

Delayed Mortality Seen After Pneumonia

Pneumonia patients discharged with high blood cytokine levels showed greater 90-day mortality.

BY JANE SALODOF MACNEIL
Southwest Bureau

SAN DIEGO — Community-acquired pneumonia patients are significantly more likely to die within 3 months of leaving the hospital if they have high concentrations of inflammatory cytokines before discharge, Dr. Sachin Yende reported at the international conference of the American Thoracic Society.

Above-normal levels of interleukin-6 (IL-6) and interleukin-10 (IL-10) were strongly associated with 90-day mortality in a large, ongoing study presented by Dr. Yende of the University of Pittsburgh Medical Center.

Predischarge IL-6 concentrations were nearly twice as high in discharged patients who died within 90 days: 10.6 pg/mL vs. 5.9 pg/mL in survivors. IL-10 levels were three times as high in the patients who died: 3.1 pg/mL vs. 1 pg/mL.

Concentrations of both cytokines were slightly higher in patients who had had sepsis while hospitalized but not significantly higher than the levels measured near discharge in those who had not had sepsis.

"People are sent home with fairly high cytokine concentrations," Dr. Yende said in an interview.

"If physicians were aware, they would not have wanted to send these patients home." The physicians were not aware, he said, because cytokine levels are not routinely ordered and the study was blinded.

The investigation follows an earlier finding that recovered community-acquired pneumonia patients have higher mortality 5 years after hospitalization than would be predicted by their age, gender, or other variables. "The increased mortality we

have seen is not because these people are older or have more chronic health conditions. It is because of this hospitalization," Dr. Yende said, adding that he and his colleagues were trying to find out why.

The cohort study collected blood daily for 1 week and once weekly subsequent-



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DR. YENDE

ly, starting with 2,320 patients who presented with pneumonia in the emergency departments at 28 hospitals. Of 1,895 patients who were admitted, 87 (5%) died in the hospital.

Among the remaining patients, 1,799 were alive at discharge and included in the cohort followed by investigators, but 126 (7%) of these patients died within 90 days. Dr. Yende reported 1,636 were still alive, and outcomes were not known for 37 (2%) of the discharged patients.

The IL-6 and IL-10 data were based on 1,452 patients in whom concentrations were measured 48 hours before discharge. Overall, the median IL-6 and IL-10 levels as measured between the 10th and 90th percentiles were 6.2 pg/mL and 5 pg/mL, respectively. In comparison, Dr. Yende said, median IL-6 levels typically range from 1.8 pg/mL in healthy persons to 98.7 pg/mL in patients with severe sepsis.

While Dr. Yende emphasized that more work needs to be done before the investi-

gators can establish causality, he speculated that an acute illness such as pneumonia might be a "feed-forward phenomenon" that leads to increased incidence of pneumonia or cardiovascular events.

"An acute event like pneumonia or sepsis may alter subsequent life trajectory even after hospital discharge," he said.

The investigators obtained 1-year data on the discharged pneumonia patients shortly before Dr. Yende's presentation. Though they had not had time for a full analysis, he reported mortality had reached 16%. The five leading causes of death at 1 year were chronic ischemic heart disease, malignant neoplasms of the respiratory system, pneumonia, cerebrovascular disease, and acute myocardial infarction.

"These are the same diseases that have been shown in cardiovascular literature to be associated with increased risk when you have elevated C-reactive protein and other inflammatory markers," Dr. Yende said.

At this point, he said, a recommendation for routine measurement of inflammatory markers would be premature. In the future, he predicted, this could become standard along with interventions and a faster follow-up visit in the physician's office.

"Normally you say [to] come back after 6 weeks," he said. "Maybe there is a role to call them back earlier and remeasure and see how things go—but right now, there isn't evidence to support that."

Asked whether pressure to send pneumonia patients home faster could be a factor, Dr. Yende said the vast majority of discharged patients are ready to go home. "They are on the road to recovery," he said. "And that is the interesting point. Even if you think they are ready to go home, perhaps there is something going on that may be completely bad." ■

Strategies Launched for Global TB

BY BRUCE JANCIN
Denver Bureau

LISBON — This year will be the one with the most cases of tuberculosis worldwide in all of history—and the greatest number of deaths due to the disease, Dr. Peter Godfrey-Faussett said at the 12th International Congress on Infectious Diseases.

