National Jewish Health®

A newsletter for physicians

CONNECTIONS

Winter 2016

Millions of Smokers May Have Undiagnosed Lung Disease

More than half of long-term smokers who pass lung-function tests have respiratory-related impairments

Many long-term smokers and ex-smokers are considered disease free because they passed lung-function tests. However, more than half of them have respiratory-related impairments when more closely evaluated with lung imaging, walking and quality-of-life tests. Many of these people likely have the earliest stages of chronic obstructive pulmonary disease (COPD), the third leading cause of death in the United States.

According to James D. Crapo, MD, professor of medicine at National Jewish Health, the impact of chronic smoking on the lungs and the individual is substantially underestimated when using lung function tests alone. Dr. Crapo is senior author of the study published recently in *JAMA Internal Medicine*. In the study, researchers evaluated 8,872 people ages 45 to

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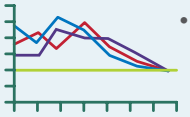
BETTER HEALTH STARTS AFTER THE *Last Cigarette*

After the last cigarette, the road to better health starts within minutes and continues for years. Here are the changes your body experiences along that journey.

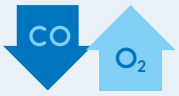
20 MINUTES

- Blood pressure decreases
- Pulse rate drops
- Body temperature of hands and feet increases



8 HOURS

- Carbon monoxide level in blood drops to normal
- Oxygen level in blood increases to normal (if no lung disease)



24 HOURS

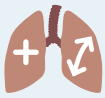
- Chance of a heart attack decreases

48 HOURS

- Nerve endings start regrowing
- Sense of smell and sense of taste improve

2–12 WEEKS

- Circulation improves
- Walking becomes easier
- Lung function improves



4–36 WEEKS

- Coughing, sinus congestion, tiredness and shortness of breath decrease

1 YEAR

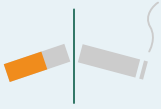
- Risk of coronary heart disease decreases to half that of smokers

5 YEARS

- From five to 15 years after quitting, stroke risk is the same as people who never smoked

10 YEARS

- Risk of cancer drops to half that of smokers
- Risk of ulcer decreases



15 YEARS

- Risk of coronary heart disease is the same as people who have never smoked
- Risk of death is the same as people who have never smoked

DISCLAIMER: If you have other health conditions, your results may differ

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80 with a 10 pack-year smoking history or the equivalent. Most had smoked considerably more, 35 to 50 pack-years. About half the participants were considered disease-free based on spirometry. When researchers considered other criteria, including impairments in physical function, respiratory symptoms, CT scans, use of respiratory medications and respiratory-specific quality of life, they found that 55 percent of the "disease-free" study participants had some form of respiratory related impairment.

CT scans found emphysema or airway thickening in 42 percent of the disease-free participants. In addition, 23 percent had significant shortness of breath compared to 3.7 percent of never smokers. And, 15 percent walked less than 350 meters in six minutes, compared to 4 percent of never smokers. The disease-free smokers also had considerably worse quality of life than never smokers, with 25 percent of them having scores on questionnaires that exceeded a threshold considered clinically significant.

Recent research has shown that lung CT screening of smokers with smoking histories of at least 30 pack-years can detect lung cancer and reduce deaths by 20 percent. Early detection of COPD may also enable early treatment that can improve symptoms and quality of life. Elizabeth Regan, MD, Assistant Professor of Medicine at National Jewish Health and an author on the study, hopes the findings will encourage long-term smokers to get lung CT screenings to detect early stages of both lung cancer and COPD.

Reference:
Crapo JD, Regan EA, et al. "Clinical and radiologic disease in smokers with normal spirometry," *JAMA Internal Medicine*, 2015 Sep 1; 175(9): 1539-49.

To schedule a lung cancer screening CT for your patient

Contact the National Jewish Health lung cancer screening coordinator at 877.713.5066. Lung cancer screening CT is now covered by private insurance, Medicare and Colorado Medicaid for high-risk patients. To learn more about screening criteria, visit njhealth.org/lung-cancer-screening-program.

Beta-blockers and COPD

Chronic obstructive pulmonary disease (COPD) patients often have comorbid cardiovascular disease. Beta blockers, however, are significantly under-prescribed in COPD patients due to the concern that they may trigger bronchoconstriction and worsening of lung function.

National Jewish Health physician James D. Crapo, MD worked with researchers from around the country to analyze data on use of beta-blockers in patients from the COPDGene cohort.

National Jewish Health physician James D. Crapo, MD, worked with researchers from around the country to analyze data on use of beta blockers in patients from the COPDGene cohort. The COPDGene study enrolled 10,300 current and former smokers aged 45-80 years. Of the full group of COPDGene participants, 3,464 had Stage 2-4 COPD based on GOLD criteria (Global Initiative for Chronic Obstructive Lung Disease) and were included in the research on the effect of beta blockers on COPD.

