available at that time. An important and encouraging finding of this study was that 45% of the cohort fell into the low-risk group, suggesting significant clinical usefulness of such an approach.

A word of caution is due in the interpretation of this study. The absolute number of adverse outcomes was small, potentially limiting the precision and generalizability of the study. A number of patients did not have hs-cTnI levels measured. This was more common in patients with active malignancy, so caution should be taken in applying the results to this group of patients. Perhaps most importantly, 10 patients identified as low risk ultimately experienced an escalation in care. Although none of these patients underwent thrombolysis or CPR or died, three of them had legitimate reasons for ICU admission (hypoxemia requiring nonrebreather mask or noninvasive ventilation or hypotension requiring vasopressor support). Of these three, one of them was in the high-risk Pulmonary Embolism Severity Index group, and, thus, the combination of a clinical score and the hs-cTnI level may have prevented this miscategorization. Prior studies have confirmed the very high negative predictive value of N-terminal pro-BNP levels in patients with acute PE. Would the addition of this biomarker reduce the number of patients inaccurately classified as low risk?[6] Further, would a panel of cardiac biomarkers (serum sodium, hs-cTnI or hs-cTnt, N-terminal pro-BNP, heart-type fatty acid binding protein, and D-dimer level) assist accurate discrimination? These are questions that deserve further investigation.

Will the results of this study modify our clinical practice regarding risk stratification of patients with acute PE? I think the answer to this is yes, particularly if the findings are confirmed in management studies. We are getting closer to the point where we can confidently tell patients with acute PE to take their medicine and go home.

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Management of Alveolar-Pleural Fistula

A Complex Medical and Surgical Problem

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Alveolar-pleural fistula (APF) and bronchopleural fistula (BPF) are uncommon yet frustrating medical and surgical problems with high morbidity and mortality. They may originate spontaneously or be encountered after bronchoscopy or thoracic surgery. However, they are almost always caused by an underlying pulmonary pathology, which seems to be the most important prognostic factor.

Reparative surgeries are never a desired first therapeutic option for APF or BPF. Pleurodesis with chemicals such as talc and thoracic surgery have had high failure rates.[1] Unfortunately, pleural and bronchoscopic interventions have had limited success as well. Bronchoscopic options for APF and BPF have been

marred by technical problems, although their conceptual foundation is appealing. Airway occluding devices and agents have been used for decades. These modalities include endobronchial Watanabe spigots (Novatech), gelfoams, endobronchial valves, and synthetic hydrogel.

A Watanabe spigot functions by blocking the airway leading to the fistula. The spigot looks somewhat like a wine bottle cork. It is grasped with forceps passed through the working channel of the bronchoscope and pushed out into the target airway. Although spigots are perhaps the most simplistic of bronchoscopic approaches, their migration was a significant problem in several studies.[2]

Prior to application of a spigot or any other endobronchial modality, the fistula is localized using information about the surgical site or by chest CT scan examination. The location is confirmed by occluding the airway with an inflated Fogarty balloon catheter or another commercially available sizing balloon. When the balloon occludes the airway leading to the fistula, bubbling stops in the water seal chamber of the chest drainage system. Balloons also provide an estimate of the size of the device needed to block the airway orifice.

Endobronchial valves are perhaps one of the most established and successful modalities for treating APF and BPF. Currently, two different endobronchial valves are available: the Zephyr valve (Pulmonx) and the Spiration IBV Valve System (Spiration, Inc). The IBV is the only valve with US Food and Drug Administration approval (humanitarian) in the United States. The experience with its humanitarian use and success in treating postsurgical BPF[3,4] led to Food and Drug Administration approval for BPF. The IBV is currently being evaluated in clinical trials for use in bronchoscopic lung volume reduction. The IBV is a one-way valve that looks somewhat like a miniature umbrella and comes in multiple sizes. The valve is loaded into a catheter passed through the working channel of the bronchoscope and pushed into the target airway to occlude it. The valve blocks the flow of air into the affected lung segment, promoting healing of the fistula. Some of the key features of the IBV are its reversibility and its shape, which allows secretions and trapped air to exit the airway while blocking the inward flow of air into the damaged lung segment. However, collateral ventilation is not addressed by endobronchial valves, which may account for the majority of valve treatment failures.

