

# Clinical Year in Review II

## Interstitial Lung Disease, Sepsis, Pulmonary Infections, and Sleep Medicine

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### INTERSTITIAL LUNG DISEASE

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Five general topics related to interstitial lung disease were discussed during this session: (1) the use of infliximab therapy for pulmonary sarcoidosis, (2) the efficacy of cyclophosphamide for scleroderma lung disease, (3) the epidemiology of respiratory bronchiolitis, (4) genetic differences in familial idiopathic pulmonary fibrosis, and (5) clinical trial results for idiopathic pulmonary fibrosis.

Tumor necrosis factor (TNF)- $\alpha$  plays a critical role in the development of the noncaseating granulomas observed in patients with sarcoidosis (1). Infliximab is a TNF- $\alpha$  antibody that binds to and neutralizes TNF- $\alpha$ , and inhibits its activity after release from pulmonary macrophages. Previous reports have demonstrated efficacy of infliximab for patients with refractory sarcoidosis (2). Based on the positive results of these previous studies, Baughman and colleagues conducted a multicenter, randomized, double-blind, placebo-controlled study of infliximab for the treatment of patients with chronic sarcoidosis and documented pulmonary involvement (3). The inclusion criteria for the study were as follows: patients with histologically proven sarcoidosis diagnosed at least 1 year before screening, evidence of parenchymal disease on chest radiograph, an FVC of  $\geq 50$  and  $\leq 85\%$  of the predicted value, and a Medical Research Council dyspnea score of at least grade 1. Treatment with at least 10 mg/day of prednisone or equivalent or one or more immunosuppressants for more than 3 months before screening was also required. A total of 138 patients were enrolled and randomized to receive intravenous infusions of infliximab (3 or 5 mg/kg) or placebo in a 1:1:1 ratio at Weeks 0, 2, 6, 12, 16, and 24. Patients were subsequently followed for 1 year. At Week 24, patients in the combined infliximab groups (3 and 5 mg/kg) had a mean increase in the percentage of predicted FVC of 2.5% from baseline compared with no change in the percentage of predicted FVC in the placebo-treated patients ( $P = 0.038$ ). No significant differences between the treatment groups were observed for any of the major secondary endpoints at Week 24, including six-minute-walk distance or dyspnea scores. After the drug had been discontinued for 7 months, the improvements in lung volumes trended back to baseline in the infliximab group. The results of this phase II trial may support further clinical trials of infliximab for patients with chronic pulmonary sarcoidosis.

The development of interstitial lung disease in patients with scleroderma is associated with a mortality rate of 42% within 10

years after the onset of the disease (4). To date, there is no proven therapy for scleroderma-related interstitial lung disease. Tashkin and colleagues performed a double-blinded, randomized, placebo-controlled trial evaluating the efficacy of oral cyclophosphamide on lung function and health-related symptoms in patients with evidence of active alveolitis and scleroderma-related interstitial lung disease (5). A total of 158 patients with documented scleroderma, restrictive lung physiology, dyspnea, and evidence of inflammatory interstitial lung disease on bronchoalveolar lavage (BAL) or high-resolution computed tomography scanning were enrolled. Important exclusion criteria included patients with clinical significant evidence of pulmonary hypertension, patients who had been taking prednisone at a dose of more than 10 mg/day or oral cyclophosphamide for more than 4 weeks, and those who had recently received other potentially disease-modifying medications. Patients received oral cyclophosphamide (up to 2 mg/kg of body weight per day depending on their development of adverse events) for a total of 1 year, and were followed for a total of 2 years. The mean change in baseline FVC in the cyclophosphamide group was a loss of 1% compared with a loss of 2.6% in the placebo group ( $P < 0.03$ ). There were also significant improvements in the TLC and dyspnea scores at 12 months in the cyclophosphamide group compared with placebo. However, there was no improvement in DL<sub>CO</sub> in the treatment group. In an important subgroup analysis, those patients with more severe disease and more parenchymal involvement appear to do better with cyclophosphamide treatment. In a similar trial, patients with pulmonary fibrosis related to scleroderma were randomized to receive cyclophosphamide intravenously once a month for up to 6 months followed by oral azathioprine maintenance therapy (6). In this smaller study of 45 enrolled patients, there was also a trend to improvement in FVC at 1 year in the treatment group.

