August 2012 Pulmonary Journal Club

While Dr. Mathew was away, we reviewed 5 articles. Some of the fellows helped out and their names are at the end of the articles they reviewed.

Butler JP, Loring SH, Patz S, Tsuda A, Yablonskiy DA, Mentzer SJ. Evidence for adult lung growth in humans. N Engl J Med 2012;367:244-7.

This is a case presentation of a 33 year old female, post pneumonectomy for treatment of right hilar adenocarcinoma, and the observation of what appears to be lung growth in the remaining left lung by means of CT and MRI imaging utilizing techniques to evaluate tissue density, alveolar microstructure (radial dimension of the acinar airways and alveolar depth), as well as utilizing spirometry. This observation had not previously been described in adult humans, placing the idea that lung growth and regeneration only occurring perinataly and in early youth at question. There have been several publications with observation of lung growth in other mammals which have been noted to occur over months to years (1).

This is a very interesting observation of lung growth post-pneumonectomy in a mid 30s female. The impact of this observation is that even after early youth, the capacity to grow lung tissue is still at hand; albeit slightly altered, as was described with the decreased alveolar depth and underlying heterogeneity. Nonetheless, if the understanding of the mechanisms by which this growth takes place, the ability to manipulate and expedite cellular function and regeneration can make a great impact on future practice and management of patients with functional lung tissue loss from any etiology. This impact may be a valuable tool in, not only post-pneumonectomy patients with underlying malignancy, but also in lung volume reduction surgery for COPD, amongst other common causes of lung disease and alveolar destruction that have at least some viable lung tissue remaining.

Joshua Jewell, MD

Navani N, Lawrence DR, Kolvekar S, et al. Endobronchial ultrasound-guided transbronchial needle aspiration prevents mediastinoscopies in the diagnosis of isolated mediastinal lymphadenopathy: a prospective trial. Am J Respir Crit Care Med 2012;186:255-260.

Endobronchial ultrasound –guided transbronchial needle aspiration (EBUS-BRNA) is emerging as an alternate diagnostic test for the staging of the non-small cell lung cancer compared to mediastinoscopy (1). The authors tested EBUS-TBNA as a first diagnostic test instead of mediastinoscopy, the “Gold Standard” for patients who present with isolated mediastinal lymphadenopathy. A prospective, multicenter single arm study was undertaken in south east England with 77 patients with isolated mediastinal adenopathy. EBUS-TBNA providing

accurate diagnosis in 67 patients (87%). When economic analysis was done on the decision tree model, the cost for EBUS-TBNA strategy was $2998 and for mediastinoscopy alone was $5115. On statistical analysis EBUS-TBNA has a sensitivity of 92%, diagnostic accuracy of 92% but only a 40% negative predictive value. Based on the low negative predictive value, the authors recommended that patients who had negative EBUS-TBNA should undergo mediastinoscopy.

This study has some limitations requiring a tertiary center with expert pulmonologists and experienced pathologists able to obtain and interpret the EBUS-TBNA samples. It was done in an area where fungal diseases are not endemic perhaps limiting its application in the Southwest. It also excluded patients who had anterior mediastinal lymphadenopathy which can't be approached by EBUS-TBNA.

The above study lends further support to the performance of EBUS-TBNA prior to mediastinoscopy in patients with isolated mediastinal lymphadenopathy.

Suresh Uppalapu, MD

Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med. 2011;365:689-98.

The authors performed a randomized trial to determine whether azithromycin decreased the frequency of COPD exacerbations. A total of 1577 subjects were screened; 1142 (72%) were randomly assigned to receive azithromycin, at a dose of 250 mg daily (570 participants), or placebo (572 participants) for 1 year in addition to their usual care. Azithromycin reduced the median time to the first exacerbation ($P<0.001$) and the frequency of exacerbations ($P=0.01$) compared to placebo. Hearing decrements were more common in the azithromycin group (25% vs. 20%, $P=0.04$) but there was no increase in death or cardiovascular deaths (see article below).