In this issue of *CHEST*, Mehta et al[5] (see page 695) describe their retrospective experience with >20 cases of APF treated with a novel modality, a synthetic hydrogel (CoSeal; Baxter Healthcare Corp). CoSeal is composed of two synthetic polyethylene glycols (PEGs). The two PEG solutions are applied endobronchially via a flexible polyurethane catheter (Duplocath; Baxter Healthcare Corp) deployed through the working channel of the bronchoscope. When the two compounds mix in the airway, they polymerize, forming a sealant plug. Within a few minutes, the sealant congeals in the airway to occlude the predetermined target airway leading to the fistula. The plug is gradually resorbed over the next 2 weeks, reducing the risk of complications such as postobstructive pneumonia and atelectasis. In their study, Mehta et al[5] were able to successfully stop air leaks in 85% of the patients within 2 ± 1 days.

Some of the unique properties of CoSeal include "auto-reversibility" (the compound resorbs in 2 weeks) and ease of use. It is also possible that the initial liquid nature of the compound may better occlude collateral ventilation channels, thus promoting healing of the fistula. Larger prospective trials of CoSeal are needed to answer questions about its effectiveness in occluding large fistulas involving multiple lung segments or lobes and its short-term reversibility in the event of therapeutic failure or worsening respiratory status.

The current bronchoscopic management of BPFs varies based on the severity of the BPF and personal experience with available modalities. For small BPF, gel foams, spigots, CoSeal, and valves can all work effectively if chosen appropriately from a technical standpoint. For instance, spigots tend to dislodge and migrate out of the location where they were originally placed compared

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with valves. Similarly, in areas with a potentially high likelihood of collateral channels, modalities such as CoSeal may work better compared with valves. For large fistulas involving the lobar bronchi or mainstem bronchi seen in patients with posttransplant dehiscence or postpneumonectomy or postlobectomy dehiscence, silicone stents or fully covered metallic stents placed temporarily may work better than other modalities. Silicone stents are generally preferred because they are easy to remove and can be made to order, such as an inverted "Y" stent with one of the main limbs cut just below the crina and sealed at the end to prevent any airflow through that particular mainstem airway. Similarly, a cone-shaped (tapered) custom-made stent can be placed from the trachea into one of the mainstem bronchi, bypassing the effected mainstem bronchi with the defect.[6,7]

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Treatment of Alveolar-Pleural Fistula With Endobronchial Application of Synthetic Hydrogel

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BACKGROUND: Alveolar-pleural fistula with persistent air leak is a common problem causing significant morbidity, prolonged hospital stay, and increased health-care costs. When conventional therapy fails, an alternative to prolonged chest-tube drainage or surgery is needed. New bronchoscopic techniques have been developed to close the air leak by reducing the flow of air through the leak. The objective of this study was to analyze our experience with bronchoscopic application of a synthetic hydrogel for the treatment of such fistulas.

METHODS: We conducted a retrospective study of patients with alveolar-pleural fistula with persistent air leaks treated with synthetic hydrogel application via flexible bronchoscopy. Patient characteristics, underlying disease, and outcome of endoscopic treatment were analyzed.

RESULTS: Between January 2009 and December 2013, 22 patients (14 men, eight women; mean age ± SD, 62 ± 10 years) were treated with one to three applications of a synthetic hydrogel per patient. The primary etiology of persistent air leak was necrotizing pneumonia (n = 8), post-thoracic surgery (n = 6), bullous emphysema (n = 5), idiopathic interstitial pneumonia (n = 2), and sarcoidosis (n = 1). Nineteen patients (86%) had complete resolution of the air leak, leading to successful removal of chest tube a mean (± SD) of 4.3 ± 0.9 days after last bronchoscopic application. The procedure was very well tolerated, with two patients coughing up the hydrogel and one having hypoxemia requiring bronchoscopic suctioning.