Respiratory bronchiolitis–interstitial lung disease (RB-ILD) is a histopathologic diagnosis related to smoking that previously had been considered to be a nonprogressive disease that improves with smoking cessation and possibly the use of antiinflammatory therapies. In this retrospective review, Portnoy and colleagues report the physiology and natural history of 32 cases with surgical biopsy–proven RB-ILD (7). The majority of these patients had either obstructive or restrictive physiology and a mixed physiologic picture was present in only 9% of patients. Only 67% of the patients were able to stop smoking after presentation with their disease. Overall, clinical improvement occurred in 28% of cases. Physiologic improvement occurred in only 10.5% of cases and was limited to those who had stopped smoking. The majority of all patients reported a worsening in their symptoms of dyspnea over time. Despite the deleterious effects of a diagnosis of RB-ILD on symptoms and physiology, only one patient died of their primary disease during the 7-year follow-up period. The results of this article challenge the previous concept that RB-ILD is a self-limiting disease that uniformly improves with smoking cessation.

To prevent possible incomplete replication and instability of the termini of linear DNA, eukaryotic chromosomes end in characteristic repetitive DNA sequences called telomeres (8). Loss of telomeric DNA due to degradation or incomplete replication is balanced by telomere elongation, which involves the synthesis of additional repeats by a DNA polymerase called telomerase (8). Telomerase has two essential components: a catalytic component, telomerase reverse transcriptase (hTERT), and an RNA component (hTR); the latter provides the template for nucleotide addition by hTERT (9). Dysfunctional telomerase activity, which had been associated with aging, smoking, and congenital dyskeratosis, results in shortened telomeres and an inability for cell replication, ultimately resulting in apoptosis and cell death. Based on the association of pulmonary fibrosis in patients with congenital dyskeratosis, the authors of the next article examined 73 probands from patients with familial pulmonary fibrosis. They detected six probands (8%) with heterozygous mutations in *hTERT* or *hTR*. Five probands had mutations in *hTERT* (two missense, two splice junction, and one frameshift), and one proband had a mutation in *hTR*. None of the *hTERT* mutations were present in 623 unaffected subjects. Importantly, the findings of an association between telomerase mutations and pulmonary fibrosis have also been independently identified in another study of 46 families with familial idiopathic pulmonary fibrosis (10).

*ELMO domain-containing protein 2 (ELMOD2)* is a gene involved with epithelial cell death and apoptosis. Hodgson and colleagues performed a genomewide scan in six families with familial idiopathic pulmonary fibrosis in Finland (11). The study revealed a shared 110 kb to 13 Mb haplotype on chromosome 4q31, which was significantly more frequent among the patients than in population-based control subjects. The shared haplotype harbored a functionally uncharacterized gene, *ELMOD2*, which was expressed in lung and significantly decreased messenger RNA expression in lung of patients with idiopathic pulmonary fibrosis when compared with healthy control subjects. These results suggest *ELMOD2* as a novel candidate gene for susceptibility in familial idiopathic pulmonary fibrosis.

Finally, one study that detected differences in gene transcription in patients with familial and sporadic idiopathic pulmonary fibrosis used a whole human genome oligonucleotide microarray (12). This study of 26 patients with idiopathic pulmonary fibrosis and 9 control subjects revealed that there is much overlap in the gene expression changes in patients with familial and sporadic disease. However, the intensity of the gene expression is higher in familial disease, raising the possibility that familial idiopathic pulmonary fibrosis is a more extreme variant of the sporadic disease. This study also revealed that there were no significant differences in gene expression between patients with usual interstitial pneumonia and nonspecific interstitial pneumonia.