This is in part because of population growth and because TB rates continue to rise. Nine million people develop active TB each year, more than one-third of them in China and India. Two million die of the disease annually, and 30% of the world's population is latently infected with *Mycobacterium tuberculosis*, Dr. Godfrey-Faussett said.

But the news is not all bad. Latest estimates by World Health Organization epidemiologists are that TB rates are actually falling in every region of the world except Africa, noted Dr. Godfrey-Faussett, professor of infectious diseases and international health at the London School of Hygiene and Tropical Medicine.

Within Africa, the highest TB rates occur in countries where the prevalence of HIV is greatest. It's now clear that traditional Directly Observed Treatment, Short Course (DOTS) programs alone will be insufficient to reduce the burden of TB in areas where the epidemic is driven by HIV, he added at the congress, which was sponsored by the International Society for Infectious Diseases.

Structured DOTS programs have been invaluable in combating TB and have cured more than 10 million people since 1994. And in a famous field study in which Chinese health authorities implemented DOTS in half the country, the prevalence of TB plummeted by 37% in a decade, compared with the rate in the other half of China.

Earlier this year at the World Economic Forum annual meeting in Davos, Switzerland, leaders of the Stop TB Partnership, including Bill Gates and Nigerian President Olusegun Obasanjo, launched a new TB strategy that builds upon traditional DOTS. The strategy puts a much greater emphasis on HIV, multidrug-resistant TB, and strengthening health systems in developing nations.

"We badly need new technology. I believe improved diagnosis is the single thing that will make the most difference for TB control," Dr. Godfrey-Faussett said. He was somewhat skeptical about the TB vaccines now going into field studies. "There's quite a lot of basic understanding needed before we're likely to have vaccines that work. A lot of people aren't that optimistic that the vaccines now going to trials will really prevent a lot of TB. We still have a lot of work to do in terms of better understanding of the immunology." ■

Flu Expert Urges More Research on Statins

BY JONATHAN GARDNER
London Bureau

PARIS — Public health authorities should develop a research agenda on the use of statins as treatment and prophylaxis in the event of an influenza pandemic, a top researcher said at an international conference on avian influenza in humans.

Data suggest that statins could be useful in combating such side effects as pneumonia, sepsis, bacteremia, and pulmonary disease, said Dr. David Fedson, coordinator of the Macroepidemiology of Influenza Vaccination (MIV) Study Group and a former professor of medicine at the University of Virginia, Charlottesville. Statins could be an alternative treatment in the first wave of a pandemic, when vaccines may be unavailable.

Statins can interfere with inflammation and with virus transport, assembly, and budding, while aiding endothelial and epithelial cell function and immune response, Dr. Fedson said. These qualities could make statins an effective treatment

option in the event that avian influenza H5N1 mutates into a form that can infect humans more easily.

Should such a mutation take place, vaccine manufacturers first will need to match their vaccine to the virus and then ramp up production, which will mean that the first regions to be affected could be defenseless against the pandemic.

"In the event of an H5N1 pandemic, the global demand will easily be on the order of 3-4 billion doses, and probably much more," Dr. Fedson said.

"Yet today, if the world's vaccine companies were asked to produce [vaccine], in 6 months they could produce enough ... to vaccinate fewer than 100 million people. Vaccination will not be a realistic possibility for 85% of the world's population that do not live in countries with vaccine companies, and it will be difficult even for those who do," he said.

By comparison, generic statins are inexpensive—\$1.75 for 5 days' worth of dosage in the United States—and they can be produced worldwide, Dr. Fedson said.

Among the evidence in favor of statins' protective qualities, Dr. Fedson said, are studies showing a reduction of up to 92% in bacteremia-attributable mortality among patients who take statins; a reduction of up to 25% in sepsis mortality among patients who have previously taken statins; and a 53% reduction in 30-day pneumonia mortality among those patients who have taken statins.

However, international health officials need to embark on a statin research agenda to explore unanswered questions, Dr. Fedson said.

To understand whether statins are an option, researchers need to perform clinical and epidemiologic studies examining hospitalization and mortality.

They also must clearly compare the effects of previous statin use with continuing statin use, and compare treatment with prophylaxis. In addition, researchers need to do animal studies with mice, ferrets, and primates, and more clearly determine the molecular mechanism of action, he noted. ■