of decline in spirometric indices, do appear to decrease the number of exacerbations and the rate of decline in health status, reduce respiratory symptoms, decrease use of health care services, and improve airway reactivity. These effects appear more marked in patients with moderate-to-severe disease.

Because very few therapies offer significant benefits to patients with COPD, and until a test is developed that will distinguish between potential steroid responders from non-responders, it is worthwhile giving all patients with COPD a trial (3-6 months) of inhaled corticosteroids to determine whether they are responsive.

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Obstructive Sleep Apnea: A Brief Overview For the Primary Care Physician

Naomi R. Kramer, MD

Obstructive sleep apnea (OSA) affects 2% to 4% of middle-aged adults.¹ It is even more common in the elderly. Although the primary care physician has the opportunity to play a pivotal role in the detection of this disorder, most physicians have had little or no formal training in OSA; and they frequently underdiagnose the disorder.^{2,3} The Walla Walla project² demonstrated that with several educational interventions for physicians and patients, the OSA detection rate significantly increased. This article will review the typical presentation of OSA, diagnostic tests, and treatment options as well as follow-up once treatment is initiated.

OSA is characterized by repetitive

partial or complete closure of the upper airway during sleep despite continued respiratory drive (Figure 1A4). The patient demonstrates increasingly negative intrathoracic pressures as increasing ventilatory effort is generated to attempt to open the airway. These events are usually associated with a brief arousal and/or an oxygen desaturation and transient hypercapnea. These repetitive respiratory-related arousals result in significant sleep fragmentation, which, in combination with the oxygen desaturation, result in subsequent daytime sleepiness and fatigue

An apnea refers to cessation of airflow for more than 10 seconds. An hypopnea is a reduction of airflow for 10 seconds. Both events are associated with continued respiratory effort. In contrast, central apneas have no airflow and no effort. The average number of apneas and hypopneas per hour of sleep is called the apnea-hypopnea index. The **American Academy of Sleep Medicine (AASM)** consensus statement⁵ suggests it is not necessary to distinguish between apneas and hypopneas. Instead, the term "respiratory events" should be used to refer to both because they have similar pathophysiology and consequence. More than five obstructed respiratory events per hour of sleep are considered abnormal.

The AASM consensus statement includes both symptoms and sleep study data in the definition of the **obstructive sleep apnea-hypopnea syndrome (OSAHS)**. OSAHS is defined as criteria A or B plus C. Criterion A: Excessive daytime sleepiness that is not better explained by other factors;

Criterion B: two or more of the following that are not better explained by other factors: choking or gasping during sleep, recurrent awakenings from sleep, unrefreshing sleep, daytime fatigue, impaired concentration; Criterion C: overnight monitoring demonstrates five or more obstructed breathing events per hour during sleep.

As these criteria suggest, fatigue and disrupted sleep are frequent symptoms of OSA. (Table 1)

Several recent studies have suggested that certain key symptoms and associations are useful in predicting who will have OSA. Kump, et al⁶ found that the three symptoms most predictive of OSA are: Self-reported snoring, witnessed apnea, and sleepy driving. The positive predictive value of their model was enhanced by including **body mass index (BMI)** and gender. Netzer, et al⁷ found a simple self-administered patient questionnaire helped identify patients at high risk for OSA. Key symptoms include persistent symptoms (≥ 3 to 4 times per week) in 2 or more questions regarding snoring, witnessed apnea or daytime sleepiness. Alternatively, persistent symptoms in conjunction with hypertension or obesity were suggestive of OSA. Simply adding questions regarding snoring, pauses, and daytime sleepiness to the primary care physician's review of systems will increase the likelihood of detecting obstructive sleep apnea. If the patient has no reliable bed partner, the lack of a history of snoring, pauses, etc. has less significance. One may then need to rely on other symptoms and associated medical conditions

The medical disorders most commonly associated with OSA include hypertension and upper body obesity. Approximately 50% of patients with obstructive sleep apnea have hypertension. Conversely, 25 to 30% of patients from a hypertension clinic will

Table 1. Symptoms of Obstructive Sleep Apnea

Snoring
Witnessed Apnea/gasping
Choking/shortness of breath arousals
Recurrent awakenings
Nocturia (three times per night)
Morning headache
Excessive daytime somnolence
Automobile accident or near miss
Decreased memory/concentration
Depression/irritability
Enuresis
Sexual dysfunction

Table 2. Risk Factors Associated with Obstructive Sleep Apnea

Hypertension
Upper body obesity
Male sex
Increasing age
Abnormal pharyngeal anatomy
Enlarged tonsils and adenoids
Redundant pharyngeal tissue
Retrognathia
Nasal obstruction
Excessive alcohol use
Untreated hypothyroidism
Acromegaly

have obstructive sleep apnea.⁸ A collar size ≥ 17 in men, ≥ 16 in women, is associated with an increased risk of OSA. Table 2 lists the predisposing or risk factors commonly associated with OSA.

Although the exact mechanism is still under investigation, sleep-related breathing disorders have been associated not only with hypertension, but also with cardiovascular disease independent of shared risk factors such as obesity, age and gender.⁸ **Sleep-related breathing disorders (SRBDs)** have also been associated with an increased risk of stroke. It is not yet clear whether this association is due to the increased stroke risk associated with hypertension or whether SRBD is an independent risk factor.⁸ In either case clinicians should have a high index of suspicion for OSA in patients with cardiovascular and cerebrovascular disease.

Although obstructive sleep apnea does not occur more commonly in patients with **chronic obstructive pulmonary disease (COPD)**, patients with both COPD and OSA (termed the overlap syndrome) may present with hypercarbia, polycythemia, and cor pulmonale at an earlier point in their disease (i.e. FEV1 > 1 liter) than if they had COPD alone. A patient with significant hypercarbia and an FEV > 1 liter should prompt a search for a concomitant disorder such as OSA or obesity hypoventilation.

Although a complete medical examination is important in the evaluation of patients for sleep apnea, certain key aspects of the examination should get special attention; specifically, weight (or BMI), blood pressure, nose, and oropharynx. It is important to note whether the nasal passages are patent or obstructed by polyps, swollen turbinates, or boggy mucosa. Snoring and obstructive sleep apnea can be created in normal non-apneic patients by plugging the nose. Visualization of the palate, uvula, tonsils, and lateral pharyngeal walls is helpful in understanding what factors may be affecting an individual's breathing during sleep.

Once the clinical history suggestive of obstructive sleep apnea is obtained and physical examination

performed, it is appropriate to consider an overnight sleep study. Full polysomnography (16 channels or more) yields the most information regarding sleep architecture, respiratory events, associated arrhythmias, oxygen saturation, and concomitant sleep disorders. It currently remains the gold standard to evaluate sleep disorders. Portable 4-channel studies are helpful in confirming a diagnosis of OSA. However, more subtle respiratory events associated with sleep fragmentation rather than oxygen saturation may be underestimated because sleep is not monitored. Similarly, portable respiratory studies are inadequate to evaluate a general complaint of excessive sleepiness which may be due to other causes such as periodic limb movement disorder. More complicated multichannel home monitors may prove useful in the assessment of OSA. Lastly, night-to-night variability in the frequency of respiratory events has been described in patients with OSA. Therefore, even a single "negative" polysomnogram may not rule out OSA in cases of high clinical suspicion.

Treatment involves behavioral interventions in conjunction with medical, dental or surgical interventions. Obesity, alcohol, tobacco, and sleep deprivation have all been shown to exacerbate OSA. Therefore, behavioral

intervention should be aimed at weight loss, reducing evening alcohol consumption, tobacco cessation and avoiding sleep deprivation. Avoiding the supine position in bed may also be helpful for some patients.

Positive airway pressure is the most effective intervention for OSA.⁹ This is most often delivered in the form of **continuous positive airway pressure (CPAP)** which applies positive pressure throughout the upper airway preventing collapse (Figure 1B). The patient wears a mask over the nose (or nose and mouth) which is attached via tubing to a "blower" and in-line humidifier. Usually a second polysomnogram is performed to titrate CPAP to the optimal pressure which eliminates snoring and obstructive events. Once the best pressure is determined, CPAP is set up at the patient's home by a medical equipment company with whom the patient's insurance company has a contract.

The array of new masks and the development of heated humidification have made CPAP much more user-friendly. If a patient feels uncomfortable exhaling against CPAP, bi-level positive airway pressure may be tried. Patients with severe COPD and hypercarbia may feel more comfortable with an expiratory pressure set 4 to 5 cm lower than the inspiratory pressure

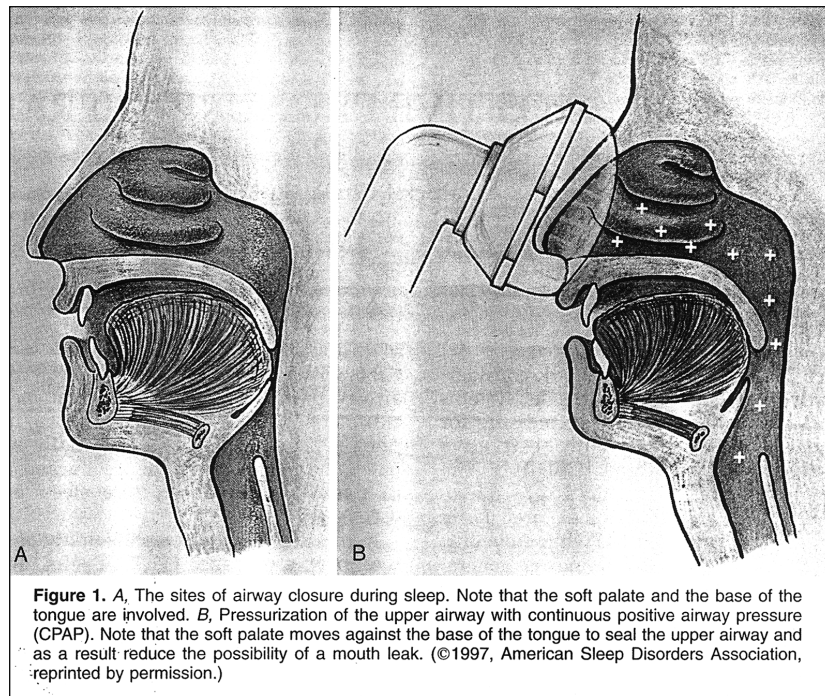


Figure 1. A, The sites of airway closure during sleep. Note that the soft palate and the base of the tongue are involved. B, Pressurization of the upper airway with continuous positive airway pressure (CPAP). Note that the soft palate moves against the base of the tongue to seal the upper airway and as a result reduce the possibility of a mouth leak. (©1997, American Sleep Disorders Association, reprinted by permission.)

rather than having a continuous pressure. CPAP is extremely effective for most patients. However, compliance is in the 50% to 70% range. This is not significantly different from compliance with other pulmonary treatments.¹⁰ With the addition of new masks, new pressure settings, and heated humidification, compliance will hopefully improve.