Finally, Dr. Noble presented the unpublished results of three clinical trials for patients with idiopathic pulmonary fibrosis. A recent randomized placebo-controlled trial of IFN- $\gamma$  was stopped at the second predefined interim analysis for lack of efficacy of both primary and secondary outcomes. Therefore, IFN- $\gamma$  should not be used for patients with idiopathic pulmonary fibrosis. Recent data have also been released from a clinical trial of pirfenidone for idiopathic pulmonary fibrosis. A total of 267 patients were studied. In a preliminary review of the data, it appears that there is a possible improvement in progression-free survival defined as death or more than a 10% decrease in vital capacity in patients who received pirfenidone. The utility of pirfenidone for idiopathic pulmonary fibrosis is also being investigated in two ongoing clinical trials. Bosentan is also being studied as a therapy for idiopathic pulmonary fibrosis. One of the

clinical trials of bosentan did not achieve efficacy for the primary outcome variable of six-minute-walk distance. However, in the subset of patients who had a surgical biopsy diagnosis of idiopathic pulmonary fibrosis, there was a significant decrease in time to disease progression or death. Based on these results, a second clinical trial of bosentan is being conducted in patients with surgically proven idiopathic pulmonary fibrosis.

## SEPSIS

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In this session, three general topics related to sepsis were discussed: (1) epidemiology, (2) the diagnosis of relative adrenal insufficiency, and (3) possible new therapies for patients with sepsis.

The population in the United States increased by 13.2% from 1990 to 2000, and continues to get older, with 12% of the population or 35 million people currently over the age of 65. Use of intensive care unit (ICU) resources also increases with the rise in age in the population, as individuals over the age of 65 occupied one-half of all ICU days in 1995. Using the National Hospital Discharge Survey, Martin and colleagues further examined the effects of age on the epidemiology of sepsis in individuals 18 years or older (13). Over the 24-year period of this study, there were 717 million hospitalizations and over 10 million hospitalizations for sepsis. The cumulative age-specific incidence of sepsis increased exponentially across all age deciles. When stratified at age 65, the relative risk for sepsis was 13.1 times higher for individuals aged 65 or older. Examining all of the patients with an identified organism associated with their sepsis, the elderly were 1.3 times more likely to have sepsis due to gram-negative organisms when compared with individuals younger than 65 years of age. In the subset of patients with pulmonary sepsis and an identified organism, 34% of the organisms were gram negative in those patients over the age of 65, compared with only 20% of gram-negative pneumonia in patients younger than 65 years. The percentage of patients who died also increased linearly with age. When patients were stratified at age 65, those 65 and older were more likely to die, with an odds ratio of 2.26 in a multivariable model.

The next article that was discussed examined the effect of a diagnosis of cancer on the epidemiology of sepsis. This study used several different databases, including the following: the National Hospital Discharge Survey; the National Cancer Institute Surveillance, Epidemiology, and End Results database; and prevalence data from other peer-reviewed journals (14). The results of this study demonstrated that the incidence rate for sepsis in patients with cancer was the highest of any of the preexisting comorbid diagnoses and was 10 times higher than the incidence rate in the general population. However, when the data were examined longitudinally, there was a dramatic decrease in the incidence rate of sepsis in patients with cancer beginning in the late 1980s. The cause of this decrease is unclear, but is likely related to less toxic chemotherapeutic agents and better generalized medical care. This study also reported that cancer was an independent predictor of mortality in patients with sepsis, with an odds ratio of 2.15 in a multivariable analysis.

The final epidemiologic article explored the effects of alcohol abuse on the incidence of sepsis. Alcohol abuse and dependence impose significant burdens on patients, their families, and society, and alcohol use is common in patients admitted to the ICU (15).