Beta blocker use was associated with a significantly lower rate of total and severe exacerbations during an average 2.1 years of follow-up. In study participants with GOLD stage 3 and 4 COPD and on home oxygen, use of beta blockers was also associated with similar reductions in the rate of total and severe COPD exacerbations. Subjects with severe COPD who are on home oxygen are a subgroup that has been considered to be at especially high risk for complications from beta blocker use.

While Dr. Crapo and the research team found that the use of beta blockers by study subjects with COPD is associated with a significant reduction in exacerbations, the use of other cardiac medications was not associated with a reduction in exacerbation risk.

Reference:
Bhatt SP, Wells JM, Kinney GL, Crapo J et al. "Beta-blockers are associated with a reduction in COPD exacerbations," *Thorax* Published Online First: August 17, 2015. Doi:10.1136/thorasjnl-2015-207251.

Recurrent Infections: Is It Caused by Immune Deficiency?

Erwin W. Gelfand, MD, chairman, Department of Pediatrics, and professor of pediatrics, National Jewish Health

All children and many adults suffer from infections, often recurrent, and the concern is whether this susceptibility represents an immune disorder. Immune system disorders are uncommon, but nonetheless, suspicion may be warranted given certain cues. Prior to the liberal availability or use of antibiotics, immunodeficiency disorders presented with severe, often overwhelming infections including lobar pneumonia, osteomyelitis, meningitis, a need for repeated hospitalization and intravenous antibiotics. Today, the clinical presentation may be more subtle, as with the early introduction of effective antibiotics, bacterial infections often do not progress to a serious outcome.

So, what are the cues? Today more than 300 genetic defects within the immune system have been identified, and with the increased application of molecular genetics, more are discovered regularly. The focus here is on primary immunodeficiency diseases, where secondary causes are eliminated. There are many secondary causes of immunodeficiency, including HIV disease, malignancy, new biologic agents (e.g., Rituxan®, anti-tumor necrosis factor [TNF]), immunosuppressive drugs, chemotherapeutic agents, skin or mucosal barrier defects and even nutritional causes. Primary immunodeficiency diseases can have an onset at any age. With the availability of molecular genetics, it is not unusual today to identify a genetically-determined primary immunodeficiency in adulthood, even in the fifth or sixth

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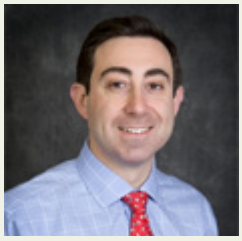
Approach to Assessing Immune Deficiency

When assessing a patient for possible immune deficiency, consider the following:

- Number of infections
- Severity of infections
- Type of infections
- Location of infections
- Need for antibiotics
- Need for hospitalization
- Failure to thrive
- School or work attendance and performance
- Is there a family history of immune disorders?
- Are the parents related? (e.g., first cousin marriages increase likelihood of a recessive condition)
- History of atopic disease (children with allergies often present with recurrent rhinositis, even pneumonia in asthmatics)
- In adults, fatigue rather than significant infection may be a presenting feature

The immune disorder clinics at National Jewish Health can help you determine the need for further evaluation, diagnosis and treatment.

The physicians in these clinics (Drs. Erwin Gelfand, Jordan Abbott, Pia Hauk and Sanny Chan) have decades of experience treating children and adults and can assist you via consultation or arranging an evaluation for a patient.



Jordan Abbott, MD

Sanny Chan, MD

Erwin Gelfand, MD

Pia Hauk, MD

Identifying Patients with Undiagnosed COPD in Primary Care Settings

National Jewish Health physicians Barry Make, MD, and Russell Bowler, MD, and their colleagues recently summarized the most common and significant variables associated with case-finding or missed cases of COPD in primary care. Although spirometry is the diagnostic gold standard for clinically significant COPD, the researchers found that a brief, easy-to-use, self-administered questionnaire may be a more practical method for identifying patients with clinically significant COPD who are in need of follow-up and diagnostic spirometry testing.

Study authors conducted an extensive literature search of PubMed and EMBASE to identify articles describing case-finding and epidemiological research to detect or characterize new cases of COPD.

In both the epidemiological and screening studies, factors that appear to be strongly associated with COPD were older age, BMI, smoking history and symptoms such as cough, wheeze and dyspnea. Other lines of research suggest that factors such as prenatal maternal smoking, low birth weight, postnatal tobacco exposure and childhood respiratory infections may predispose individuals to COPD. Factors not included in the screening studies and not statistically significant in the epidemiological studies reviewed included income, fatigue/tiredness, cardiac co-morbidity and taking breathing medications or antibiotics.