Dental appliances work by moving the lower jaw and hence the tongue forward away from the palate and posterior wall of the pharynx. Eveloff et al¹¹ found that it also elevates the palate. The overall efficacy of a dental appliance for mild to moderate OSA is approximately 60%. The better appliances are adjustable so that the position of the jaw may be adjusted according to tolerance and symptoms. A follow-up sleep study with the dental appliance in place is necessary to document adequate control of OSA. Severe OSA is not likely to be controlled with a dental appliance alone.

Surgical options for OSA include traditional uvulopalato-pharyngoplasty (UPPP) alone or in conjunction with procedures to move the lower jaw forward.¹² Tracheostomy is extremely effective but rarely offered now because of its cosmetic effects and associated complications and because CPAP is so effective. The overall efficacy of UPPP is approximately 50%. Laser uvuloplasty (which removes less tissue) should be considered only for snoring not OSA. For patients with OSA who demonstrate narrowing posterior to the tongue, other procedures such as the inferior sagittal mandibular osteotomy and genioglossal advancement with hyoid myotomy and suspension (GAHM) may be considered. Bi-maxillary mandibular advancement (LeForte 1 procedure) has also been done for obstructive sleep apnea. The Stanford group¹² has studied this extensively and has found a high success rate. However, lower success rates have been published from other centers. This more invasive procedure is usually reserved for those who fail UPPP or GAHM or have significant craniofacial abnormalities. It should be performed in centers experienced with this operation.

Because the overall efficacy of the standard uvulopalatopharyngoplasty is not high, all OSA patients who undergo surgery should have a follow-up sleep study approximately three months after surgery to reevaluate the degree of residual sleep apnea. They may show some improvement in symptoms and snoring with continued underlying significant sleep apnea.

The reason to treat OSA is to alleviate symptoms and to decrease the associated morbidity and mortality. Excessive sleepiness, impaired concentration, neurocognitive function and mood have all been shown to improve with CPAP treatment of obstructive sleep apnea.¹³ Similarly, Findlay et al¹⁴ has shown that performance on driving simulator tests significantly improves after CPAP is initiated.

... clinicians should have a high index of suspicion for OSA in patients with cardiovascular and cerebrovascular disease



Reduction in blood pressure has been demonstrated in hypertensive patients following treatment of OSA with CPAP. Similarly, mortality data from He, et al¹⁵ showed that for patients with severe OSA, both CPAP and tracheostomy, but not UPPP were associated with improved survival compared to no treatment. Partinen, et al¹⁶ demonstrated that patients with OSA successfully treated (by tracheostomy) had fewer cardiovascular events than those who were conservatively treated (weight loss recommendation).

Office follow-up for patients with sleep apnea following treatment should include questions again regarding residual snoring, witnessed pauses, excessive daytime sleepiness, sleepy driving, mood and neurocognitive function. If the patient is using CPAP or a dental appliance, it is important to ascertain how many nights per week

and how many hours per night they are using it. Nasal symptoms may limit CPAP use. Therefore, specific questions regarding nasal congestion and coryza need to be asked. Symptoms may improve with use of topical nasal steroids or oral antihistamines. The use of an in-line heated humidifier with CPAP significantly increases moisture delivery to the upper airway and decreases nasal irritation and symptoms. This is especially important in New England where indoor heating dries out the air.

Other questions that are important in follow-up for patients on CPAP regard comfort with their mask and skin integrity. Pressure points may be alleviated with small pads or cushions. A dry mouth in the morning may point to air leaking through the mouth, which a chin strap may ameliorate. Mask and head straps do wear out and need to be replaced periodically. Patients' use or tolerance of the machine may decrease as the materials wear. They may be more comfortable with new equipment. Lastly, if the patient redevelops symptoms of excessive sleepiness or snoring or has a significant weight change while on CPAP, it would be reasonable to reevaluate the optimal pressure with a repeat sleep study.

In summary, OSA is a common disorder with significant morbidity and mortality. The morbidity relates to the sleepiness and associated automobile accidents, associated cardiovascular diseases, and neurocognitive and personality changes. In the review of systems, the primary care physician can easily screen for this treatable, but often overlooked, disorder. In addition, if a patient complains of fatigue or snoring, a more detailed history regarding other sleep symptoms is appropriate.

If symptoms and/or associated disorders suggest OSA, it is reasonable to refer the patient to a sleep center for further evaluation. Once treatment is initiated and the patient stabilized, the primary care physician can join the subspecialist in screening for recurrence of OSA symptoms and assessing compliance with treatment.

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End of Life Issues In the Critically Ill

Nicholas S. Ward, MD, and Aidan O'Brien, MD

The process of dying has changed drastically in the last century. In the past, doctors simply did all they could for a patient. When their treatments failed, their patients died, almost always in their homes. Currently, in the United States about 80% of people die in a healthcare facility (60% in acute care facilities),¹ despite the fact that about 90% of Americans polled say they would wish to die at home.² This disparity is caused by two factors. First, many people die while undergoing treatments meant to postpone death. Second, many families feel they are unable to care for a dying person or are uncomfortable having a loved one die at home. The net result is that most people will die in a hospital, or other healthcare facility, and most likely undergo high levels of medical care. The Robert Wood Johnson Foundation estimates that about 20% of Americans will die in an intensive care unit or be treated in an intensive care unit just prior to death.

Two conclusions can be drawn. First, a tremendous amount of healthcare is being delivered to dying patients. This has been reflected in several studies like that of Cher and coworkers in 1997 showing that a relatively large percentage of Medicare expenditures goes to treat patients in the last weeks of their lives.⁴ Second, doctors practicing in America today must learn skills not necessary in the past. Doctors need to recognize patients who are going to die despite medical care and help decide which of the medical therapies are appropriate and which are not. They need to guide their patients through a maze of medical options in an attempt to balance preservation of life with quality of life, a daunting task. This paper will review some of the major medical, ethical, and legal issues involved in these end-of-life decisions. This paper will focus only on patients who become critically ill acutely, not those with long-term, progressive, terminal illness.

HOW ARE CRITICALLY ILL PATIENTS DYING IN HOSPITALS?

Most Americans today are dying in healthcare facilities. Furthermore, studies have shown that the vast majority of these deaths, about 75% or more, occur only after the patient, or family, has decided to limit care.⁵⁻⁷ In two landmark studies, Predergast and coworkers helped define just how patients die in ICUs. In their first study, they compared deaths in their ICU from two time periods, 1987-88 and 1992-93, to determine how often CPR was performed prior to death and how often limits were placed on care prior to death. Their data showed that the incidence of CPR in their ICU had declined from 49% to 10% and that the incidence of limiting care by withholding or withdrawing some therapy had increased from 51% to 90% of all ICU deaths.⁸

To compare their data with the rest of the country, the same investigators did a large follow-up study, a year later. They collected data from over 6,000 patient deaths occurring in 131 ICUs in 38 states over a 6 month period and analyzed the data for the incidence of various limits of care. They found that on the average only 25% of patients dying in ICUs got CPR prior to death. About 70% of patients had some restriction on care prior to death and almost 50% of patients actually had some medical therapy withheld or withdrawn prior to death.⁶ It is important to note that these were deaths occurring in an ICU, a place established for the most aggressive care.

The other data to emerge from this study was the variability among ICUs. The incidence of patients dying with full aggressive measures ranged from 4% in one ICU to 79% in another. Likewise, the incidence of withdrawing medical support ranged from 0% to 79%, depending on the ICU. While the overall practice of limiting care in ICUs is common, there is tremendous variability from place to place in end-of-life care.

WHO DECIDES?

Surrogate Decision making

The vast majority of people will die with some limit of care in place, whether in or out of an ICU. Unfortunately, the patient rarely participates in these decisions. Someone else generally decides to limit a dying patient's care 60 to 70% of the time.^{7,9} Only about 15 to 20% of patients have an advance directive at admission to hospital; and those advance directives are often inadequate to handle anything but the most obvious treatment decisions. Therefore, the burden of difficult decisions falls to a proxy (a legal delegation) or surrogate (a non-legal delegation). Most often, this is a family member.

The process of surrogate decision making is fraught with problems. While most would agree that family or friends are the best people to decide for the patient, several studies have shown that patients rarely discuss specific treatment options with their proxies; and surrogate decisions correlate poorly with what the patient would actually want done.^{10,11} Furthermore, a study by Hare et al. showed that surrogates often valued different aspects of dying, such as pain and suffering, than the patients, who were more concerned with burdening families and amount of time left to live.¹⁰

Legal Issues

All fifty states recognize the legality of a patient's right to refuse medical care although there remains some controversy and confusion about specific issues. The legal issues involved in proxy decision-making can be confusing. Perhaps because it is impossible to account for the many family and social relationships that may be the source of medical surrogates, most states have few laws dealing with this issue and have purposely kept the codes vague and malleable.¹² Most states, including Rhode Island, will accept a

properly drafted written advance directive as sufficient legal guidance to limit care. Unfortunately, most advance directives or living wills are too vague, using phrases such as “terminal illness” and “little chance of recovery” that are subject to interpretation. COPD and congestive heart failure may be considered terminal illnesses by some people and not by others. In contrast, some people may consider diseases such as early stage lung cancer not eminently terminal.