Using the University Health System Consortium database, O'Brien and colleagues identified 9,981 adults who were admitted to an ICU over 6 years (16). A total of 822 patients, or 8.2%, had a diagnosis of sepsis using validated ICD-9 (International Classification of Diseases, ninth revision) codes, and 12% had a diagnosis of alcoholism or alcohol dependence. The results of this study demonstrated that sepsis was associated with an increased risk of having a diagnosis of alcoholism. In addition, alcoholism was associated with an increased mortality in the septic patients. These three epidemiologic articles will increase the awareness of the diagnosis of sepsis in the elderly, in patients with a diagnosis of cancer, and in individuals with a diagnosis of alcohol abuse. In addition, the identification of these epidemiologic associations may enable earlier therapeutic interventions for patients with sepsis. Finally, understanding the mechanism through which these diagnoses alter the susceptibility to sepsis may lead to the development of specific therapies for these subgroups of patients.

In the late 1990s, the concept of relative adrenal insufficiency emerged as a common problem in patients with septic shock and is associated with an increased mortality. In a *post hoc* analysis of patients with a diagnosis of relative adrenal insufficiency, adrenal replacement therapy decreases 28-day and hospital mortality (17). However, there is still controversy concerning the most accurate diagnostic tests for relative adrenal insufficiency. Some studies have advocated using baseline cortisol levels, whereas others have recommended the response to corticotropin stimulation testing. However, it is unclear whether to use the absolute number or change in cortisol levels when interpreting the response to corticotropin stimulation testing. Furthermore, one study demonstrated a more accurate diagnosis of relative adrenal insufficiency using free cortisol levels in critically ill patients (18).

Annan and colleagues studied four different groups of patients: two consecutive cohorts of patients with sepsis, a group of ICU control subjects, and healthy control subjects (19). The goal of the study was to determine the best diagnostic criteria to identify patients with relative adrenal insufficiency. All individuals underwent a random blood test for cortisol measurements, followed by the administration of a 250- $\mu$ g dose of cosyntropin, with blood drawn 60 minutes after its administration. Finally, patients underwent a metyrapone stimulation test, which was used as the gold standard to diagnose adrenal insufficiency. In brief, metyrapone is an inhibitor of adrenal 11 $\beta$  hydroxylase, which is an enzyme that converts 11-deoxycortisol to cortisol. When administered orally at midnight, metyrapone will normally induce low cortisol levels, stimulate corticotrophin releasing hormone and adrenocorticotropic hormone (ACTH), and make the adrenal gland produce increased levels of 11-deoxycortisol. After the administration of metyrapone, the diagnosis of both primary and secondary adrenal insufficiency can be made by measuring ACTH and 11-deoxycortisol levels.

In this study, the prevalence of relative adrenal insufficiency was 59 to 60% in the patients with sepsis, and the majority of patients had evidence of secondary adrenal insufficiency. The presence of secondary adrenal insufficiency would not be detected with a routine corticotropin stimulation test. Using the metyrapone test results as the gold standard, the best predictors of abnormal adrenal function were either a baseline total cortisol level of 10  $\mu$ g/dl or less or a change in cortisol in response to a corticotropin stimulation test of less than 9  $\mu$ g/dl. The best predictors of normal adrenal function were a post-corticotropin stimulation cortisol level of greater than 44  $\mu$ g/dl or a change in cortisol of greater than 16.8  $\mu$ g/dl. In a validation cohort, the diagnosis of relative adrenal insufficiency was correctly diagnosed in 85% of patients using an algorithm based on the total cortisol

levels and the change in cortisol in response to a corticotropin stimulation test.

Statins are potent lipid-lowering agents that have become the most commonly prescribed drug in the United States due to their ability to reduce the risk of cardiovascular events. More recent findings have demonstrated that statins have other important antiinflammatory, antioxidant, and antithrombotic effects. In view of their strong effects on inflammation, statins may represent a new therapy for sepsis, and animal models have demonstrated that statins may prevent the development of sepsis and modulate its severity. The first study examining a possible therapeutic benefit of statins in preventing sepsis was a Canadian population-based cohort study of nearly 150,000 patients who were older than 65 years, admitted for an acute cardiovascular event, or who underwent an arterial revascularization procedure. All patients also had to survive at least 3 months after hospital discharge (20). A third of patients were started on statin therapy during the 3 months after hospital discharge. Propensity scores were calculated based on the results of a logistic regression modeling technique that identified variables determining why patients were prescribed statin therapy. A subset of these statin users were then matched in a 1:1 fashion with non-statin users based on their propensity score in an attempt to create a pseudorandomized clinical trial. From the entire cohort, a total of 34,584 non-statin users were identified who were similar to the statin users except for the use of a statin. Patients were followed until death or hospital admission for sepsis, with a mean follow-up time of 2.2 years. The incidence of sepsis was significantly reduced in the statin users, from 88 to 71 cases of sepsis per 100,000 people each year. After adjustment for demographic factors, sepsis risk factors, other comorbidities, and measures of health care, the effects of statin therapy on the incidence of sepsis remained.

