COMMENTARIES

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 confonted 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 of1862, 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 litle 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 generalists 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.

Allan Erickson, MD, is Associate Professor of Medicine, Brown Medical School.

Correspondence:
Allan Erickson, MD
Veterans Administration Medical Center
Providence, RI 02908
phone: (401) 273-7100
fax: (401) 457-3364
e-mail: Allan_Erickson@brown.edu

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 guidelines[4] 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 statification 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. (Figure 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 interpreted 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 jejunooilela 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 at increased risk for development of disease by the presence of concomitant medical problems. (Figure 2)

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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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E. Jane Carter, MD, is Clinical Assistant Professor of Medicine, Brown Medical School.

Correspondence:
E. Jane Carter, MD
Tuberculosis Clinic
Miriam Hospital
Providence, RI 02906
phone: (401) 793-2427
fax: (401) 793-2266
e-mail: E_Jane_Carter@Brown.edu

Steroid Therapy in Chronic Obstructive Pulmonary Disease

Aidan OBrien, 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. (In1997, 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 ≥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 Affairs 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 corticosteroids 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 Britain[38] and the Lung Health Study[39] 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 bronchodilator (as defined by the American Thoracic Society as a ≥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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Aidan O'Brien MD, is Staff Physician at the Providence VA Medical Center and at the RI Hospital, and Assistant Professor of Medicine, Brown Medical School.

Nicholas S. Ward MD, is Associate Director, Rhode Island Hospital Medical Intensive Care Unit, and Assistant Professor of Medicine, Brown Medical School.

Correspondence:
Aidan O'Brien, MD
Division of Pulmonary and Critical Care Medicine
Providence VA Medical Center
830 Chalkstone Avenue
Providence, RI 02908
phone: (401) 273-7100,x3436
fax: (401) 457-3364
e-mail: Aidan_O'Brien@Brown.edu