CONCLUSIONS: Bronchoscopic administration of a synthetic hydrogel is an effective, nonsurgical, minimally invasive intervention for patients with persistent pulmonary air leaks secondary to alveolar-pleural fistula. CHEST 2015; 147(3):695-699

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ABBREVIATIONS: AP = alveolar-pleural

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An alveolar-pleural (AP) fistula is a communication between the pulmonary parenchyma, distal to a segmental bronchus, and the pleural space. The term is often used interchangeably with bronchopleural fistula, which, by definition, is a communication between a mainstem, lobar, or segmental bronchus and the pleural space. The two terms, however, refer to distinct clinical problems with different natural histories and management options. AP fistulas are extremely common and are reported to occur in most large series in about 33% of patients after thoracic surgeries, depending on how and when they are defined.[1,2] The hallmark of an AP fistula is a prolonged air leak via a closed pleural drainage system. Prolonged pulmonary air leaks secondary to AP fistula may cause considerable morbidity, prolonged hospital stay, and increased health-care costs.[3] Common causes of AP fistula include postsurgical bullous emphysema, advanced pulmonary sarcoidosis, radiation fibrosis, interstitial lung diseases, and necrotizing pneumonia. The treatment of patients with AP fistula secondary to underlying pulmonary disease is often very challenging due to the decreased ability of the diseased lung to heal. Furthermore, most of these patients are not ideal surgical candidates.

Because poor performance status caused by pulmonary disease may increase the risk associated with surgical

FOR EDITORIAL COMMENT SEE PAGE 590

intervention, alternative therapies are needed. Treatment of prolonged air leaks by intrapleural administration of sclerosing agents has shown little efficacy and variable patient tolerance.[4] Endobronchial approaches include the application of absorbable gelatin powder (Gelfoam; Pfizer Inc); the use of fibrin glue in conjunction with endovascular, metallic, ring-shaped coil placement[5,6]; and endobronchial valves.[7-13] The results of these nonsurgical approaches appear promising and, for some patients, may be the only treatment option after all conventional treatments have failed and the potential for high risk of morbidity with surgical intervention is present. The aim of this study was to analyze our experience of AP fistula closure with a synthetic hydrogel (CoSeal; Baxter Healthcare Corporation) applied by flexible bronchoscopy.

Materials and Methods

Between January 2009 and December 2013, all patients treated with endobronchial synthetic hydrogel application for AP fistula were reviewed. The institutional review board at the University of Florida approved this study (#IRB201400004). The following data were retrospectively abstracted from patients' medical records: demographic information, etiology of the air leak, number of days with air leak prior to first bronchoscopic synthetic hydrogel application, lobe(s) isolated by hydrogel application, other therapeutic interventions performed before and after hydrogel application, number of bronchoscopic attempts, and number of days to removal of the chest tube after final hydrogel application. The primary end point was success of bronchoscopic synthetic hydrogel application in resolving the air leak, determined by chest-tube removal. Secondary end points evaluated included median number of days to stoppage of air leak and to chest-tube removal following final session of synthetic hydrogel application. These variables were analyzed using simple descriptive statistics.

All patients underwent CT imaging of the chest. The procedure was performed with conscious sedation, spontaneous breathing, and flexible bronchoscopy. Prior to synthetic hydrogel application, the chest drainage system was observed to assess the air leak. The severity of air leak was determined based on extent of bubbling in the chest-drainage system. A balloon-tipped, single lumen, 5F catheter (Arrow International Inc) was inserted into the lobar airway suspected of supplying the air leak. For selective bronchial occlusion, the balloon was inflated to block the airflow to that region of the lung. The air-leak rate through the chest tube was then assessed qualitatively for reduction. If the leak rate was reduced, the balloon catheter was deflated and repositioned into a more distal airway. The process was repeated to identify the segmental or subsegmental airway or airways that, when occluded, offered the greatest reduction in air-leak rate. These airways were then targeted for synthetic hydrogel application. If we were unable to isolate the airway responsible for a persistent air leak, or if the leak disappeared with administration of sedation, the likely culprit lobe was estimated by reviewing chest CT scans, and that lobar airway was targeted for synthetic hydrogel application. There were no contraindications to application of synthetic hydrogel. If the patient could tolerate a flexible bronchoscopy under conscious sedation, they were considered candidates for hydrogel application.