The second statin study used a multicenter cohort of over 1,000 dialysis patients who were followed from the time of initiation of dialysis (21). The primary outcome variable was hospitalization for a diagnosis of sepsis. On average, these patients were followed more than 3 years. Similar to the previous study, a protective effect of statin use was demonstrated on the development of sepsis.

These studies examining the effects of statin therapy are encouraging. However, due to the observational study design, the possibility of confounding by indication for treatment because of lack of randomization and unmeasured bias affecting the results cannot be entirely excluded. Further limitations of the first article are the lack of generalizability, because only patients older than 65 were included (20). In addition, even though the results were statistically significant, the effect size was fairly small, and a total of 595 patients would need to be treated to prevent one episode of sepsis. In regard to the limitations of the second article, which examined patients with chronic renal failure, treatment factors including the use of statins were only assessed at the time of study entry. However, this type of misclassification will usually underestimate the magnitude of the effect. Based on these limitations, both articles concluded that a randomized clinical study of the use of statins to prevent the development of sepsis is necessary.

The final article discussed in this session was a meta-analysis examining the use of intravenous immunoglobulins for sepsis (22). Intravenous immunoglobulins were first used as adjuvant therapy for sepsis beginning in the 1980s. The most publicized trial of immunoglobulin therapy was the negative HA-1A trial of an IgM monoclonal antibody against LPS (23). Monoclonal preparations contain immunoglobulins developed from a single cell line targeting a specific antigen, whereas polyclonal preparations are obtained from pooled sera containing different

immunoglobulins not necessarily directed at specific antigen sites. The use of polyclonal immunoglobulins has also been examined in patients with sepsis. This present meta-analysis identified 20 trials including 2,621 patients. The results demonstrated that the use of polyclonal immunoglobulins was associated with a reduction in the mortality rate, with a risk ratio of 0.74, and a number needed to treat of only nine patients to prevent one fatality from sepsis. Important secondary findings in this meta-analysis included a positive survival benefit of intravenous immunoglobulins in those trials that enrolled patients with severe sepsis and septic shock, in those that used a dose of greater than or equal to 1 g/kg, and in those that administered therapy for more than 2 days. Similar to the statin trials, the authors concluded that, based on the limitations of meta-analyses, a randomized clinical trial of intravenous immunoglobulins should be performed before this therapy is routinely used for patients with sepsis.

## PULMONARY INFECTIONS

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In this session on pulmonary infections, five topics were discussed: (1) the recently published community-acquired pneumonia (CAP) guidelines, (2) short-course antibiotic therapy for CAP, (3) diagnostic techniques of ventilator-associated pneumonia, (4) rapid identification of antibiotic resistance, and (5) pneumococcal macrolide resistance.

Based on the opinions of experts representing both the American Thoracic Society and the Infectious Diseases Society of America, there were a few important changes recommended regarding the guidelines for the diagnosis and treatment of CAP (24). It is now recommended that blood cultures should not be routinely collected unless in the setting of severe CAP or the presence of specific risk factors, such as liver disease or immunosuppression. The reasons for this recommendation were that blood culture results rarely alter therapy, and that false-positive blood culture results are associated with a three times increased use of vancomycin and a 1-day increase in hospital length of stay. The guidelines also recommended the use of *Legionella* and pneumococcal antigen testing for all patients with severe CAP. Finally, the early administration of antibiotics for patients with CAP was again encouraged, but a specific time window was not defined.