Nevertheless, these directives can help prevent futile or unwanted care when no other surrogate is available. More often they are useful in family decision-making when an unconscious patient faces potentially futile care. The previously stated wishes of the patient in an advance directive can assuage guilt or uncertainty regarding end-of-life decisions. They can also be helpful when surrogates disagree as to a course of action. Since a surrogate, by definition, represents what the patient would decide if able, the advance directive can be a helpful guide.

Sometimes advance directives can spur discord - for instance, when the written directive differs from a surrogate's decision. In most states including Rhode Island, the law recognizes a properly drafted and witnessed directive as the legal opinion that should be followed; however, many physicians would be wary of ignoring the requests of a living surrogate, especially if it is a spouse or other close family member. In such situations, attempts should be made to build consensus among all parties prior to making any decision. Most state laws regarding written advance directives also allow for some flexibility in the physician's obligation to follow them. For example, if a physician questions the validity of the directive or feels ethically unable to follow the directive, in most states the directive will not be binding.

Predicting Outcomes

A central problem complicating end-of-life decisions is the difficulty of predicting outcomes in critically ill patients. The combination of multiple

coinciding medical problems and rapidly changing clinical status can make this a very difficult task. Essentially the physician has three tools: published outcomes, severity scores, and personal experience. All can be helpful yet all have limitations.

Perhaps the most glaring problem of severity scores is that they say nothing about morbidity, disability, or survival after hospitalization.



Severity Scores

Severity Scores have been available for almost three decades. In most severity score algorithms data are collected during the first twenty-four hours of admission and used to compile a score that, theoretically, predicts risk of death during hospitalization. These scoring systems were developed by reviewing data from thousand of ICU patients and employing logistical regression models to choose some important input variables. Other variables were simply chosen based on presumed clinical value. These scores were then validated prospectively on patients.

Unfortunately, there are several problems with these systems. First, these scoring systems make predictions based on hospital outcomes at the time of their creation. As medical treatments improve, the scores need to be updated. In the 1970s, for example, ARDS had a mortality approaching 80%; thus the diagnosis might justifiably increase a patient's severity score. Today ARDS has about a 40% mortality; thus a severity scoring system employing the diagnosis of ARDS, or even components of the diagnosis such as hypoxemia, would need to be adjusted. Some commercially available proprietary severity scoring systems such as APACHE III® are updated and revalidated on a regular basis to avoid this problem but many widely in use

today, such as APACHE II, are based on patient data collected as long as two decades ago.

Also, most models derive their predictions from factors present at or shortly after admission to the ICU, and do not provide updated mortality estimates as the patient's condition changes. Furthermore, severity scores often give intermediate mortality estimates such as 60% instead of clear yes or no answers. Even these numbers are subject to confidence intervals. Perhaps the most glaring problem of severity scores is that they say nothing about morbidity, disability, or survival after hospitalization. These factors are often just as important as risk of death in making end-of-life decisions. A patient may accept a 30% chance of survival if it were followed by a high quality of life, while not accepting a 70% chance of survival if it were likely to entail a poor quality of life.

OUTCOMES RESEARCH

Many of the same problems encountered with severity scores apply to outcomes data. While published outcomes studies remain an essential tool for helping clinicians predict a course of illness, they suffer from two major problems.

First, the population studied for a particular illness may not share the same characteristics as your particular patient. In a recent large multicenter clinical trial of a new therapy for sepsis, the mortality in the control (untreated) population was 31%.¹³ It is important to note, however, that this trial excluded patients with renal failure, liver failure, pancreatitis, AIDS, and variety of other co-morbid conditions, thus limiting the usefulness of these data for prognostic purposes.

Second, therapies can change and improve rapidly. In a series of four published studies by different authors between 1981 to 2000 examining the mortality of *pneumocystis carinii* pneumonia in ICU patients, the mortality decreased from 86% to approximately 50%.¹⁴⁻¹⁷ Similar changes in outcome over time have been reported with a variety of other illnesses such as ARDS as treatments have improved.

PATIENT AUTONOMY VS. MEDICAL PATERNALISM

A central problem to the end-of-life decision making-process is defining the role of the physician. Usually the physician is a combination of educator and advisor, but this is not always the case. In the past physicians were more likely to dictate courses of action or treatment plans for their patients, a concept referred to as medical paternalism. In many parts of the world to this day, medical decisions are made this way, with little input from the patient or family. In these cultures patients are comfortable with this kind of decision-making. More recently in the United States, the concept of patient autonomy has dictated medical decision-making. In its extreme form, patient autonomy holds that the physician's role is to educate the patient about the problem and offer plausible treatment plans, with their risks and benefits. The patient would then independently choose a course of action. Many physicians use this model of practice today, or a variant of it, feeling that it empowers patients, freeing them from physician bias.

In contrast to this philosophy, many physicians and patients feel the physician is obliged to offer a recommend course of action. While the discrepancies outlined here may not be of great significance in deciding whether to choose one medication over another, they take on tremendous significance when the decision is life or death. Ultimately, each physician must determine the degree of involvement he or she feels is warranted in end-of-life decisions.

CONCLUSION

In summary, the process of dying in America is changing rapidly. While the physician has always had an important role in the dying process, that role has now changed. Today's physician must not only be adept at administering comfort measures, he or she must decide when to initiate those measures over other therapies aimed at

restoring health. Because the dying process now involves the healthcare system more and more, physicians need to have good end-of-life skills more than ever. Failure to address these issues will result in patients getting more potentially futile care at the expense of their own comfort and increasing costs to the healthcare system.

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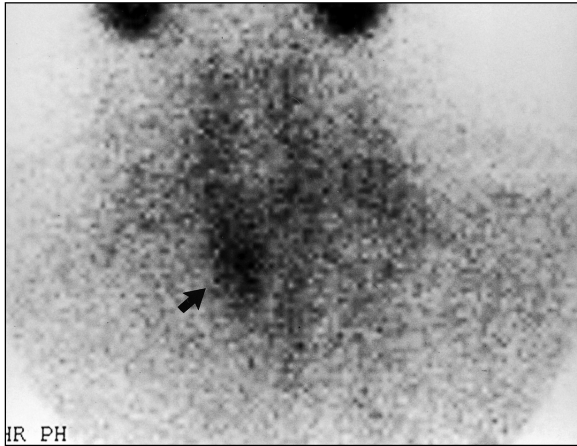
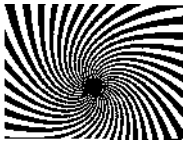


Figure 1.

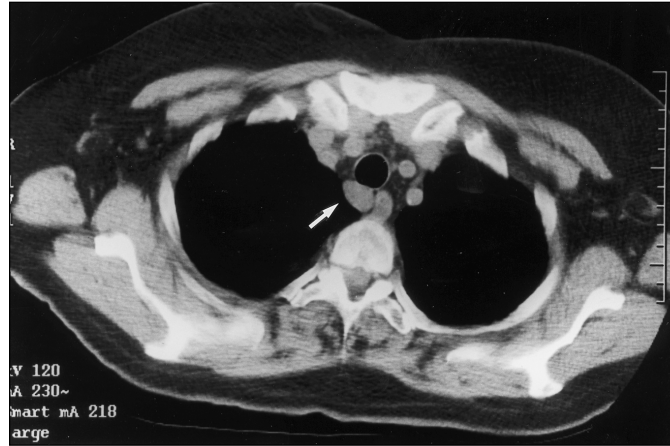


Figure 2.

Retrotracheal Parathyroid Adenoma

A 70 year-old female had elevated serum calcium on routine biochemistry profile. Her parathyroid hormone level was subsequently found to be in the 200-300 mg % range (normal up to 72mg %). As part of the diagnostic work-up, a parathyroid scan was performed using Technetium-99m sestamibi, which showed a persistent focus of abnormal increased activity posterior, inferior, and medial to the right lobe of the thyroid gland [Figure 1]. The neck ultrasound was normal. Computed tomography of the neck was performed [Figure 2], which demonstrated a 1 cm mass (arrow) posterior to the right aspect of the trachea, corresponding to the finding on the parathyroid scan. The mass was resected and proved to be a parathyroid adenoma.

Approximately 3% of parathyroid adenomas are located ectopically within the mediastinum. Preoperative localization reduces the morbidity and surgical exploration time when the adenoma is in an ectopic location. Most studies show a sensitivity for detection of parathyroid adenomas of 90% using technetium 99m-sestamibi, with less sensitivity for MRI, CT scan, or ultrasound. In this case, the retrotracheal position of the adenoma obscured its visualization on ultrasound.

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Update On Treatment For Congestive Heart Failure

Andrew Sucov, MD

BACKGROUND

Congestive Heart Failure (CHF) is a common diagnosis in the United States, with approximately 1 million hospital admissions and 40,000 deaths yearly attributable to it.¹ In Rhode Island, the impact of CHF is also large - approximately 3,500 admissions and 80 deaths annually (personal communication from RI Department of Health). In late 1994, the **Agency for Health Care Policy and Research (AHCPR - now AHRQ)** released a guideline for management of CHF, which was updated in 1999. This review will predominantly focus on two treatment modalities - the use of ACE inhibitors and spironolactone. Other common treatments will be summarized at the conclusion of the review.

PATHOPHYSIOLOGY

CHF is the end result of myocardial damage or overload, usually as a result of atherosclerotic cardiovascular disease. The heart is not capable of keeping up with the body's demand for oxygenated blood, leading to neurohumoral activation throughout the body, most notably an increase in adrenergic tone and stimulation of the **renin-angiotensin-aldosterone (RAA)** system. These responses, when kept in balance, enable the heart to function further along the pressure-volume (Starling) curve and maintain cardiac output; but when they become out of balance, serve to put additional stress on the heart and overload the body with fluid. Chronic management seeks to rebalance the physiologic changes and enable the heart to perform, without producing systemic side-effects, along with preservation or even improvement of cardiac function.