The synthetic hydrogel used for the study was CoSeal, which is designed to act as a sealant around a sutured site. This synthetic hydrogel is composed of two synthetic polyethylene glycols, a dilute hydrogen chloride solution, and a sodium phosphate/sodium carbonate solution. The different components are mixed per the manufacturer's instruction prior to procedure.[14] Since the delivery system provided with this synthetic hydrogel is incompatible with bronchoscopic application, we applied the hydrogel endobronchially via a flexible polyurethane catheter deployed through the working channel of the bronchoscope (Duplocath; Baxter Healthcare Corporation). A few milliliters of polyethylene glycol solution diluted with hydrogen chloride and sodium phosphate/sodium carbonate solution was injected simultaneously into the airway through two separate channels in the catheter. Figure 1A shows the hydrogel in liquid form, immediately after application in the airway. When the two compounds mix in the airway, they polymerize, leading to formation of a congealed sealant plug. After a sufficient amount is injected to occlude the target airway, the bronchoscope and the catheter are withdrawn as a single unit, taking care to not allow excess sealant in liquid form to come in contact with the bronchoscope. Within a few minutes, the sealant congeals in the airway to occlude the airway leading to the fistula. Figure 1B demonstrates formation of a congealed plug after several minutes of application. Any excess sealant, once congealed, is then removed bronchoscopically to prevent occlusion of the normal airway lumen. Over the next 24 h, the plug further expands, sealing the airway. The plug that forms is gradually resorbed over the next 2 weeks and, thus, long-term damage or scarring to airways is uncommon.

Following synthetic hydrogel application, patients were allowed to recover from sedation according to standard hospital practice. Vital signs were closely monitored. Chest radiography was used daily to assess for pneumothorax. The chest-drainage device was assessed daily for air leak.

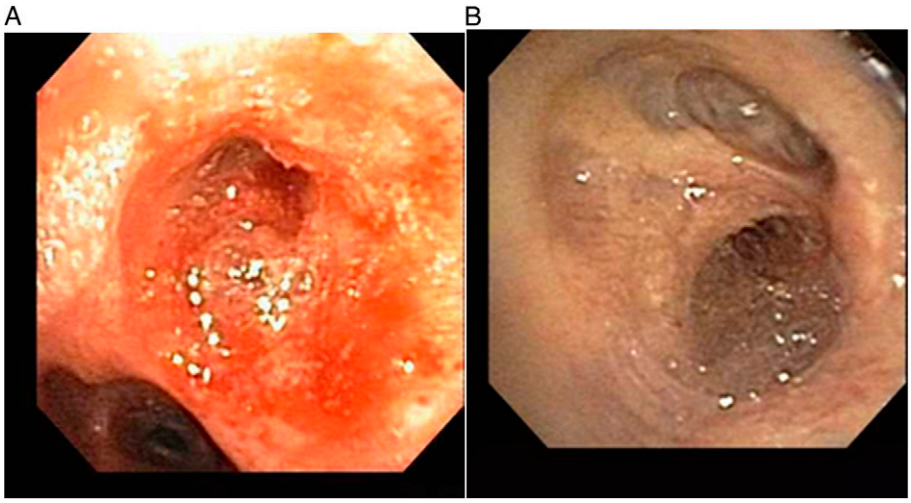

Figure 1 – *A, Synthetic hydrogel, in a right upper lung bronchus, in liquid form immediately after application. B, Synthetic hydrogel forming a congealed plug several minutes after application in a right lower lung bronchus.*

Results

Fourteen men and eight women (mean age ± SD, 62 ± 10 years) underwent endobronchial synthetic hydrogel application at the University of Florida Hospital between January 2009 and December 2013. A total of 31 applications were performed in these 22 patients, with two patients having three applications and five having two applications. The primary etiology of persistent air leak was necrotizing pneumonia (n = 8), postthoracic surgery (n = 6), bullous emphysema (n = 5), idiopathic interstitial pneumonia (n = 2), and sarcoidosis (n = 1). The average number of days of air leak prior to first endobronchial hydrogel application was 10 (SD ± 6 days), with the longest time being 27 days and shortest being 4 days. Synthetic hydrogel application was performed to occlude the right upper lobe in three patients, right middle lobe in three patients, right lower lobe in eight patients, left upper lobe in five patients, and the left lower lobe in three patients. Following application, there was cessation of air leak in 19 (86%) of these patients, leading to successful chest-tube removal. The average duration between the final session of synthetic hydrogel application and cessation of air leak was 2 days (SD ± 1 day), and the duration to removal of chest tube was 4.3 days (SD ± 0.9 days). Once the air leak was sealed after synthetic hydrogel application, 11 patients had doxycycline pleurodesis, and four had talc pleurodesis prior to removal of chest tubes, to prevent further recurrence of pneumothoraces.

Of the three patients in whom synthetic hydrogel application failed to seal the leak, one was discharged home with a Heimlich valve, and two died during the hospitalization; none of the events was related to complications of the procedure. Each of the three patients had three separate attempts at endobronchial gluing, separated by at least 4 days each. Two of the three patients had necrotizing pneumonia as the cause of AP fistula and one had a postsurgical leak.