The optimum length of antibiotic treatment for adults with CAP is unknown. A recent study demonstrated that 750 mg of levofloxacin per day for 5 days is at least as effective as 500 mg/day for 10 days for the treatment of mild to severe CAP (25). The next article that was discussed in this session examined the effectiveness of discontinuing antibiotic therapy after 3 or 8 days in patients with mild to moderate CAP who required hospital admission (26). The study was a multicenter randomized trial that enrolled 186 non-ICU patients with CAP and a pneumonia severity index (PSI) score of less than 110 who were initially treated with intravenous amoxicillin alone. This therapy is considered to be the standard of care for treating CAP in the Netherlands. After 3 days of treatment, 148 patients had substantial clinical improvement. A total of 121 of these 148 patients were then randomized to receive either 5 more days of oral amoxicillin or 5 days of placebo. The clinical success rate at Day 10 was 93% for both groups and at Day 28 was 90 and 88% for the 3-day and 8-day treatment groups, respectively. Both groups had similar resolution of clinical symptoms. Radiologic success rates were similar in both groups at Days 10 and 28. Based on

these results, there is no difference in discontinuing antibiotics after 3 or 9 days in hospitalized patients with pneumonia who improved after an initial 3-day treatment course. The implications of a shorter course of antibiotic therapy include a possible reduction in health care costs of patients with CAP, less frequent antibiotic-related complications, such as *Clostridium difficile*-associated diarrhea, and possibly a decrease in the emergence of resistant organisms.

Whether bronchoscopic techniques are useful in the diagnosis of ventilator-associated pneumonia remains controversial (27, 28). The next study compared the outcome of patients with suspected ventilator-associated pneumonia who were randomized to either BAL with quantitative culturing or endotracheal aspirate with nonquantitative culturing (29). A very important exclusion criterion for this study was the exclusion of patients with known infection or colonization with *Pseudomonas* species or methicillin-resistant *Staphylococcus aureus* (MRSA). The study implemented an antibiotic adjustment protocol based on culture results. Unlike other previous studies, the results of Gram staining were not incorporated into clinical decisions, and therefore there were no adjustments of antibiotics until after culture results were obtained. If the culture was negative, antibiotics were discontinued except in patients with a high pretest likelihood of pneumonia or at the discretion of the physician. When culture results were positive, the use of a single antibiotic with the narrowest spectrum was encouraged. The primary outcome variable of this study was 28-day mortality, and, overall, 740 patients were enrolled. Compared with other studies of patients with suspected ventilator-associated pneumonia, there was a low percentage of patients with drug-resistant or high-risk organisms, likely related to the exclusion of patients with known infection or colonization with *Pseudomonas* species or MRSA. The results demonstrated no difference in 28-day mortality, use of targeted antibiotic therapy, ICU or hospital length of stay, or antibiotic-free days. An important limitation of this study was that Gram stains were not used to guide initial therapy and therefore all patients received either meropenem (1 g every 8 h) and ciprofloxacin (400 mg every 12 h) or meropenem alone as initial therapy for suspected ventilator-associated pneumonia. Because a mandatory initial antibiotic regimen was used and patients with known infection or colonization with *Pseudomonas* species or MRSA were not included in this study, there was a very high (89%) rate of adequate initial antibiotic therapy. Finally, because of the exclusion of patients with known infection or colonization with *Pseudomonas* species or MRSA, the initial antibiotic coverage was already narrow, did not include coverage for MRSA, and only one-half of the patients received double coverage for gram-negative organisms. Based on these limitations, it is unclear whether the results of this article will alter the use of invasive techniques in the diagnosis and management of ventilator-associated pneumonia.

