pneumonia group, giving a mortality rate of 9.6% in this subgroup, this is still substantially below the ≥25% expected mortality for pneumonia severity index class V, and the 20% plus mortality rates reported in most observational studies of severe CAP.

Lack of randomized controlled trial data in severe CAP is also a problem with respect to assessment of the impact of antibiotic therapy on length of hospital stay. Patients who survive severe episodes of CAP have substantially longer hospital stays, especially those initially requiring-intensive care. Conversely, social issues and comorbid diseases are often reasons for longer-than-usual hospital stays in patients with CAP. These factors are not accounted for in the severity assessment used by Brown and colleagues but may have impacted on the choice of antibiotics and therefore influenced the results.

A number of possible explanations for the benefit of macrolides observed by the retrospective studies have been put forward including antibiotic synergy, coverage of unrecognized atypical pathogens, and immunomodulatory effects. Debate over whether any or all of these are plausible is immaterial until the issue of whether mortality in severe CAP is lower than expected mortality, either for any of any all of these are plausible. The absence of any prospective data and the serious questions raised by the retrospective studies are both cause for concern and justification for urgent prospective study.

In conclusion, while the study by Brown and colleagues does not provide any definitive answers, it raises the same questions as previous retrospective studies that highlight the deficiency of prospective data in severe CAP. With the unacceptably high mortality rate in severe CAP, the role of macrolides, quinolones, and combination antibiotic therapy needs to be resolved by randomized, prospective studies as a matter of urgency.

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The Variability of Sarcoidosis
Can We Predict It?

Sarcoidosis is a multiorgan disease in which some patients never require therapy and others receive long-term treatment. The prevalence of the disease varies throughout the world. The wide array of rates of disease and clinical outcomes appear related more to the host’s response than to the etiologic agent. Each of us possesses genetic polymorphisms that account for our uniqueness. These polymorphisms influence our risk for acquiring a particular disease, the manifestation of the disease, and the resolution of disease. Sarcoidosis is one of many diseases in which the study of polymorphisms may lead to greater insight regarding disease manifestations.
The genetic diversity of sarcoidosis has been observed in disease manifestations for Japanese vs Scandinavians and for African Americans vs whites in the United States. However, investigators have experienced difficulty in attributing an ethnic group’s difference to a particular genetic polymorphism. Hence, many studies of sarcoidosis have compared sarcoidosis patients to race-matched and age-matched control subjects. The reported differences are then more likely due to the disease than to a coincidental relationship. Studies that have compared various ethnic groups have found that genetic patterns may lead to different patterns of the disease, depending on the ethnic group.

Genetic studies often have been developed around candidate genes. Their products are particular proteins or groups of proteins that have biological importance in the disease. However, finding an association does not always mean that the gene product is the cause for the disease. The gene may be linked to another gene that is the true disease modifier. Also, a variable response may not change the risk for the disease, but it may alter the outcome of the disease once it occurs.

The granuloma, which is the hallmark of sarcoidosis, is initiated by the complex of the antigen-presenting cell, usually a macrophage, and the T lymphocyte. The release of cytokines associated with a T helper type 1 cell response leads to granuloma formation. Candidate genes include the major histocompatibility complex (MHC) area, especially the human leukocyte antigen (HLA). Studies in familial and matched control studies have indicated that some HLA patterns are associated with an increased risk for sarcoidosis.

The angiotensin-converting enzyme (ACE) is elevated in 60 to 80% of patients with active sarcoidosis. Studies have suggested that ACE polymorphisms can lead to different serum ACE levels. Some groups, but not all groups, have found that ACE polymorphisms are associated with an increased risk for acquiring the disease. In a study by Maliarik et al., the deletion of a nontranslated portion of the ACE gene was associated with an increased risk for sarcoidosis in African Americans but not in whites. The importance of the enzyme in sarcoidosis remains unclear, since ACE inhibitors have never been shown to modify the disease. The variability seen with ACE polymorphisms may be explained by a linked neighboring gene.

Tumor necrosis factor (TNF)-α has been shown to be secreted in increased amounts in patients with active sarcoidosis. Studies have demonstrated that patients with chronic disease who are unresponsive to therapy with prednisone have persistent TNF release. Therapy to block TNF, such as thalidomide or anti-TNF antibodies, has proved to be useful. Studies of polymorphisms of TNF have been promising. The TNF gene is closely associated with the MHC genome area. The association between sarcoidosis presentation and TNF polymorphisms could be related to MHC changes or vice versa.

In this issue of CHEST (see page 1520), Morohashi and colleagues report on another candidate gene, vascular endothelial growth factor (VEGF). This is a logical protein to study, since it is part of the mononuclear cell response during the formation of a granuloma. The investigators chose to study single nuclear polymorphisms of the VEGF gene in a homogenous population of Japanese subjects. One polymorphism (the T allele at position +813) was associated with a decreased risk for sarcoidosis. Previously, this particular polymorphism was associated with lower VEGF plasma levels in healthy control subjects. Because reduced VEGF release inhibits the monocyte inflammatory response, one could argue that this is a biologically plausible reason for protection from sarcoidosis.

It has been previously reported that cigarette smokers have lower levels of VEGF in their lungs. Epidemiologic studies have found that sarcoidosis patients are less likely to be cigarette smokers. One hypothesis for this relationship is that cigarette smoking may be protective, since it down-regulates VEGF. We are not recommending cigarette smoking to prevent sarcoidosis, but the modification of VEGF may be a new therapeutic target that was identified by this genetic study.

