Continuing Controversy: Pneumococcal Vaccine and COPD

Enthusiasm for pneumococcal vaccines has waxed and waned for decades. Although demonstrated effective among United States Army recruits in 1945, pneumococcal vaccines were little utilized in an era which saw mortality from bacteremic disease decrease from greater than 70 percent in the pre-penicillin era, to 15-45 percent in more recent literature. Recognition of this persistent mortality has led to the resurgence of interest in pneumococcal vaccines. However, because the overall incidence of serious disease is estimated to be relatively low, vaccination of the entire population has not been determined to be cost-effective. Instead, the vaccine has been recommended for certain groups of patients believed to be at increased risk for serious pneumococcal disease, including patients with chronic obstructive pulmonary disease (COPD). This recommendation presumes: a) that pneumococcal disease is more common in these patients, b) that these infections are more severe and/or lethal in these patients, and c) that the efficacy of vaccination in these patients would approximate that reported in normal individuals. However, the validity of these beliefs and assumptions has been questioned. The article by Davis et al in this issue (see page 204) adds fuel to this controversy.

Because patients with COPD frequently have pneumococci in their sputum, it might be expected that pneumococcal pneumonia and associated bacteremia would be more common in these patients. Davis et al did find among COPD patients a relatively high incidence of pneumonia in which pneumococci were demonstrable in sputum; however, a relatively low incidence of associated bacteremia was also noted. Arguably, the study size was relatively small, and the criteria for selecting sputum samples less exclusive than required by some centers. However, despite use of more stringent sputum criteria, a similarly low incidence of systemic infection was recently reported in a larger study of elderly veterans which included COPD patients. Therefore, the incidence of deeply invasive (systemic), pneumococcal infections may not be accurately estimated by examination of sputum in patients with chronic airways disease among whom the incidence of associated bacteremia appears surprisingly low, and perhaps overestimated previously. Importantly, bacteremic patients demonstrate the greatest mortality and are believed to represent those most likely to benefit from stimulation of circulating antibodies with a vaccine.

The antibody data obtained by Davis et al make a number of points. The elevated prevaccination antibody titers suggest that naturally acquired immunity may play some role in inhibiting bacteremia, thereby limiting pneumococcal disease to the lungs in COPD patients. However, the relatively high incidence of pneumococci demonstrable in the sputum of these patients suggests that increased circulating antibody titers may be relatively ineffective in erradicating these organisms from the airways of such patients. Therefore, other factors may play more important roles locally, including altered cellular and mechanical clearance mechanisms. That a vaccine will only variably enhance circulating antibody titers in these patients has been demonstrated by others as well. Similarly, a blunted antibody response to vaccination has been noted in patients with concurrent pneumococcal infections. Limited data have suggested that an antibody titer of 300 nanograms antibody nitrogen per milliliter may be protective in humans, although the applicability of these levels to all serotypes and all patients remains unclear. For example, serum opsonic activity has been reported to be variably elevated in chronic bronchitis patients, but was not significantly enhanced by vaccine stimulation of antibody titers in these patients.

Clearly, the most important question is whether the vaccine will reduce morbidity and/or mortality in these patients, and the limited number of patients studied by Davis et al does not permit such analyses. However, the data reported do raise questions regarding the likelihood of demonstrating a benefit of vaccination where circulating antibody enhancement appears reduced and a relatively low incidence of systemic disease may be present. Other authors have retrospectively estimated vaccine efficacy by comparing the vaccine/nonvaccine serotypic ratios of pneumococci isolated from blood of vaccinated and unvaccinated patients. While not statistically significant as an isolated subgroup, efficacy was suggested among patients with chronic lung diseases. However, such an approach assumes that vaccination does not induce a shift toward non-vaccine serotypic infections, which
unfortunately might be inferred (though not statistically proven) from data trends in the Davis study, the study of veterans,7 and a study of elderly, institutionalized patients.8

In the absence of convincing data, the importance of a pneumococcal vaccine for patients with COPD will likely remain controversial. Advocates of the vaccine argue: a) that the high costs of a large, prospective study of this specific group are prohibitive, and b) that withholding the vaccine in patients with COPD may be unethical.3 In support of the former, the relatively low incidence of bacteremic disease would require following large numbers of patients for several years to obtain meaningful data regarding invasive infections. However, regarding the latter, the study of veterans’ demonstrated a statistically significant increased mortality among vaccine recipients (although the significance of this finding was unclear and may have reflected some other differences in the groups studied). Additionally, the relatively low incidence of systemic disease would factor negatively in a cost-benefit analysis, while the relatively increased incidence of non-pneumococcal infections noted by Davis et al would tend to obscure clinical benefits in individual patients. Finally, the decreased duration of protection suggested by antibody titers following vaccination may necessitate repetitive immunization (though not currently recommended); the resultant increased cost of vaccination may make a large study more fiscally rational.

A number of other questions remain unanswered, including potential differences in baseline titers and vaccine responses of younger COPD patients; however, the age range studied by Davis et al likely reflects the majority of COPD patients. The inclusion in the currently available vaccine of polysaccharide from 23 rather than 14 pneumococcal serotypes (of 84 identified) may more completely represent the serotypes to which COPD patients are currently exposed, although a serotypic shift might then occur in a vaccinated population. Lastly, exploration of animals models, as discussed by Davis et al, provides an alternate method of estimating clinical vaccine efficacy, but the applicability of such data to normal or diseased humans remains to be established.

James H. Williams, Jr., M.D., F.C.C.P.
Orange, California

REFERENCES

Physiologically Responsive Cardiac Pacemakers

A Role for Electrical Impedance?

The control of pacemaker rate by impedance-based respiratory minute ventilation is a concept with a great deal of logic. Since the introduction of closed chest pacing as an emergency therapeutic procedure in the first third of this century, pacemaker technology has progressed to the development of physiologically responsive devices. The ultimate is, of course, that finely tuned, multiple-sensor-dependent system, employed by the normal heart which enables it to transport oxygenated blood at a rate commensurate with metabolic needs/activity. Working in consort with the cardiovascular system is the body's gas exchange system, which must be equally responsive to the body's metabolic needs. In those many patients in whom the latter has not been damaged by pulmonary disease but is still responsive, it is reasonable to use this system to coordinate the output of the heart.

The control of cardiac output, especially its augmentation during exercise, is predominantly accomplished by acceleration of the heart rate; only modest increases can be achieved via the Starling principle, especially in the failing left ventricle with a fixed stroke volume. In those patients whose hearts can no longer respond to...