A delay in the administration of adequate antimicrobial therapy is a risk factor for mortality in patients with ventilator-associated pneumonia. Unfortunately, initial antibiotic therapy is usually inadequate in 20 to 30% of patients with ventilator-associated pneumonia. Sensitivity results generally take 48 to 72 hours to obtain, because first the organism is cultured and identified, and then testing for antibiotic susceptibility is performed. This sequential processing of samples may lead to a prolonged period of inadequate antimicrobial therapy. In a study by Bouza and colleagues, a new method of determining antibiotic susceptibility was compared with standard testing methods in a randomized manner (30). In the experimental group, sputum, BAL fluid, or endotracheal aspirate was placed directly on a culture plate with antibiotic strips before growing a pure culture of the organism. With the experimental technique, there was

some difficulty in the interpretation of antibiotic susceptibility if more than one organism grew on the culture plate. However, the use of this rapid antibiotic susceptibility technique resulted in a higher percentage of adequate days of antibiotic therapy, more ventilator-free days, improvement in the number of febrile days, and a lower incidence of *C. difficile*-associated diarrhea. Only 3% of patients received antibiotics to which the isolate was believed to be sensitive based on the rapid test but ultimately determined to be resistant. Although these results are very encouraging, the experimental techniques need to be independently replicated, because implementation of these results would require the development of new skills for microbiology technicians.

Between 15 and 35% of pneumococcal isolates in North America and Europe have either low- or high-level resistance to macrolides. Low-level resistance to macrolides is often considered to have no clinical significance. Reported treatment failures are uncommon and appear to be related to the presence of high-level resistance. Therefore, macrolide monotherapy is commonly used for the outpatient treatment of CAP. The goal of this study was to determine whether *in vitro* pneumococcal macrolide resistance is a risk factor for failure of macrolide therapy (31). The study was a prospective population-based surveillance study of all CAP cases with pneumococcal isolates in metropolitan Toronto. Macrolide failure was defined as pneumococcal bacteremia occurring during either the oral macrolide treatment period or within 2 days after completion of therapy. During the 5 years of surveillance, there were 1,696 episodes of pneumococcal bacteremia, of which 60 (3.5%) were considered a failure of outpatient macrolide therapy. Resistant isolates were more common among cases of bacteremia after failure of macrolide therapy than among cases of bacteremia after failure of nonmacrolide antibiotics. In contradiction to our prior understanding of macrolide resistance, low-level resistance and high-level resistance were equally overrepresented among macrolide failures. In conclusion, the overall rate of failure of macrolide therapy remains fairly low. However, it may be reasonable to avoid macrolide monotherapy in patients with pneumonia who have had recent macrolide exposure.

## SLEEP MEDICINE

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Four general topics related to sleep medicine were discussed during this session: (1) the effects of chronic intermittent hypoxia on atherosclerosis, (2) the diagnosis and management of sleep apnea without the use of polysomnography, (3) the effects of sleep apnea on driving performance, and (4) alternative therapies for obstructive sleep apnea.

There is increasing epidemiologic evidence that severe, untreated obstructive sleep apnea is associated with the development of cardiovascular events (32, 33). The aim of this study was to determine whether chronic intermittent hypoxia similar to that which occurs in obstructive sleep apnea produces atherosclerosis in mice (34). The study had four groups: control mice fed a normal diet and not exposed to intermittent hypoxia, a group that received a high-cholesterol diet and were not exposed to intermittent hypoxia, a group that received intermittent hypoxia for 12 hours per day and that were fed a normal diet, and a combined challenge group that were exposed to intermittent hypoxia for 12 hours per day and received a high-cholesterol diet. The overall duration of the study was 12 weeks. During this

interval, control mice and mice exposed to only a single challenge (either diet or intermittent hypoxia) did not develop atherosclerosis of the aorta. In contrast, mice on both the high-cholesterol diet and with chronic intermittent hypoxia developed significant atherosclerosis. A high-cholesterol diet also resulted in increased serum lipids that were further increased by chronic intermittent hypoxia. Chronic intermittent hypoxia was associated with hyperglycemia and decreased insulin levels, especially in those mice that were fed a normal diet. This is the first study demonstrating that chronic intermittent hypoxia can contribute to the development of atherosclerosis. However, it appears that the presence of a high-cholesterol diet is necessary to produce the deleterious effects of chronic intermittent hypoxia. One concern with this study is that the frequency and magnitude of the intermittent hypoxia is large because animals were exposed to 5% inspired oxygen 60 times per hour. Therefore, further studies are required to more fully elucidate the mechanism through which chronic intermittent hypoxia produces atherosclerosis.