ACE INHIBITORS

ACE inhibitors have reproducibly been shown to reduce mortality and reduce progression of disease, especially in patients with higher **New York Heart Association (NYHA)** levels of disease severity.^{1,2} As a result of their efficacy and safety, the guideline and major textbooks recommend them as standard treatment for virtually all patients with CHF, especially those with systolic dysfunction (LVEF < 40%). ACE inhibitors function via two different pathways - vasodilation and blocking renin-angiotensin-aldosterone. In acute management, ACE inhibitors function primarily as vasodilators, improving cardiac output.³ On a chronic basis, their role is more attributable to local moderation of renin-angiotensin-aldosterone levels.² These help limit vasoconstriction and water retention. Given their generally well tolerated status and clear impact on mortality, current recommendations would suggest that these should be first line agents, used ahead of diuretics, in patients of any functional class. While patients may symptomatically improve at low doses, higher doses have been shown to reduce mortality and patients should be titrated to these

levels when possible (captopril 150 mg/d, enalapril and lisinopril 20 mg/d).²

Up to 10% of patients may have contraindications to ACE inhibitors. A new class of agents, the **angiotensin receptor blockers (ARB)**, seems to avoid the angioedema and cough side effects. While it would appear that these agents should have similar impacts on CHF morbidity and mortality as ACE inhibitors, the literature to date does not support a mortality benefit in CHF patients.⁴ Until literature supports a mortality benefit, the ARB should remain second line. Another second-line alternative for patients with ACE inhibitor contraindications is the combination of hydralazine and nitrates.²

SPIRONOLACTONE

Spironolactone is an aldosterone antagonist and a weak diuretic on its own. In combination with either other diuretics or ACE inhibitors its effect on volume status may be quite significant. The benefits of spironolactone are two-fold - it does not have the same negative effects on electrolytes as the most commonly used diuretics, and as aldosterone is an essential component of the neurohumoral response to CHF, use of spironolactone makes mechanistic sense to combat the deterioration in function and mortality.⁵ The major concern for increased use of spironolactone is on potassium levels, as both ACE inhibitors and spironolactone may elevate the levels. Close monitoring should accompany any switch in diuretic medication. A recent report suggests that addition of spironolactone to standard treatment (ACE inhibitors, beta blockers and diuretics) led to reduced mortality and hospitalization in patients with NYHA class III or IV CHF.⁶ As this is only a single well-performed study, its results can't be seen as conclusive for all patients. Regardless, the original guidelines suggest using spironolactone in patients with NYHA class IV CHF, further supported by this study. Additional studies may extend these results to patients of less severe dysfunction.

OTHER TREATMENT OPTIONS

For patients in NYHA class II or III failure, beta blocker (beta-1 selective or mixed alpha and beta blocker) use is considered to be first line, along with ACE inhibitors.² They appear to have a greater effect on mortality than ACE inhibitors, likely because of effects on neurohumoral status, arrhythmia suppression and reversal of pathophysiologic cardiac remodeling (carvedilol may also increase LVEF).⁷ Contraindications include advanced AV block, MNA class IV failure and significant reactive airway disease.

Traditional diuretics have powerful effects on volume status, but no evidence suggests a mortality benefit. There is a significant negative effect on potassium and magnesium, which may predispose patients with CHF to arrhythmias. Routine use should be

limited to patients with fluid retention, and typically in combination with ACE inhibitors and beta blockers.²

Digoxin use has declined in the past few decades. No evidence suggests a mortality benefit in CHF. Electrolyte imbalances and toxicity are significant concerns, especially when combined with diuretics. Digoxin may be useful in patients who are unresponsive to ACE inhibitors and beta blockers or those with atrial fibrillation requiring rate control.²

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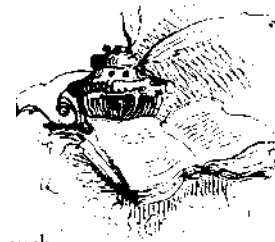
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6SOW-RI-HF-02-06

– A Physician's Lexicon –

A Radical Perspective on Words



The radiologist, enjoying the radiant sunshine of a glorious spring morning, interrupted his lunch of irradiated radishes to examine the forearm of a political radical thought to have sustained a limb fracture. One look at the X-rays, however, eradicated any doubt that the radius had indeed been fractured.

This contrived paragraph contains eight words, of widely different meaning, each a descendant of the Latin word, *radix*, meaning root.

Mathematicians preceded physicians in exploiting the word, *radix* [as well as its plural, *radices*, and its diminutive, *radicle*]. They defined *radix* [or, in English, radius] as any straight line connecting two points; more specifically, as a measurement of any linear spoke between the center and its surrounding circle. A radius then came to mean any extension from some central point spreading [or radiating] out in all directions. Early anatomists perceived the principal forearm bone, the radius, as a spoke extending from the trunk of the body to its periphery. The neuroanatomists were also not shy in expropriating *radix*. The proximal nerve roots of the spinal cord are named the radicles; and inflammatory disease of these structures, radiculitis.

Language usage over the centuries corrupted the word *radix* to the word, ray, confining its meaning to a beam of light extending outward from a solitary source of illumination. [But when physicists then demonstrated that there were rays other than those within the range of visible light, the

meaning broadened to embrace such entities as X-rays and gamma rays.] Physicians trained in the diagnostic and therapeutic uses of these rays were called radiologists, and these emanations came to be known as radiations [and when intentionally generated, the process was called irradiation].

A shiny new fabric was synthesized by chemists during the last century. Because it glistened, they called it rayon.

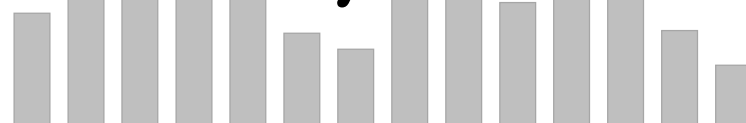
As science contrives new technologies, the belabored word, *radix*, was repeatedly incorporated into many new words such as radio, radium, radioactive, radiobiology, radiopelvimetry, radectomy [the extraction of dental roots] and even radar [an acronym of Radio Detecting and Ranging].

Botanists, perhaps because they are more grounded in earthy reality, retained the original Latin meaning of *radix*; and thus small plant roots are called radicles and a particularly pungent root-derived vegetable is called a radish.

To a mathematician, a radical is a numeral which modifies a numeric root. But to an earlier historian a radical was a person who sought out the fundamental or root meaning of things. Gradually, though, a radical came to mean an extremist, someone favoring extreme solutions to social problems. The word has now taken on a negative connotation as when Robert Frost said: "I never dared be radical when young for fear it would make me conservative when old."

– Stanley M. Aronson, MD

Health by Numbers



Rhode Island Department of Health
Patricia A. Nolan, MD, MPH, Director of Health

Edited by Jay S. Buechner, PhD

Health Status, Access to Care, and Health Risk Behaviors Among Urban Rhode Islanders, 2000

Jay S. Buechner, PhD, Colleen Ryan, MPH, Jana E. Hesser, PhD

One of two defining goals of Healthy People 2010 is “to eliminate health disparities among segments of the population, including differences that occur by gender, race or ethnicity, education or income, disability, geographic location, or sexual orientation.”¹ At the national level the discussion of differences by geographic location emphasizes the elevated rates of mortality and morbidity from injury and from chronic and infectious diseases among residents of rural areas, as well as their lower utilization of preventive screening services and higher prevalence of risky behaviors.¹

In a highly urbanized state such as Rhode Island, rates for many adverse health outcomes and risky behaviors are higher in core urban areas than in the surrounding suburbs, small towns, and rural areas.² The reasons for these elevations are much the same as for rural areas in other parts of the country; i.e., lack of health insurance coverage, poverty, low educational achievement, inadequate access to health care providers, and riskier occupations. Here we present data from the 2000 Behavioral Risk Factor Surveillance System (BRFSS) on the differences in behavioral health risks faced by residents of five core urban areas compared with residents of the rest of the state.

Methods

The Rhode Island Department of Health (HEALTH), through the BRFSS, has surveyed a sample of Rhode Island adults by telephone each year since 1984 concerning key health risk behaviors, health insurance coverage, and participation in health screening. Funded by the Centers for Disease Control and Prevention (CDC), Rhode Island’s BRFSS is part of a national effort covering all 50 states, DC, and three territories that monitors these health risk factors.³

In 2000, HEALTH’s professional survey contractor for the BRFSS conducted 3,544 interviews (approximately 295 each month) of randomly selected Rhode Island residents ages 18 and older living in households with telephones. CDC defines the methodology used for the BRFSS by all BRFSS participants.³

The BRFSS asks for information on town of residence from each respondent. The five Rhode Island cities grouped as core urban were Central Falls, Newport, Pawtucket,

Providence, and Woonsocket. In the 2000 Census, they had a total population of 335,473 (32.0% of the state’s 1,048,319 residents) and 977 BRFSS respondents (28.6% of the 3,421 providing city/town of residence). The remaining 34 cities and towns had a total population of 712,846 (68.0%) and 2,444 BRFSS respondents (71.4%).

Results

In 2000, urban residents among BRFSS respondents in Rhode Island were more likely to report their general health status as fair or poor (21%) than their suburban and rural counterparts (12%). (Figure 1) This disparity was not mirrored in the selected specific health status measures on the survey, where urban residents showed prevalence rates either similar to (asthma, diabetes) or lower than (arthritis, permanent tooth loss) other residents.

On three measures of access to health care collected by the BRFSS, urban residents were uniformly more likely to report limited access than other respondents. They were more likely to lack health insurance and less likely to have had a routine medical checkup or a dental visit during the past year. (Figure 1)

Table 1. Definitions of Health Risk Indicators

Indicator	Definition
Poor or Fair Health	Self-rated general health is fair or poor
No Routine Checkup	Has not had a routine health checkup within past year
Uninsured	Has no health care coverage (ages 18-64 years only)
Current Smoker	Smokes cigarettes regularly or occasionally
Overweight	Body mass index (BMI)* ≥ 25.0 kg/m ²
Too Few Fruits and Vegetables	Eats fewer than 5 servings of fruits and vegetables a day
Currently Has Asthma	Ever been diagnosed with asthma by a physician and currently has asthma
Ever Had Arthritis	Ever been diagnosed with arthritis by a physician
Ever Had Diabetes	Ever been diagnosed with diabetes by a physician, other than during pregnancy
No Dental Visit	Has not seen a dentist within past year
Permanent Tooth Loss	Has lost one or more permanent teeth due to decay or infection

*BMI is defined as weight in kilograms divided by height in meters squared.