The literature review described in this research lays the groundwork for a multi-method screening approach for identifying undiagnosed, clinically-significant COPD in a primary care setting. The findings from this study are being used in further work to develop a simple questionnaire able to identify undiagnosed, high-risk COPD patients in primary care. Such a questionnaire, combined with values from a peak flow meter, may further refine the patient population for whom spirometry is needed.

Reference:
Bowler RP, Make BJ, et al. "Identifying Patients with Undiagnosed COPD in Primary Care: Insight from Screening Tools and Epidemiologic Studies." *Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation*, Original Research, Volume 2, Issue 2.

Important Phone Numbers and Contact Information

Physician Line (consultations, referrals, resources) 800.652.9555 or njhealth.org/referrals

Patient Appointments 800.621.0505

Clinical Trials 303.398.1911 or njheath.org/clinicaltrials

Advanced Diagnostic Laboratories 800.550.6227 or njlabs.org

Professional Education 800.844.2305 or njhealth.org/cme

Physician Relations Team:

Mark Minner-Lee | 970.420.5265

Mike Kingsbury | 303.728.6584

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decade of life. Primary immunodeficiencies are more common in males than females, as many genes controlling immune function reside on the X chromosome.

Lack of one or more components of the immune system results in an immune disorder. Our ability to fight infection resides in different immune compartments, which together orchestrate an effective and defensive immune response. The innate immune arm comprises components that don't need prior experience and include the complement system, neutrophils and other granulocytes, and natural killer (NK) cells. The adaptive immune system, that arm enhanced by prior experience, naturally through exposure or following vaccination, is comprised of T lymphocytes and B lymphocytes.

Defects in a specific component or compartment often manifest with infection due to specific organisms. Thus, neutrophil defects (low absolute number or function) often present with recurrent staphylococcal infection, whereas T lymphocyte defects are seen in patients with recurrent viral, fungal or opportunistic infection (e.g. Pneumocystis jiroveci). Defects in B lymphocyte function (as a result of low or absent numbers or functional abnormalities) resulting in low immunoglobulin levels, particularly IgG, lead to recurrent infections with encapsulated bacteria (S. pneumonia, H. influenza, N. meningitides). Similarly, some of the complement deficiencies present with infection due to encapsulated organisms.

Complement defects in the classical or alternative pathway are not common. Late component defects (C5-9) may present with meningitis, whereas early component defects (C1q, r, s, C4, C2) may present with a lupus-like illness. C2 deficiency is the most common complement component defect and may present with upper respiratory tract infections. In some patients, recurrent bacterial sepsis and infections at other sites are seen. The rare C3 deficiency presents with recurrent infections due to encapsulated organisms.

Laboratory Assessment of Immune Deficiency

Laboratory testing has become increasingly sophisticated, including molecular/genetic assessments. If initial screening tests suggest concern for an underlying immune disorder, then referral to a specialist with expertise may be indicated to reduce costs and focus the evaluation.

Tests for immune deficiency usually include:

- Complete blood count (in addition to other parameters, provides absolute neutrophil and absolute lymphocyte numbers)
- Quantitative serum immunoglobulins (IgG, IgA, IgM)

Of note:

- A complete blood count and quantitative immunoglobulins are usually sufficient to diagnose >90 percent of patients with a primary immunodeficiency.
- Most patients diagnosed clinically with sinusitis really only have rhinitis.
- The most common cause of recurrent otitis media and rhinosinusitis is underlying allergy.

Other Common Primary Immunodeficiency Diseases

With the increasing awareness and diagnosis of immune deficiency disorders, many names have been assigned based on specific genetic defects. Disorders of B lymphocyte function and immunoglobulin production (hypogammaglobulinemia) are the most common and include selective IgA deficiency, X-linked agammaglobulinemia characterized by the absence of B lymphocytes and common variable immunodeficiency disease (CVID), a heterogeneous group of diseases marked by low immunoglobulin levels, failure of normal antibody production and both significant or low-grade infection.

Primary disorders of the T lymphocyte system are much rarer compared to the secondary deficiency arising from HIV infection and include severe combined immunodeficiency disease or SCID, now also recognized to comprise a number of different genetic disorders. Many of these patients have low absolute lymphocyte numbers, although this is not universal. Since 2012, newborn screening for SCID has been carried out by the State of Colorado with evaluations of suspected babies at National Jewish Health. Other disorders seen are DiGeorge syndrome, characterized by congenital heart defects, hypocalcemia and variable T lymphocyte function, and a large spectrum of molecular/genetic defects.

The most common disorder of the neutrophil system is a low absolute number either resulting from a genetic defect or secondary to a drug or viral infection. Among the neutrophil functional defects, chronic granulomatous disease, X-linked or autosomal recessive, is the most common.

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