

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Joel E. Richter, MD

GERD in Lung Transplant Patients

Daniel Sifrim, MD, PhD
Barts and The London School
of Medicine and Dentistry
Wingate Institute of Neurogastroenterology
London, United Kingdom
Catholic University of Leuven, Belgium

G&H What is the prevalence of gastroesophageal reflux disease in patients with lung disease compared to the general population?

DS Increased gastroesophageal reflux disease (GERD) is observed in many patients with respiratory disorders, that is, chronic unexplained cough, asthma, and other less common respiratory disorders such as pulmonary fibrosis and cystic fibrosis, as well as patients who require lung transplantation. It is clear to both respiratory doctors and gastroenterologists that the prevalence of GERD in patients with respiratory disorders is higher than expected by chance; GERD is much more common in both pre- and post-lung transplant populations than in the general population. In the pre-lung transplant population (ie, patients with end-stage respiratory disorders), there is a high prevalence of GERD because of mechanical issues, that is, pressure gradients due to cough, airway constriction, cough-inducing reflux, and medication taken to control the severity of respiratory symptoms, which might affect the antireflux barrier at the gastroesophageal junction. In the post-lung transplant population, the prevalence of GERD is also much higher than in the general population, 35–70%, according to different studies. Inversely, the prevalence of respiratory symptoms in patients with GERD is also increased. The Montreal consensus defined extraesophageal GERD syndromes and, within this category, recognized established associations between reflux and cough, laryngitis, and asthma.

G&H Could you expand further on the current understanding of the relationship between GERD and lung disease?

DS We know that some patients have both GERD and respiratory disorders. Some of these patients respond to antireflux therapy, with improvement in their respiratory symptoms. However, we still cannot predict with certainty those patients that will respond positively, probably due to the lack of complete understanding of the causal association between GERD and lung disease. As of yet, no biomarker has been found that clearly identifies respiratory patients in whom reflux is the causal factor.

Currently, there are three main pathophysiologic hypotheses. One is that gastric contents are microaspirated into the airways. Another possibility is that gastric contents in the esophagus trigger a vagal reflex beginning in the esophagus that incites a change in the airway, by provoking either inflammation or constriction. A third possibility is that GERD makes the airway hypersensitive and reactive to multiple stimuli (ie, cold air or viral infection). This hypersensitivity is initiated by reflux but thereafter may become independent from reflux. If this is the case, the treatment of reflux might have little or no impact on the patient's respiratory symptoms.

Most of the current literature agrees that antireflux therapy in patients with respiratory disorders is less efficient than antireflux therapy for patients with typical GERD symptoms such as heartburn or regurgitation. We need to identify the factors that can predict a positive

response to antireflux therapy and use them to identify the patient phenotype that will be the most likely responder to antireflux therapy.

G&H Does the presence of GERD affect outcomes for lung transplantation?

DS This is a topic that is somewhat controversial. The first data in the literature suggested that patients with increased GERD were more prone to develop chronic rejection and bronchiolitis obliterans syndrome (BOS), suggesting the need for GERD treatment to postpone transplant or improve the prognosis of these patients. More recent data, however, do not confirm the concept that by eliminating reflux, we completely prevent the development of BOS.

G&H Does adjusting GERD medical therapy or performing a pretransplant fundoplication have any prophylactic effects on the need for lung transplantation or the outcomes of the procedure?

DS I am not aware of any data justifying the modification of medical therapy to avoid transplantation; pretransplant GERD treatment will not eliminate the need for transplantation, as far as I understand. In terms of the effect of pretransplant GERD treatment on post-transplant survival or disease evolution, there is not much known. One or two reports have suggested this possibility, but this theory has not been reproduced in the literature as of yet. In terms of medical treatment with proton pump inhibitors and transplantation outcomes, this is definitely not the case because proton pump inhibitors do not stop reflux; they only modify the pH of the refluxate and transform acid reflux into weakly acidic or nonacid reflux containing bile acids, pepsins, and other substances that, if aspirated in the post-transplant setting, would provoke similar damage and eventually bad outcomes in these patients. As for pretransplant antireflux surgery, the possibility that it would modify the evolution of post-transplant outcomes is unknown. In general, patients who undergo lung transplant are in critical condition and are very delicate. The risk of antireflux surgery in these patients is much higher than in the common GERD population, as they have a higher rate of complications and even mortality. At this time, I am not convinced that pretransplant antireflux surgery is indicated.