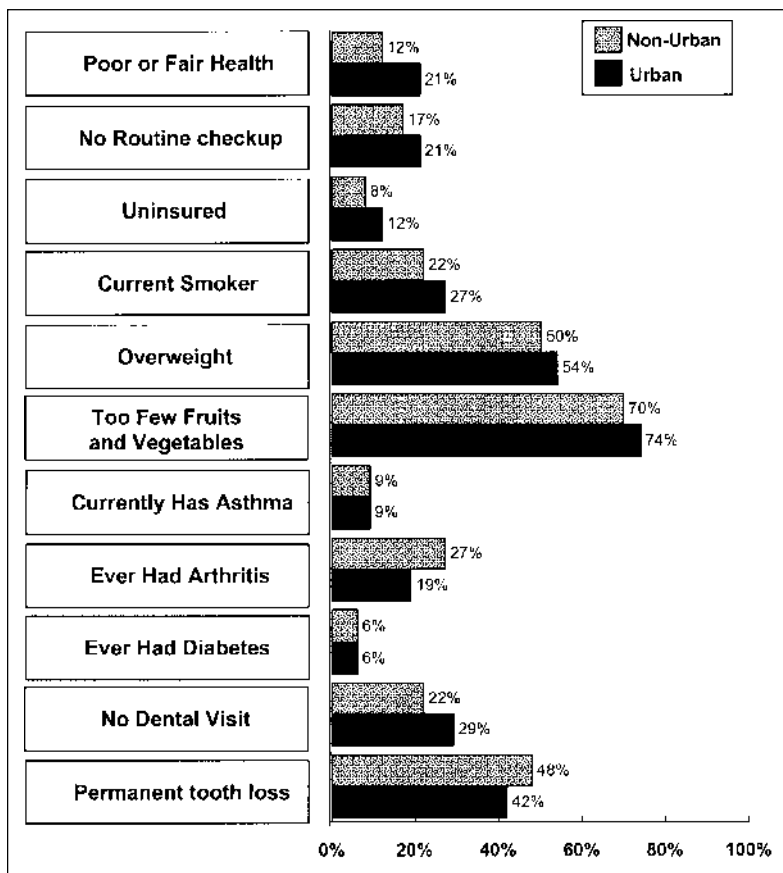


Figure 1. Health Risks among Adults Ages 18 and Older, by Urban Residence.

Urban Rhode Islanders were also more likely to participate in certain risky health behaviors than other respondents. More of the urban respondents smoked cigarettes and were overweight, and fewer reported eating five or more servings of fruits and vegetables per day. (Figure 1)

Discussion

Residents of core urban areas in Rhode Islanders fare worse than suburban and rural residents in measures of access to health care and health risk behavior, as well as in a global measure of health status. These patterns may stem from other characteristics of urban residents that are related to health, such as low incomes, lack of access to nearby health care providers, minority race and ethnicity, and lack of health coverage. Previous analyses of HEALTH survey data have described the association of some of these underlying factors with health indicators,^{4, 6} and the results of those studies can help illuminate the results presented here.

Currently, many of the efforts in the state to address health disparities among urban residents target population segments defined by poverty, race and ethnicity, and lack of health coverage. Examples are programs in the areas of nutrition (WIC), maternal and child health services, women's cancer screening, minority health promotion, and health care coverage (RIte Care, RIte Share). Some programs have a geographic component to their targeting, such as programs to prevent lead poisoning

among children, which target areas with high proportions of older housing, and federal programs to ameliorate differences in the supply of health care professionals. It is of note that under one such federal program, all five of the cities grouped as core urban in this study are designated as shortage areas, either for their entire populations or for residents with family incomes under 200% of the federal poverty level.⁷ In combination, these programs are working toward the objective of eliminating the health disparities between urban and other Rhode Islanders by the year 2010.

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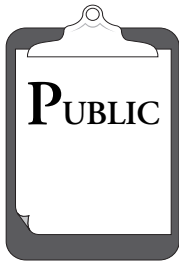
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Quick Reference Guide For Asthma Diagnosis and Treatment

The National Heart, Lung, and Blood Institute (NHLBI) first issued Guidelines for the Diagnosis and Management of Asthma in 1991.¹ At the time, it was considered a landmark in the management of asthma, and the publication of an updated version of the Guidelines in 1997 was considered no less important.² In community planning sessions conducted by the Rhode Island Asthma Control Program, primary care physicians, pulmonologists, allergists, and emergency medicine physicians alike have referred to the Guidelines as a major asset in the physician's armamentarium against asthma, the "gold standard" against which all approaches to asthma management should be evaluated.

Nonetheless, the Guidelines has not been widely used in front-line medical practices. Like many "gold standards," the Guidelines is comprehensive, complex, and cumbersome. The latest version is almost 150 pages long. As many physicians in Rhode Island and throughout the country have noted, the format of the Guidelines is especially ill-suited for use in hectic primary care practices.

In response, Dr. Charles Sherman and Dr. Sidney Braman of the Rhode Island Asthma Control Program have developed a Quick Reference Guide for Asthma Diagnosis and Treatment. The Guide is based on the NHLBI's Guide-

lines for the Diagnosis and Management of Asthma, and reflects the most up-to-date configuration of stepped care (step up and step down) for asthma. As they developed the Guide, Drs. Sherman and Braman discussed it with physicians from a variety of specialties, modifying it on the basis of their comments.

The practice of medicine undergoes steady, sometimes rapid change, and the medical management of asthma is no exception. For this reason, Drs. Sherman and Braman consider the Quick Reference Guide for Asthma Diagnosis and Treatment to be a working document, subject to periodic updates and continuing discussion in the medical community. As such updates occur, the Asthma Control Program will keep physicians throughout Rhode Island informed. We hope you find the present Guide to be a help in your practice.

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Quick Reference Guide for Asthma Diagnosis and Treatment

Charles Sherman, MD

- Updated December, 2001 -

Sidney Braman, MD

DIAGNOSIS

Subjective:
(1 or more)

- Wheezing
- Chest tightness
- Dyspnea
- Cough ± sputum

Objective:
(1 or more)

- Airflow obstruction ($FEV_1 < 80\%$ predicted)
- Reversibility post-bronchodilator ($FEV_1 > 12\%$ increase)
- Bronchoconstriction post-methacholine ($FEV_1 > 20\%$ decrease)
- AM/PM peak flow variability ($> 20\%$)

EDUCATION

- Use of peak flow meters
- Trigger avoidance
- Warning signs of exacerbations
- Medication effects and side effects
- Asthma management plan

TREATMENT

Symptoms:

Medications:

Step-up:

Mild intermittent
($\leq 2x/week$)

- PRN: short-acting beta agonist

Step-up:

Mild persistent
($> 2x/week$; $< daily$)

- Low dose inhaled corticosteroid
- +/- long-acting beta agonist
or leukotriene receptor antagonist
- PRN: short-acting beta agonist

Step-up:

Moderate persistent
(daily)

- Moderate dose inhaled corticosteroid
+ long-acting beta agonist
- +/- leukotriene receptor antagonist
- PRN: short-acting beta agonist

Step-up:

Severe persistent
(continuous)

- High dose inhaled corticosteroid
+ long-acting beta agonist
- +/- leukotriene receptor antagonist
- +/- oral steroids
- PRN: short-acting beta agonist

Step-down:

Improved

- Slowly reduce medication as tolerated

Point of View: Marfan Syndrome: Be Aware Of Life-Threatening Complications



Dianne N. Abuelo, MD

In April 1991 Allison Bowman, 17 years of age, collapsed and died in the yard of her North Providence home. She was 6 feet 1 inch tall and was known to have the Marfan syndrome. The following day an 11-year-old boy, also known to be affected, collapsed and died in his East Providence school cafeteria. These 2 tragic events occurring on consecutive days shocked Rhode Island and heightened awareness of this rare, but potentially lethal disorder.

Allison is just one of many individuals - primarily young adults - who had her life cut short due to Marfan syndrome and unexpected aortic dissection. A heritable disorder of connective tissue, the Marfan syndrome manifests itself in many body systems - particularly the skeletal, ocular and cardiovascular systems. Physical signs can include a tall, lanky body habitus, myopia, dislocated ocular lenses, mitral valve prolapse and dilatation of the aortic root. In about 75% of cases, the Marfan syndrome, an autosomal dominant condition, is inherited from a parent, but one quarter of cases results from a spontaneous mutation. Before the benefits of pharmaceutical treatment and surgery, the average life span was in the 40s. Now with the correct diagnosis and proper management, affected people can live into their 70s. With such an optimistic prognosis, why are people still dying early from this disorder?

One of the reasons for premature deaths is that people are still not being diagnosed early, before the situation becomes life-threatening. An accurate, early diagnosis is critical to set the management plan for a patient who, although faced with a chronic, progressive condition, could have a chance to live a normal life span with the disorder. In the emergency department, recognition of outward signs of the disorder may help to save the life of an individual who may be suffering an aortic dissection, a common complication of the Marfan syndrome.

When a parent has a positive diagnosis, it is incumbent upon the physician to ensure that all children be evaluated in the attempt to confirm or refute the diagnosis. The same holds true for patients who do not have a family history of the disorder, but present outward signs that may indicate the Marfan syndrome. Because of the high rate of spontaneous mutation, physicians must be particularly alert to the combination of findings that could indicate the Marfan syndrome or a related connective tissue disorder that shares similar life-threatening complications. Affected individuals should receive genetic counseling. Questionable cases can be referred for evaluation by a medical geneticist.

Although the gene for the disorder has been found, there is unfortunately no simple genetic test to establish the diagnosis. Instead, the evaluation must include physical examination, a slit-lamp examination to look for a dislocated lens and an echocardiogram to assess the size and function of the aorta. Many of the characteristics associated with the Marfan syndrome are common in the general population, so the clinician should combine findings and assess the overall presentation of the individual to determine if there is enough evidence to make the

diagnosis by current clinical criteria. If immediate findings are not conclusive, patients should still be followed to ensure they do not develop aortic enlargement at a later date.