The second study that was discussed evaluated a novel diagnostic and treatment strategy for patients with a high pretest probability of obstructive sleep apnea (35). The assignment of patients with a high pretest probability of obstructive sleep apnea was based on the results of two questionnaires: an Epworth Sleepiness Scale score of 10 or greater and a Sleep Apnea Clinical Score of 15 or greater. Because the use of these two questionnaires maintains a high degree of specificity, patients enrolled into this study only represented a small fraction of subjects (3.7%) referred for assessment of sleep-disordered breathing. Overall, 68 subjects were randomized into one of two treatment groups: an in-laboratory pathway with a full sleep study and in-lab continuous positive airway pressure (CPAP) titration or the use of an auto-adjust system for 1 week that would determine the optimal amount of CPAP to be used. After 6 to 12 days, an overnight oximetry study was performed to determine the efficacy of the CPAP therapy, and, if there were residual events, the pressure was then increased by 1 to 2 cm H<sub>2</sub>O. After 3 months of treatment, there was no difference in the apnea-hypopnea index between the two groups. There was also no difference in the extent of the reduction of Epworth Sleepiness Scale. Of interest, the mean hours of CPAP use was greater in the auto titration group. The results of this study demonstrate that, for patients with a high pretest probability of obstructive sleep apnea, there is no need to perform an in-laboratory sleep study or CPAP titration because equivalent outcomes are obtained with the use of an auto-adjust system.

Approximately 4,500 people die each year in motor vehicle accidents involving commercial drivers. In a large proportion of these accidents, falling asleep while driving is considered to be a major contributing factor. Whether the presence of obstructive sleep apnea in commercial drivers contributes to the development of these accidents is unclear. This study involved an in-depth investigation of a total of 406 drivers: 247 considered to be at high risk for sleep apnea and 159 who were considered to be at low risk (36). Risk assessment for the presence of sleep apnea was based on the results of the Multivariable Apnea Prediction model. Subjects underwent actigraphy for 1 week to assess sleep duration at home, in-laboratory polysomnography, and multiple tests of daytime performance. The study demonstrated that a substantial percentage of these drivers had performance impairment, as 29% had a multiple sleep latency period of less than 5 minutes. Two of the major determinants of performance impairment and excessive sleepiness were severe sleep apnea defined as an apnea-hypopnea index of greater than 30 episodes per hour and a sleep duration of less than 5 hours. A diagnosis of sleep apnea was present in 26.2% of commercial

drivers: the sleep apnea was considered mild in 15.7%, moderate in 5.8%, and severe in 4.7% of drivers. Sleep duration of fewer than 5 hours also occurred in 13.5% of commercial drivers. Only 6.2% of commercial drivers obtained an average sleep duration of more than 8 hours while at home. Therefore, identifying and treating drivers with severe obstructive sleep apnea is one strategy that may reduce excessive sleepiness in commercial drivers. This study also identified that chronic short sleep duration or insufficient sleep is also a common problem in commercial drivers.

The didgeridoo is an instrument developed by Australian Aborigines that is a long wooden tube that requires strong blowing. Based on the observation from a didgeridoo instructor that some of his students experienced reduced sleepiness and snoring after practicing with the instrument for several months, investigators performed a randomized clinical trial of didgeridoo playing for patients with sleep apnea (37). The study enrolled 25 patients who had snoring and moderate sleep apnea defined as an apnea-hypopnea index of between 15 and 20 events per hour. Patients in the treatment group practiced the didgeridoo an average of 5.9 days/week for 25.3 minutes. There was a significantly larger fall in the Epworth Sleepiness Scale score and a greater fall in the apnea-hypopnea index in the didgeridoo group at the four-month endpoint. This provocative study raises the possibility that training of the upper airway muscles may be of value in patients with mild to moderate obstructive sleep apnea.

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