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Immunostimulation
Does It Work in COPD?

What constitutes immunostimulation is a matter of debate. Immunity is a highly complex mechanism with multiple functions. Activation of macrophages, enhanced antigen presentation, and increased lymphocyte responses are some of the functions of immune cells likely to promote phagocytic activity. Correction of an aberration in immunity is a function-directed rather than a general phenomenon. Immunostimulation therefore is a confusing nomenclature. *Immunoregulation* or *immunomodulation* are other terms used for the same phenomenon, which are as poorly defined as immunostimulation. It is perhaps better understood as the process of maintaining the immune system in a "state of alert" that is capable of efficiently handling microbial infections. This is precisely the objective that is desired to handle the invading organisms.

Immunostimulation has been advocated as a management strategy in COPD for the purposes of preventing acute exacerbations. Exacerbations are most commonly caused by infections, and prevention of infections is likely to prevent most of the acute exacerbations. Undoubtedly, acute exacerbations of COPD characterized by aggravation of respiratory symptoms and decline of function significantly add to the disease morbidity and mortality. Reduction in the number of acute exacerbations does improve the quality of life, decrease the overall morbidity, and lessen the costs of disease management. Several therapeutic and preventive strategies have been adopted for this purpose from time to time. Long-term inhaled corticosteroids, mucolytic agents, and antioxidants have been employed in different studies with limited benefits. Use of immunostimulation agents is one such option included in the management recommendation of the Global Initiative of Chronic Obstructive Lung Disease (GOLD), as well as some other guidelines, including those from this country. But the evidence in favor of their use is available only from a limited body of data.

Oral purified lyophilized extracts such as OM 85-BV of bacteria that are commonly responsible for respiratory infections in COPD have been employed as immunomodulating agents in some European countries for over 2 decades. Several other reports were published in the following years. But their role was not clearly established. Now, after the publication of the Prevention of Acute Respiratory Infection by an Immuno-stimulant (PARI-IS) study and its incorporation in the GOLD document, there is a rejuvenated interest in the subject and a search is on to find a clear answer.
and colleagues in this issue (see page 1645) have systematically reviewed the available evidence and presented important findings. The authors have reviewed 13 trials on two commercially available agents: OM 85-BV, LW50020, or SL-04. They had retrieved “seventy one potentially relevant reports,” of which 58 were excluded. A meticulous meta-analysis was performed using fixed and random effect models, which concluded that although the evidence is not enough to suggest the role of immunostimulators in prevention of exacerbations, they do improve symptoms in patients of COPD. This in itself is an important conclusion to keep the interest in the subject alive.

Incidentally, there were very few trials with high global score of quality assessment, ie, only one trial with a score of 6 and two trials with scores of 4 each. This is a great limitation to reach any final conclusion. For this very reason, the authors have recommended further research on the subject. The PARI-IS study, which was a large, double-blind, placebo-controlled, randomized trial and scored the best quality global scores by the authors of this article, suggested the beneficial effect of the immunostimulation in COPD by reducing the likelihood of severe respiratory events to hospitalization. The average duration of an exacerbation was shown to be reduced in three other trials, while prevention of exacerbations was reported in one large trial of acceptable quality and another small trial of low quality. An important advantage of preventive treatment with immunostimulation has been shown in another study on cost-effectiveness analysis in Switzerland. Incidentally, immunotherapy with OM-85 BV was found to be useful also in prevention of respiratory tract infections (RTIs) in children, as well as in adults employed in a car factory who were highly susceptible to acute RTIs.

While the search to find answers to this riddle will continue, the question a clinician faces is whether to use the drug or wait until we accumulate more clinical experience and know the immunologic pathway that is effectively stimulated, useful to prevent, and fight infection in these patients. The use of immunostimulators is clearly an option that a clinician can exercise as per the needs of his patient. The cutaneous eruptions and urologic problems seen in up to 3 to 8% of patients in some trials would limit the use of immunostimulation on a large scale. But the additional benefit of symptomatic relief and reduction in the hospitalization period, however small these may be, would be difficult to deny to a patient who has no other option.