Ongoing cardiology management of the Marfan patient is necessary to assure that progressive problems do not become life-threatening. Patients with the Marfan syndrome are advised to modify their lifestyles to avoid strenuous exercise, contact sports and other activities that would put undue stress on the aorta. Beta-blockade can slow aortic enlargement. When the aorta reaches a critical size (5.0-5.5 cm), surgery is recommended to replace the enlarged portion of the aorta and, if necessary, the aortic valve. Recent studies have shown that this elective aortic surgery is quite effective, with an operative mortality rate of only 1.5%.

In an emergency situation, recognizing the signs of the Marfan syndrome - which puts people at 100-fold increased risk of aortic dissection - is essential so that the proper imaging studies can be conducted and interpreted in time to institute life-saving procedures. One recent case was the death of Tony Award-winning playwright Jonathan Larson (Rent), who was seen in two New York City hospitals with incorrect diagnoses and then died shortly thereafter of an aortic dissection.

Although aortic dissection is uncommon, there are thought to be 5,000-10,000 dissections per year in the United States; but the number may be underreported because without autopsy evidence, deaths are attributed to "heart attack" or "sudden death" when the cause is actually an aortic dissection. There is a fatality rate of more than 90% associated with an acute aortic dissection originating near the heart without urgent surgical intervention.

The primary symptom of an aortic dissection is severe pain, usually in the chest, but occasionally in the abdomen when the tear begins in the lower part of the aorta. A standard chest x-ray cannot be conclusive in identifying an aortic dissection. An imaging study of the aorta (echocardiogram, MRI, CT scan or transesophageal echocardiogram) can confirm or disprove the diagnosis. Symptomatic aortic dissections or aneurysms require emergency surgery. Newer surgical techniques may allow treatment by catheterization.

For more information for physicians and families about the Marfan syndrome, contact the **National Marfan Foundation (NMF)**, 800-8-MARFAN or <http://www.marfan.org>. The NMF is offering a CME video (for two AMA Category 1 credits), *Emergency Diagnosis and Treatment of Aortic Dissection*, free of charge to physicians, emergency administrators and hospital education coordinators.

ACKNOWLEDGEMENT

The author acknowledges the helpful input from the National Marfan Foundation.

Dianne Abuelo, MD, is Director of the Genetic Counseling Center, Rhode Island Hospital, and Associate Professor of Pediatrics, Brown Medical School.

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Vital Statistics

Rhode Island Department of Health
Patricia A. Nolan, MD, MPH, Director of Health

Edited by Roberta A. Chevoya

Rhode Island Monthly Vital Statistics Report

Provisional Occurrence Data
from the
Division of Vital Records

Underlying Cause of Death	Reporting Period			
	February 2001	12 Months Ending with February 2001		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	265	3,057	309.3	4,296.5**
Malignant Neoplasms	173	2,375	240.3	6,781.5
Cerebrovascular Diseases	41	491	49.7	745.0
Injuries (Accident/Suicide/Homicide)	29	370	37.4	6,799.5
COPD	55	487	49.3	440.0

Vital Events	Reporting Period		
	August 2001	12 Months Ending with August 2001	
	Number	Number	Rates
Live Births	1137	13,095	13.2*
Deaths	786	10,208	10.3*
Infant Deaths	(8)	(93)	7.1#
Neonatal deaths	(8)	(79)	6.0#
Marriages	917	8,550	8.6*
Divorces	362	3,424	3.5*
Induced Terminations	437	5,488	419.1#
Spontaneous Fetal Deaths	51	977	74.6#
Under 20 weeks gestation	(49)	(907)	69.3#
20+ weeks gestation	(2)	(70)	5.3#

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,048,319

(c) Years of Potential Life Lost (YPLL)

Note: Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

* Rates per 1,000 estimated population # Rates per 1,000 live births
** Excludes two deaths of unknown age.

Letter to the Editor:

On December 1, 2001, **Neighborhood Health Plan of Rhode Island (NHPRI)** made a dramatic addition to its services. It implemented a contract with employees and administrators of 19 human service agencies, offering them Neighborhood Solutions, a full-service health insurance product, made possible through their association as the **Provider Resources and Benefits (PRB)** group. These employees - many of whom may already be your patients - will now be able to access the high-quality care at a reasonable cost.

Because this extension of NHPRI's service may affect you personally, we want to keep you up-to-date about our Neighborhood Solutions product and how it works.

Neighborhood Solutions is intended to offer critical, long-term-oriented health insurance coverage in a cost-effective manner. It is designed to impart the benefits of large group purchasing, volume discounts and price stability, to collections of small groups. Most important, it helps workers get appropriate care at the appropriate time - including those who opt for supplementary, case management services.

More than 2,500 employees and 5,000

covered lives will benefit from this program. Participants include: Easter Seal of Rhode Island/ Cranston Arc, Fogarty Center, Spurwink/RI, J.Arthur Trudeau Memorial Center, Corliss Institute, the Blackstone RI Arc, West Bay Residential, Avatar, Bridges, COVE, Looking Upwards, Olean Center, Ocean State Community Resources, Perspectives Corp., Re-Focus, Gateways, LIFE, Inc., and LaPlante Center.

Neighborhood Solutions features standard care such as prescription coverage, hospitalization, and office visits. Subscribers can also opt for two supplemental programs - a waiver of co-payments for Preferred Primary Care Physicians, and another, Care Solutions, for chronic, catastrophic or complicated illnesses.

How will it work?

For Neighborhood Solutions, NHPRI is contracting with Health Care Value Management - an existing network vendor - to augment our provider network in Rhode Island and southeastern Massachusetts. Employees who select a Preferred Primary Care Physician will not have a co-pay for that physician's service. Should the member see a physician other than their Preferred

Primary Care Physician, a \$10 copay will apply. If the physician does not belong to either Health Care Value Management or NHPRI's networks, additional member co-insurances and deductibles will apply, as with in any out-of-network program.

If a patient chooses a Preferred Primary Care Physician, s/he must notify us. The system is set up to waive the office visit co-pay for such a member, and an ID card will be issued specifying it. All subscribers will have access to our case management program, "Care Solutions," for certain diagnoses, where we will further waive pharmacy co-payments, for a limited period of time.

Neighborhood Solutions has the potential to improve the health care of our citizens significantly, while improving health care access: a worthy effort, indeed.

We urge physicians to call us anytime, if they need more information, at (401) 459-6000.

- **Christopher F. Koller**
CEO, Neighborhood Health Plan of Rhode Island

THE RHODE ISLAND MEDICAL JOURNAL

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Issued Monthly under the direction of the Publications Committee

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NINETY YEARS AGO

[FEBRUARY, 1912]

The October 1911 meeting, held at Rhode Island Hall [at Brown] drew 60 members and 3 guests. Drs. Frank E. Peckham and Roland Hammond presented radiographs, demonstrating the treatment of fractures. Dr. Walter L. Munro retorted that he believed "radiography is not an unmixed blessing, that often too much work is done upon cases which would do better if left alone."

At the November 1911 meeting, with 68 members and 4 guests, the total contribution subscribed toward the library was announced: \$14,890. Also, Dr. R.P. Campbell of McGill University read a paper on the diagnosis of syphilis. The discussion focused on the importance of spirochetes in early lesions, the difference between the Noguchi and Wasserman reactions {"for the most part the two give identical results"}, and the confounding influence of leprosy, tuberculosis and scarlet fever.

James L. Wheaton, Jr., MD, contributed "The Open Air School: Its Development and Purpose." He explained: "One of the greatest problems today ...should be what is the best method to be employed in the building up and in the making of a more healthful human race..." He found 60% of school-rooms "foul-smelling, sickish and contaminated with the decomposed breath of scholars," with unsterilized, uncleaned books. Inspired by the open-air treatment of tuberculosis, however, Pawtucket made one room in every new school house an open-air room, with windows open on 3 sides. Children in those rooms, moreover, washed and brushed their teeth before lunch and dinner. Absences declined, from 17% to 13% (even though children lacked clothing and had work to do at home); and children gained weight, from 4 to 12 pounds.

FIFTY YEARS AGO

[FEBRUARY, 1952]

In "Diathermy Regulations," Charles P. Williamson, Esq., legal counsel to the Rhode Island Medical Society, clarified Federal Communications Commission rulings on the use of the equipment.

Harry Hecker, MD, and Raymond E. Stevens, MD, contributed "Nephrosis - A Long Remission after ACTH." A 14 year-old schoolboy was admitted with "swelling of his legs of 2 days duration." Seventeen days previously, he had had a head cold, which cleared, without treatment, in 3 to 4 days. He was placed on 10 mm of ACTH every 6 hours for 5 days, with no benefit. He was subsequently re-hospitalized with a swollen abdomen and chest. He was

put on 20 mm ACTH every 6 hours for 6 days, but after a weight gain (from 140 pounds to 197 pounds) and edema, therapy was discontinued. Subsequently he was put on 40 mm of ACTH qid; he felt better immediately, and returned both to school and to his job as a delivery boy.

Arthur Kern, MD, in "Dermatoses of the Newborn," reviewed conditions that could lead to death: impetigo neonatorum, epidermolysis bullosa, congenital defects of skin, sclerema neonatorum, ichthiosis congenita.

TWENTY FIVE YEARS AGO

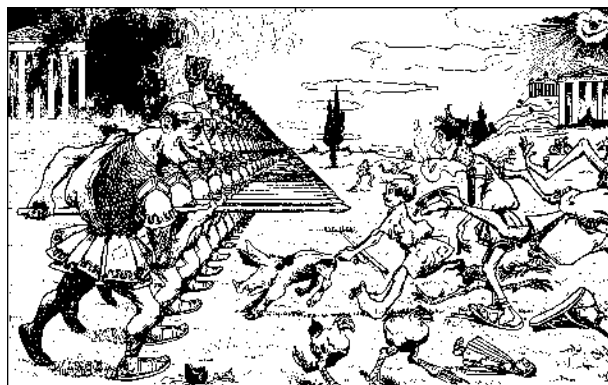
[FEBRUARY, 1977]

Stanley M. Aronson, MD, MPH, described "Brown and the State Hospitals," with details on the concrete results of the liaison: a new 32-bed teaching rehabilitation service at the Center General Hospital, supervised by Drs. Carl Granger and David Greer; a federally-subsidized study of the Institute of Mental Health and the regional Mental Health Centers, under the supervision of Dr. Sylvia Sherwood of Brown and the IMH Project Director, Stanley Oglesby; discussions of a comprehensive plan for mental retardation, with attention to the Ladd School population.