G&H In GERD patients who have undergone lung transplant, is the GERD more severe or difficult to treat?

DS The GERD in these patients should not be more difficult to treat, though there are a few caveats here.

First, patients undergoing medical treatment for GERD should be aware that the combination of proton pump inhibitors with other drugs for transplantation (ie, immunosuppressive agents, antibiotics, steroids, and additional therapy) may eventually increase side effects. Second, patients taking proton pump inhibitors frequently have bacterial overgrowth in the stomach. The risk of aspiration is not eliminated by proton pump inhibitors and, therefore, the patients might still have aspiration with nonacid gastric contents, including bacteria or bacterial products, which, in terms of bronchial inflammation, is at least as dangerous as aspiration of typical acid gastric contents.

G&H In general, how effective is medical or surgical therapy for GERD in post-lung transplant patients?

DS Medical antireflux therapy has not shown, thus far, a significant change in the evolution of patients after lung transplant. In contrast, there are several reports (most of them from the same transplant team) showing a positive effect of post-transplant antireflux surgery. Of course, these results should be reproduced in other centers before recommending this therapy.

G&H What is the role of azithromycin for treating reflux in lung transplant patients?

DS This medication was initially developed as an antibiotic but has other anti-inflammatory effects that have been demonstrated to be very useful in the treatment of patients with chronic inflammatory respiratory disorders (ie, cystic fibrosis) and in post-lung transplant patients. We have also recently demonstrated that this macrolide antibiotic has the potential to reduce GERD because of its prokinetic effect on gastric and esophageal motility. Whether or not the positive effect of azithromycin in the evolution of lung transplant patients also involves its antireflux prokinetic effect remains a matter of research. I believe that the most important effect of azithromycin is related to its anti-inflammatory properties rather than its antireflux properties.

G&H Are there any special concerns or contraindications when treating GERD in patients who have undergone lung transplant?

DS There are no special concerns when using medical therapy. The use of antireflux surgical therapy would depend upon the functional status of the patient. I do not believe that antireflux surgery should be provided in a patient who is unstable, from the cardio-respiratory perspective, but apart from this, there are no contraindications.

G&H Are there any upcoming studies on this topic that you are anticipating?

DS There is a very important upcoming randomized study from a group in Belgium on the effect of azithromycin that will likely illuminate the role of this important medication in the evolution of patients post–lung transplant. For future studies, there remains a need for a more standardized protocol of indication and technique for antireflux surgery in patients with lung transplant. This standardization will likely be developed by the appropriate associations or groups of interest working on lung transplant at the moment. In addition, as mentioned earlier, there is a need for further research to identify markers of aspiration or reflux that might define the phenotype of lung transplant patients that will benefit from antireflux therapy.

Dr. Sifrim acknowledges Veerle Mertens, MSc, and Prof. Lieven Dupont, MD, PhD, from the Catholic University of Leuven, Belgium for their co-authorship of our studies on GERD and lung transplant and the preparation of this manuscript.

Suggested Reading

Blondeau K, Mertens V, Vanaudenaerde BA, Verleden GM, Van Raemdonck DE, et al. Nocturnal weakly acidic reflux promotes aspiration of bile acids in lung transplant recipients. *J Heart Lung Transplant.* 2009;28:141-148.

Mertens V, Blondeau K, Pauwels A, Farre R, Vanaudenaerde B, et al. Azithromycin reduces gastroesophageal reflux and aspiration in lung transplant recipients. *Dig Dis Sci.* 2009;54:972-979.

Blondeau K, Mertens V, Vanaudenaerde BA, Verleden GM, Van Raemdonck DE, et al. Gastro-oesophageal reflux and gastric aspiration in lung transplant patients with or without chronic rejection. *Eur Respir J.* 2008;31:707-713.

Burton PR, Button B, Brown W, Lee M, Roberts S, et al. Medium-term outcome of fundoplication after lung transplantation. *Dis Esophagus.* 2009;22:642-648.

King BJ, Iyer H, Leidi AA, Carby MR. Gastroesophageal reflux in bronchiolitis obliterans syndrome: a new perspective. *Heart Lung Transplant.* 2009;28:870-875.