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Preventing Medical Errors, Avoiding Litigation
Not Easy To Do in 2004

For physicians who desire a better understanding of the current malpractice crisis in America, I suggest they read James Mohr’s article entitled “American Medical Malpractice Litigation in Historical Perspective,”1 in which Mohr reviews the medical and legal factors that have contributed to periodic malpractice crises3 in the last 150 years: the innovative medical factors that have contributed to periodic malpractice litigation today achieves its presumed social goals: to deter unsafe medical practices, to fairly compensate patients injured by negligent practices, and to institute corrective justice.2 Mohr cites the following medical factors that have contributed to periodic malpractice crises3 in the last 150 years: the innovative pressures on American medicine, the spread of uniform standards, and the creation of medical malpractice liability insurance. Contributing legal factors include contingent fees, citizen juries, and the nature of tort pleading in the United States. I do not intend to review Mohr’s article here, but I would like to elaborate on the first factor, innovation in medicine, as an entry point to my discussion of Thomas McLean’s article in this issue of CHEST (see page 1672).

Mohr recounts how radiographic technology in the early 20th century significantly aided physicians by offering them greater opportunities to visualize abnormalities that could not previously be detected by history or physical examination. Physicians enthusiastically embraced the new technology, just as they embrace new technology today, because it gave them more power to perform their professional duties: cure patients and relieve suffering. However, the development of radiography also gave litigation lawyers more objective evidence of potential physician negligence: missed diagnoses, excessive radiation, and failure to act on a radiographic abnormality. “Objective” is the key word here: the previously undetectable lung mass can now be viewed on the screen by physicians and trial lawyers alike.

Lung cancer is the most common cause of cancer in men and women in the United States, with close to 170,000 cases diagnosed in 2002.4 Unless the cancer is discovered in the very early stages of disease, patients have a poor prognosis (overall 5-year survival rate is 15%).4 Today, the undetectable lung nodule on a routine radiograph can be seen on CT scans. Should we use this technology to screen smokers? The US Preventive Services Task Force recently concluded that evidence is insufficient to recommend for or against screening.5 Those physicians who choose to screen their patients will experience the same potential benefits (finding an early lung cancer) and the same potential risks of malpractice litigation (increased chance for missed diagnoses, and false-positive workups that may lead to medical complications) as early 20th century physicians did when x-rays were first introduced. Once again, physicians must carefully balance the benefits and harms of new technologies, not only for their patients, but also for themselves. In other words, ordering a CT scan for a smoker is not necessarily the right thing to do, either from a patient benefit or a defensive medicine point of view.

In his study, McLean set out to determine why physicians who treat lung cancer get sued. He retrospectively reviewed a publicly available database Lexis Nexis’ “Jury Verdict and Settlements, Combined” for all cases involving lung cancer and malpractice between January 1, 1999, and December 31, 2003. Verdicts and settlements were voluntarily submitted by lawyers. Data therefore represents a small, nonconsecutive, and select sample of cases. McLean then compared his data to the Physician Insurers Association of America (PIAA) Lung Cancer Study published in 1992.6 The results are as follows: radiologists (27% of all physicians sued in current study; 31% in the PIAA study) and primary care physicians (30% in current study; 42% in the PIAA study) were the most likely physicians to be sued, primarily for failure to diagnose lung cancer (the basis for suits in 80% of current study; 23.3% in the PIAA study). He also showed how the financial awards to plaintiffs have dramatically increased since the PIAA study (mean award was $172,272 in the PIAA study; $632,261 in the present study).6 Although McLean discovered that failure to diagnose lung cancer is the main reason doctors were sued, he does not explain why the PIAA study found this reason to be a much smaller percentage (23.3%). Data regarding other ostensible reasons for suits (surgical or chemotherapy complications, false-positive diagnoses) were not provided by the PIAA study.6

I suspect there are deeper reasons why these patients sued their doctors. Not every doctor who misses the diagnosis of lung cancer gets sued. What distinguishes doctors who are sued from the ones that are not sued? Worse outcomes? Poor communication? Unrealistic patient expectations?6

There is increasing evidence that excellent patient-physician relationships and good communication reduce the risk of malpractice litigation, particularly for primary care physicians.7–11 Physician behaviors associated with reduced malpractice claims include appropriate use of humor, solicitation of patient opinions, checking for patient understanding, and encouraging patients to

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