Daniel C. Wistran, MD, and Constantine Georas, MD, in "Idiopathic Hemochromatosis, Long Term Treatment and Hepatoma: A Case Report and Review of Literature," described a 48 year-old woman, the first patient with long-term follow-up developing hepatoma despite treatment.

A.A. Savastano, MD, and Louis Corvese, MD, in "Experience with the Garden Operation in Resistant Tennis Elbow," explained that in resistant cases "lengthening of the extensor carpi radialis brevis tendon is effective."

Thomas W. Pearlman, Esq., discussed, "Should a Physician Incorporate? Some Considerations in Light of the Pension Reform Act of 1974." He concluded: "Whether you incorporate or not, you should not lose the tax benefits under a pension plan."



Bioterrorism and Physicians



Andrew W. Artenstein, MD, Marguerite A. Neill, MD, Steven M. Opal, MD

The deliberate use of microbial agents or their toxins as weapons and instruments of terror has become a focal point of our national debate due to the intentional transmission of anthrax to persons in the United States in October 2001.¹ While the threat of biological weaponry and bioterrorism is not novel, its imprint on the daily lives of most Americans has only become manifest with these events. These issues have been the subjects of preparatory activities and discussions for a number of years within public health, infectious diseases, military and other governmental spheres. Due to the unpredictable nature of the perceived and real threats, however, our paradigms for response and clinical management require continual reassessment.

Biological weapons have been used against both military and civilian targets throughout history. During the Cold War, both the United States and the Soviet Union maintained programs to develop these agents as offensive weapons.² The U.S. program ended by presidential decree in 1969; the Soviets continued to pursue an active program until, at least, the dissolution of their Union. The orphaned materials and the unemployed scientists from the dismantled Soviet effort still represent a significant unintended hazard of glasnost. The documentation by United Nations inspectors of the weaponization of massive quantities of anthrax and botulinum toxin by the Iraqis during the Gulf War dramatically illustrates the persistent threat posed by biological agents.³

THREAT ASSESSMENT

Attributes contributing to the choice of pathogen as a bioterrorism agent are a high attack rate and severe clinical disease, but operational requirements are that it can be produced in adequate quantity, concentration and form and delivered in a fashion to effectively transmit infection. Aerosolization is the most likely route of bioterrorist attack due to the potential for widespread dissemination; however, large-scale release may not be necessary for a "successful" outcome from a terrorists' viewpoint. The recent transmission of anthrax in the U.S. has clearly shown that targeted deployment and delivery of biological agents using such primitive technology as mail can achieve at least some terrorist goals: anxiety, fear, and diversion of resources.

Broader terrorist aims in civilian populations, ill and dying patients, would be addressed in larger scale biological attacks.

These would likely require either state sponsorship or direct support from governments or other organizations with significant resources, contacts and infrastructure. While the development of biological agents for use in terrorism requires significant technical equipment and expertise, these weapons present a distinct economic advantage over conventional or nuclear weaponry. For these reasons they may be among the weapons of choice for developing countries.

SENTINEL EVENTS AND DIAGNOSTIC PITFALLS

Bioterrorism is generally insidious; clinical illness will be recognized before the circumstances of a release event are known. Owing to the clinical incubation period of days to weeks for most of the potential threat agents and the geographic dispersal of Americans around metropolitan areas and other potential targets, casualties will likely be staggered in their temporal presentation for medical care and seen at diverse locations in areas surrounding a target. Early clinical recognition is further hampered by the fact that the initial symptoms and signs of many of these agents are flu-like and non-specific, and even in the later stages of illness, most physicians are inexperienced with the clinical appearance of these diseases. Additionally, as agents of bioterrorism are laboratory- and man-manipulated, their associated clinical presentations may differ from those in natural occurring disease. Nonetheless, physicians and other health care workers are likely to be the first responders in this setting and must therefore use clues obtained from patient history, exam and epidemiologic data and an active index of suspicion to guide their diagnostic and therapeutic approach.

THREAT AGENTS

The CDC and others have classified biological threat agents into three categories based upon the feasibility of their production and deployment, transmission properties, their capacity to cause mortality and/or morbidity, and their potential to cause social disruption.⁴ (Table

1) Category "A" agents have been successfully weaponized and tested in the past and would reliably cause high mortality, morbidity and social disruption when disseminated. Category "B" agents have also been successfully weaponized and tested in the past but have greater potential use as incapacitating agents rather than causes of high mortality. Category "C" largely represents emerging threats, and the miscellaneous group refers to some agents that have been either attempted or considered by various rogue states. Table 2 (insert) provides a syndromic differential diagnosis regarding some of these illnesses; Table 3 provides data on transmission and infection control procedures.

Anthrax is a zoonotic disease of herbivores that occurs in many geographic regions. Sporadic human infection results from contact with animal products or tissues contaminated by *Bacillus anthracis* endospores.⁵ This agent has been successfully weaponized by nation-states as well as terrorist organizations³ and has been recently used as a weapon against individuals in the U.S.⁶ Naturally-occurring human disease is usually a cutaneous infection; less than 5% of cases are from inhalational or gastrointestinal routes of transmission. It would be anticipated that inhalational disease would be the form seen in a bioterrorist attack.⁷ The recent inhalational cases in the U.S. have resulted from the aerosolization of spores inside letters by processing through high-speed mail sorting equipment or direct inhalation of spores on mail; cutaneous infections have resulted from handling contaminated mail.⁶

After the inhaled spores reach the terminal alveolar spaces of the lung, they are taken up by macrophages and transported to the mediastinal lymph nodes. There the spores germinate into vegetative, recognizable Gram-positive bacilli and subsequently disseminate hematogenously.⁵ After an average incubation period of 2-7 days, clinical illness is manifest initially by non-specific symptoms: fever, malaise, myalgias, headache, chills, non-productive cough and abdominal pain in the majority. This symptom complex overlaps considerably with

Table 1: Biological agents of concern for use as weapons
(see text) [after reference 4]

Category A	Category B	Category C	Miscellaneous
Anthrax	Q fever	Hanta viruses	HIV-1
Botulism	Viral encephalitides	Tickborne viruses	Adenoviruses
Plague	Brucellosis	Yellow fever	Influenza
Smallpox	Glanders	Drug-resistant TB	Rotaviruses
Tularemia	Staph. enterotoxin B		Hybrids
Viral hemorrhagic fevers	Ricin roxin		

Table 3: Transmission and infection control by agent/disease

Agent/disease	Incubation period	Person-to-person transmission	Infection control precautions
Inhalation anthrax	2-43 days	No	Standard
Botulism	12-72 hours	No	Standard
Pneumonic plague	1-6 days	Yes	Droplet
Smallpox	7-17 days	Yes	Contact + airborne
Tularemia	1-14 days	No	Standard
Viral hemorrhagic fevers	2-21 days	Yes	Contact + airborne
Viral encephalitis	2-14 days	No	Standard
Q fever	2-14 days	No	Standard
Brucellosis	5-60 days	No	Standard

influenza and other viral respiratory tract infections. Recent data suggest that nausea, vomiting, and shortness of breath appear to be significantly more commonly seen in anthrax as compared with viral respiratory tract illnesses, while rhinorrhea is common in viral respiratory tract illnesses but rarely seen in anthrax.⁸

Patients typically present for medical attention an average of 3.5 days into the illness, after which significant clinical deterioration occurs with dyspnea, chest pressure, hypoxemia and not infrequently, abdominal pain.⁶ In the absence of antimicrobial therapy blood cultures are invariably positive within 24 hours. Chest roentgenography may reveal mediastinal adenopathy with or without pulmonary infiltrates and pleural effusions in most cases. Disease progresses rapidly with respiratory failure, shock, hemorrhagic meningitis (50%) and death.

Recent clinical experience in the U.S. has shown that early administration of appropriate antimicrobials and aggressive intensive care support has lowered the case fatality rate from the previously published 85%⁵ to ~50%.⁶ Treatment recommendations are beyond the scope of this paper and have been recently reviewed.⁷ Combination antimicrobial therapy including a quinolone, with the addition of high-dose penicillin G for suspected CNS disease, has been advocated. Theoretical rationale exists for the addition of clindamycin due to its inhibition of protein, particularly toxin, synthesis in some bacteria. Limited cutaneous disease may be treated with a single agent. Post-exposure prophylaxis has been shown to be effective in animal studies and has been used extensively among those thought to be at risk from the recent mail exposures. The greatest difficulty with prophylaxis has been the precise determination of those at risk. The licensed inactivated anthrax vaccine is of limited availability and is not currently in use for civilians.

Botulism, an acute neurologic disease caused by *Clostridium botulinum*, occurs in sporadic outbreaks in the U.S. as a result of ingestion of foodborne toxin or the bacterium itself. The toxin, however, has been weaponized for use as an aerosolized agent of bioterrorism.³ Botulinum toxin blocks the release of the neurotransmitter acetylcholine from presynaptic

vesicles thereby inhibiting muscle contraction.⁹ The disease presents as an acute, symmetric, descending, flaccid paralysis that begins in the bulbar musculature and is associated with dilated pupils, ptosis, dry mouth, a clear sensorium and the absence of fever. Both the foodborne and the inhalation route of botulinum intoxication appear to be clinically indistinguishable.

Case fatality rates from foodborne botulism have declined to approximately 5% over the last four decades, largely as a result of improvements in supportive intensive care and mechanical ventilation. The symptoms, however, may last for weeks to months until reinnervation of paralyzed muscle fibers occurs from the generation of new motor axon twigs. Treatment with an equine antitoxin, available in limited supply from the CDC, may ameliorate symptoms if given early in the course. Clinicians should remain alert to the possibility that any single case of botulism could be the result of bioterrorism, either through intentional contamination of food or via an aerosol exposure. A large number of cases, multiple focal outbreaks, or the absence of a common dietary exposure upon detailed epidemiologic investigation may be clues to an intentional release.