The reduction of COPD exacerbations is quite plausible since erythromycin, another macrolide, has been previously reported to reduce COPD exacerbations (3). Macrolides are known to have anti-inflammatory effects which may explain the reduction in COPD exacerbations. Other antibiotics such as the tetracyclines also have anti-inflammatory effects and could be an alternative if an antibiotic other than a macrolide is appropriate.

Richard A. Robbins, MD

Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med. 2012;366:1881-90.

Macrolides are frequently used as therapy for acute infections and are increasingly being used as chronic therapy for chronic lung diseases such as

cystic fibrosis, asthma or COPD (see article review above). However, several published reports have associated azithromycin with QT prolongation and resultant arrhythmias. The authors studied a Tennessee Medicaid cohort to detect an increased risk of death related to short-term cardiac effects of azithromycin, amoxicillin, or no antibiotics. During 5 days of therapy, patients taking azithromycin had an increased risk of both cardiovascular death and death from any cause compared to amoxicillin or no antibiotic. However, the incidence was low with an estimated 47 additional cardiovascular deaths per 1 million courses. For patients in the highest decile of cardiovascular risk scores, there were an estimated 245 additional cardiovascular deaths per 1 million 5-day courses of azithromycin therapy.

Azithromycin has been the best studied of the macrolides. In addition to its antimicrobial effects, macrolides also have anti-inflammatory effects which may explain its efficacy, at least in part, in some chronic disorders. Other antibiotics such as the tetracyclines also have anti-inflammatory effects but have not been studied nearly as extensively as the macrolides.

How one should use this data is unclear. Pulmonologists often treat elderly, sick patients with macrolides for acute disorders such as an exacerbation of COPD. These patients are at an increased risk for death not only because of their underlying lung disorder but also because of age and associated diseases, including cardiovascular disease. If a patient with an exacerbation of COPD was given azithromycin and died, a not infrequent occurrence, it seems unlikely that azithromycin contributed to the patient's death. It is more likely, but still rare, if the patient has known cardiovascular disease. On the other hand, discretion might suggest it may be medically/legally advisable to use another antibiotic. This is especially true in those with known cardiovascular disease or those receiving another drug known to cause QT prolongation such as amiodarone.

Richard A. Robbins, MD

Tyrrell GJ, Lovgren M, Ibrahim Q, et al. Epidemic of invasive pneumococcal disease, western Canada, 2005-2009. Emerg Infect Dis 2012;18:733-40.

In western Canada an epidemic of serotype 5 invasive pneumococcal disease was reported: 52 cases during 2005, 393 during 2006, 457 during 2007, 104 during 2008, and 42 during in 2009. These patients were more likely to be younger, male, First Nations heritage or homeless. Restriction fragment-length polymorphism typing indicated that the epidemic was caused by a single clone, which multilocus sequence typing identified as sequence type 289.

At first read, this appears to be a catastrophe with large number of patients dying from an epidemic of an aggressive pneumococcus. Note the title where invasive and epidemic are used, but the title is misleading. Invasive pneumococcal disease is defined as isolation of S. pneumoniae from a normally sterile site. For

the large majority of cases this means blood with 95% of the isolates coming from blood in this series. However, large observational studies have not demonstrated an increased mortality or complications in patients with a positive blood culture compared to those whose blood is sterile (4). In this article, identification of type 5 invasive pneumococcal disease was actually associated with a ***decreased*** mortality compared to other invasive pneumococcal serotypes (3.2% vs. 14.1%). Furthermore, although the cases of serotype type 5 increased, it is unclear if there was an increase in pneumococcal disease. The incidence of pneumococcal pneumonia, the most common clinical manifestation of S. pneumonia, is known to vary from year. Figure 2 of the manuscript suggests that if there was an increase in isolation of invasive pneumococcal serotypes this was accompanied by an increase in both serotype 5 as well as other serotypes.

This is an interesting epidemiologic study but the use of words such as epidemic and invasive, although technically correct, are misleading. Clinicians need to be aware of the definitions of these terms in order to prevent overreaction to reports such as this one.

Richard A. Robbins, MD

References

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