The authors also tried to examine the potential impact of VEGF polymorphisms on disease presentation. They noted a relationship between changes at –627 and the FEV1/FVC ratio. Airway obstruction is not a major condition of most patients with sarcoidosis, and the relationship reported here was clinically insignificant. This study failed to identify a relationship between specific VEGF polymorphisms and organ involvement in sarcoidosis. However, this study further illustrates one of the dilemmas encountered when only one ethnic group is analyzed.

The study by Morohashi et al of 103 sarcoidosis patients included 71 patients with ocular disease and only 7 with skin disease. In a study of American sarcoidosis patients in which specific definitions of organ involvement were developed and applied to all the patients studied, the incidence of ocular and skin disease ranged between 10% and 20% for both organs. In the American study, there was more ocular and skin disease in the African American vs the white population, but the amount of eye disease was significantly less than that seen in Japan.
Most sarcoidosis patients experience a self-limited course, while others have chronic disease. Chronic disease is attributed to various factors, including host response to the disease. Studies of genetic polymorphisms may provide useful prognostic information as well. Certain HLA polymorphisms have yielded prognostic information. ACE polymorphisms have provided useful prognostic information in one study of Scandinavian subjects, but not in subjects from another ethnic group.

These conflicting results may be attributed to a lack of standard classification for chronic disease. Everyone agrees that the sarcoidosis patient with normal findings on a physical examination and from laboratory tests who is receiving no therapy has disease resolution. However, universal agreement is more difficult for the classification of the asymptomatic patient with persistent changes on chest roentgenograms who has not received therapy for > 2 years.

As we continue to acquire the genetic profile of patients with sarcoidosis, it will be imperative to refine our clinical phenotype of these patients. Some of the variation reported in different studies may be due to different classification schemes. In the future, one hopes that investigators will agree on a standard evaluation of organ involvement and disease severity. Studies of genetic polymorphisms may prove to be useful in the prediction of the risk for disease, organ involvement, response to specific therapy, and chronicity of disease. Genetic profiling must be studied in various ethnic groups to determine its applicability. As various research groups are acquiring DNA banks for studies on new candidate genes, it is imperative that clinical information is acquired and reported in a standard fashion so that the genotype can be matched with the phenotype.

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The Conundrum of Sleep Breathing Disorders in Heart Failure

Many years ago Hippocrates stated, “In whatever disease sleep is laborious, it is a deadly symptom; but if sleep does good, it is not deadly.” Today, a potential role for sleep disorders in the pathogenesis and complications of cardiovascular disorders is a concept that has gained support.1,2 Specifically, several studies3,4 have been performed in order to analyze the underlying mechanisms and the clinical importance, as well as the effects and consequences of sleep apnea in patients with heart failure. In this issue of CHEST (see page 1536), the article by Sin et al from Toronto reports on the relationship of systolic BP to obstructive sleep apnea in patients with heart failure. Before discussing their findings in detail, we briefly summarize our knowledge regarding the association of sleep apnea, heart failure, and hypertension.

Epidemiology

Observations from epidemiologic studies point toward an association between obstructive sleep apnea and heart failure. Thus, the Sleep Heart Health Study5 demonstrated that the presence of obstructive sleep apnea was associated with relative odds of 2.38 for heart failure independent of other known risk factors. This risk exceeded that for all other cardiovascular diseases examined, including hypertension, coronary artery disease, and stroke. Two series3,4 have evaluated the presence of sleep breathing disorders in patients with heart failure with systolic dysfunction. In one of the studies,3 51% of men with heart failure experienced sleep breathing disorders, 40% had central sleep apnea, and 11% had obstructive sleep apnea. In addition, the other study by the Toronto group4 demonstrated that the prevalence of obstructive sleep apnea was even higher (ie, up to 37%) in the 450 patients with heart failure who were studied. This work also demonstrated that an increase in body mass index in men and increasing age in women were risk factors for the development of sleep apnea in patients with heart failure.

The association of sleep apnea and hypertension has also been the focus of epidemiologic studies.3-7 Because of the importance of hypertension as a risk factor for the development of heart failure,8 and because of the prevalence of sleep apnea in both, one could ask, does obstructive sleep apnea contribute to the development of heart failure or is it a consequence of heart failure?

Does Heart Failure Contribute to the Development of Obstructive Sleep Apnea?

First, patients with heart failure and obstructive sleep apnea are predisposed to underlying periodic breathing disorders. Tidal volumes measured during hypopneas often have a waxing-waning appearance, which is typical Cheyne-Stokes respiration, compared to patients with obstructive sleep apnea and normal cardiac function who have abrupt rises and rapid falls in tidal volume.1 Second, the accumulation of edema in the soft tissues of the neck and pharynx on reclining could narrow the upper airway and make it more collapsible, therefore causing obstructive sleep apnea.1 Regardless the underlying cause in patients with heart failure and obstructive sleep apnea, the application of continuous positive airway pressure reverses the airway collapse.

Does Sleep Apnea Contribute to the Development of Heart Failure?

The most obvious mechanism and the link to the development of heart failure in patients with obstructive sleep apnea would be hypertension.8 Other risk factors, such as ischemia, decreased left ventricular contractility secondary to hypoxia and cardiac myocyte injury, which are related to catecholamine stimulation, and also can contribute to the development of heart failure in patients with sleep apnea.1,2

Some experimental studies have demonstrated that obstructive sleep apnea per se can lead to the development of pulmonary edema and to the development of left ventricular hypertrophy and left ventricular dysfunction. Fletcher et al9 demonstrated in dogs the development of subtle degrees of pulmonary edema after 8 h of exposure to recurrent obstructive apneas. Parker et al10 have shown that dogs who were exposed to obstructive apneas during sleep for several weeks to months showed an increase in left ventricular mass and a reduction in left ventricular ejection fraction in association with the development of hypertension. The association of obstructive sleep apnea and the development of left...