Smallpox is caused by the variola virus, which although the most prolific disease killer in world history, was eradicated by an intensive global campaign by WHO in the 1960s and 1970s.¹⁰ The last naturally occurring case was in Somalia in 1977. A generation of physicians and other health care providers has therefore come to medical practice without having seen a case of smallpox. The U.S. ceased routine civilian vaccination in 1972, and since variola virus does not circulate in the environment, over half of the U.S. population (those under age 30) is susceptible to smallpox. Adults who had been previously vaccinated or multiply re-vaccinated probably have some residual immunity, but the extent of protection against either infection or mortality remains unknown. It is known that the Soviets weaponized and stockpiled smallpox, and it is feared that these agents may have fallen into terrorists' hands.¹¹ These aspects, coupled with its 30% mortality rate and capacity for secondary spread among close

contacts, make the threat of bioterrorism using smallpox a potential public health catastrophe on a global scale.

Smallpox is spread from person-to-person by close contact via respiratory droplets and, in certain instances, by fine particle aerosols. Following an incubation period of 7-17 days, the patient develops fevers, chills and prostration. Within one or two days, a maculopapular rash erupts on the face, distal extremities, and mucous membranes of the mouth and oropharynx and spreads in a centrifugal distribution.¹² These lesions subsequently evolve to papules, vesicles and pustules over about 8 days in synchronous fashion, i.e. they are all in the same stage of development. After about three weeks, the lesions scab over and separate. The patient with smallpox is infectious from the onset of rash until all of the scabs have separated. Classically, varicella accounts for most of the diagnostic confusion; however, the rash of chickenpox is centripetal (i.e. begins on the trunk and spreads outward), the lesions are in varying stages of development (i.e. asynchronous) and do not involve the palms or soles.

The treatment for smallpox is largely supportive. Strict isolation with airborne precautions is necessary for cases. Tracing and vaccination of household and close personal contacts (i.e. face-to-face contacts) and vaccination of health care workers caring for cases is crucial to limiting the spread of infection. It is known that vaccination within four days of infection can either ameliorate the course or prevent disease altogether.¹² Only limited supplies of the vaccine exist in the U.S., but there is a current national plan to acquire adequate vaccine supplies to immunize the entire U.S. population if necessary. While there are no antiviral drugs of proven efficacy in the treatment of smallpox, this is an area of active investigation and some available agents have shown promise in animal models of related poxviruses.

Bacterial pathogens that cause primarily pneumonic disease are considered to be prime candidates for use as agents of bioterrorism. Aerosolized preparations of *Yersinia pestis*, *Francisella tularensis* and *Coxiella burnetii* could result in human and animal cases of pneumonic plague, tularemia, and Q fever, respectively. Plague is perhaps the most feared of these agents due to its propensity for person-to-person spread via respiratory droplets.¹³

In its naturally occurring form primary pneumonic plague is rarely transmitted to humans from respiratory secretions of infected animals, such as domestic cats.¹³ After a one to six day incubation period, prominent systemic and respiratory symptoms ensue, typically with multilobar pulmonary infiltrates on chest roentgenogram. Cough productive of purulent sputum and/or hemoptysis are classically described, although the frequency of the latter is not clear. In the absence of effective treatment patients rapidly progress to multiorgan system failure

Table 4: Useful Websites, Phone Numbers

*www.bt.cdc.gov	CDC, Bioterrorism and Response
*www.hopkins-biodefense.org	Johns Hopkins Center for Civilian Biodefense Studies
*www.usamriid.army.mil	U.S. Army Medical Research Center for Infectious Diseases
*www.usamriid.army.mil/education/bluebook.html	USAMRIID Medical Management of Biological Casualties handbook
*www.health.state.ri.us/biot/home.htm	Rhode Island Dept. of Health BT site
RI DOH disease reporting: (401) 222-2577/after hours, weekends: (401) 272-5952	

with cardiovascular collapse and disseminated intravascular coagulation. The diagnosis can be made by identification of the characteristic small Gram-negative coccobacillary forms with "safety pin" (bipolar staining) appearance on Gram stain.¹³ The organism is readily identified in sputum and may be found in the peripheral blood of patients dying of septicemic plague. The microbiology lab should be notified in advance if this agent is suspected. Recommendations for treatment and prophylaxis have been recently reviewed.¹⁴

Pneumonic plague can be transmitted via respiratory droplet nuclei from person-to-person, usually after close contact (<2 meters) with the index case.^{13,14} This puts healthcare workers, hospital employees and other patients at risk in a hospital environment and raises the specter of secondary and tertiary spread, especially in poorly ventilated indoor settings. Prompt recognition of pneumonic plague and adherence to strict respiratory isolation precautions can prevent secondary cases; early initiation of appropriate antimicrobials may render the patient non-infectious and avert a lethal outcome.

Naturally occurring tularemia has several discrete clinical forms, but the intentional release of *F. tularensis* would likely cause a pulmonary syndrome at low inocula. After an incubation period of one to fourteen days, patients experience the abrupt onset of a febrile illness with upper respiratory symptoms, pleuritic chest pain and variable progression to pneumonia with or without hilar adenopathy.¹⁵ The mortality rate exceeds 30% without appropriate antimicrobial treatment. Diagnosis is usually based upon clinical features and accomplished after ruling out other agents; the organism is an extreme biohazard in the laboratory, and therefore lab personnel should be notified in advance when isolation is attempted in clinical specimens. The antimicrobial approach to tularemia is similar to that of plague.¹⁵ This illness is not spread person-to-person via respiratory secretions.

Q fever is a respiratory illness caused by a rickettsial organism that, although not generally fatal, can result in debilitating symptoms that may persist for many weeks.¹⁶ Approximately 50% of affected individuals will have frank pneumonia following a non-specific febrile illness. The diagnosis is generally retrospective and therefore treatment should be based on clinical presentation.

Viral hemorrhagic fever agents are considered potential weapons of terror as they are

generally highly infectious in aerosol form, transmissible in healthcare settings, and lethal. Many of these agents, including Ebola, Marburg, Lassa fever, Rift Valley fever and Bolivian hemorrhagic fever viruses have been extensively studied by the government of the former Soviet Union.¹¹ These viruses have similar clinical presentations and overlapping clinical syndromes: fever, conjunctival injection, myalgias, prostration, increased vascular permeability and microvascular damage manifest by diffuse petechial hemorrhages.¹⁶ Full-blown hemorrhagic fever evolves into shock with diffuse hemorrhaging and multi-organ system dysfunction. Blood and other bodily fluids from these patients are extremely infectious necessitating strict contact and airborne precautions. Treatment is largely supportive and should include the early use of vasopressors if needed. Ribavirin has been shown to be useful in some patients with Lassa fever, Rift Valley fever and Congo-Crimean hemorrhagic fever.¹⁷

Venezuelan equine encephalitis (VEE) is highly infectious in aerosol form and is a potential threat agent. Although uncommonly fatal, VEE may cause a disabling neurologic syndrome with sequelae in some.¹⁶ The disease is not transmitted person-to-person, and therapy is largely supportive.

CONCLUSION

As first responders to the threat of bioterrorism, physicians must be forward-thinkers, professionally prepared and personally ready for proactive roles within our local communities and our hospitals. A variety of resources are available to guide this effort. (Table 4) As physicians we must not only recognize and accept our responsibilities to the patients in our care, but we must fulfill our responsibilities as caretakers of the public health by working in tandem with public health authorities to optimize public safety.

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Table 2. Clinical presentations and syndromic differential diagnoses of selected agents of bioterrorism

IF PATIENT HAS:	CONSIDER:	IN ADDITION TO:
Few days of non-specific "flu-like" symptoms with nausea, emesis, cough +/- chest discomfort, without coryza or rhinorrhea → abrupt onset of respiratory distress +/- shock +/- mental status changes, with CXR abnormalities (wide mediastinum, infiltrates, pleural effusions)	Inhalational anthrax	Bacterial mediastinitis, tularemia, ruptured aortic aneurysm, SVC syndrome, histoplasmosis, coccidioidomycosis, Q fever, psittacosis, Legionnaires' disease, influenza, sarcooidosis
Pruritic, painless papule → vesicle(s) → ulcer → edematous black eschar +/- massive edema and regional adenopathy, +/- fever, evolving over 3-7 days	Cutaneous anthrax	Recluse spider bite, atypical Lyme disease, staphylococcal lesion, Orf, glanders, tularemia, rat-bite fever, echinyma gangrenosum, plague, rickettsialpox, atypical mycobacteria, diphtheria
Cough, fever, dyspnea, hemoptysis, lung consolidation +/- shock	Pneumonic plague	Severe bacterial or viral pneumonia, inhalational anthrax, pulmonary infarct, pulmonary hemorrhage
Sepsis, DIC, purpura, acral gangrene	Primary septicemic plague	Meningococemia; Gram-negative, streptococcal, pneumococcal or staphylococcal bacteremia with shock; overwhelming post-splenectomy sepsis, acute leukemia
Synchronous, progressive papular → vesicular → pustular rash on face, extremities > trunk → generalization +/- hemorrhagic component, with systemic toxicity	Smallpox	Atypical varicella, drug eruption, Stevens-Johnson Syndrome, atypical measles, secondary syphilis, erythema multiforme, meningococemia, monkeypox (with African travel history)
Acute febrile illness with pleuropneumonitis, bronchiolitis +/- hilar lymphadenopathy; variable progression to respiratory failure	Inhalational tularemia	Inhalational anthrax, influenza, mycoplasma pneumoniae, Legionnaire's disease, Q fever, plague
Acute onset of afebrile, symmetric, descending flaccid paralysis that begins in bulbar muscles, dilated pupils, dry mucous membranes with normal mental status and absence of sensory changes	Botulism	Brain stem CVA, polio, myasthenia gravis, Guillain-Barre syndrome, tick paralysis, chemical intoxication