Major complications included coughing up the hydrogel plug (n = 3), requiring a second procedure for reapplication of synthetic hydrogel, and hypoxemia (n = 1), requiring emergent bronchoscopy with suctioning of a dislodged congealed plug from the trachea. No deaths were attributed to the synthetic hydrogel or application of glue.

Discussion

Prolonged pulmonary air leak leads to considerable morbidity for patients, such as prolonged hospitalization, empyema, fever, and pneumonia.[15] The treatment of these patients, most of whom have structural lung disease, is often very challenging, as they are not optimal surgical candidates. This has prompted the need for a nonsurgical, minimally invasive approach to treat patients with this condition. A plethora of bronchoscopic procedures have been reported for the management of AP fistula, including glutaraldehyde-sterilized lead shot,[16] gel foam and tetracycline,[17] autologous blood patch,[16] human fibrin glue (Tissucol; Immuno AG), gelatin-resorcinol mixture,[18] oxidized regenerated cellulose (Surgicel; Johnson & Johnson),[19] albumin-glutaraldehyde tissue adhesive (BioGlue; CryoLife, Inc),[20] cryoprecipitate fibrin glue,[21,22] and endobronchial one-way valves.[7-13] Although several studies have looked into each of these approaches, larger, retrospective case series exist for bronchoscopic application of fibrin

sealant and endobronchial one-way valves. The success rate for each of these approaches in sealing air leaks has been reported between 80% and 90%.[22,23] There are disadvantages, however, with each of these methods. Fibrin glue has mainly been studied in bronchopleural fistula and can only be used to seal small defects, making it less effective in cases of AP fistula. Endobronchial valves are expensive and need frequent follow-up with subsequent procedure(s) for valve removal. We report bronchoscopic application of a synthetic hydrogel (CoSeal) as an alternative to the aforementioned approaches.

To date, no published series to our knowledge has looked into the use of this synthetic hydrogel in management of AP fistula. After bronchoscopic application, the hydrogel forms a semisolid gel plug, preventing airflow into a targeted area of the lung where the air leak originates. Elimination of air leak allows evacuation of pneumothorax and pleural apposition, thereby enabling the lung to possibly re-expand and heal.

Our experience shows that the application of a synthetic hydrogel is effective for most patients with AP fistula, following primary and secondary pneumothoraces or following thoracic resections. Complete cessation of air leaks following hydrogel application was achieved in 86% of patients, leading to chest-tube removal in the next few days. The procedure itself was very well tolerated with few adverse events. Our success rates for sealing the air leak and successful chest-tube removal have been similar to past studies looking at fibrin and cyanoacrylate glues for bronchopleural fistulas and endobronchial valves for AP fistula.[22,23]

The main advantages of this sealant are that it can be easily applied, does not need prior preparation, can be readily removed if bronchial obstruction occurs, and is self-absorbable. The hydrogel plug continues to expand over 24 h after application, which facilitates complete closure of the airway(s) leading to the fistula. Moreover, treatment can be applied with the same flexible bronchoscope used to confirm diagnosis of the AP fistula, and the technique does not interfere with or delay reparative surgery, should this be considered necessary. The only drawbacks of the technique are the possible occlusion of the working channel of the bronchoscope, cough leading to displacement of the gel plug, and potential for respiratory compromise by displacement of the gel plug to occlude a proximal airway. To avoid dislodgement of plug and respiratory compromise, we applied the least amount of hydrogel necessary to isolate the target airway and suctioned excess hydrogel, especially from the proximal airway toward the end of the procedure. We also prescribed antitussives for the next 48 h to prevent significant coughing. However, in our experience, these complications were uncommon. The cost of bronchoscopic treatment is significantly less than any surgical procedure.

Among the limitations of this study we should highlight is that this was a descriptive, retrospective series and comparisons between different bronchoscopic techniques cannot be made. Second, treatment decisions for these 22 patients were not made according to a protocol. This case series, nonetheless, contributes additional information to support this nonsurgical approach to the management of persistent pulmonary air leaks. Further, it serves as a basis to study synthetic hydrogel in a controlled, randomized, and prospective fashion. Our series and those of Scappaticci et al[21] and Mora et al[22] are the largest reported series published on bronchoscopic treatment with sealants. Nevertheless, ours is the largest series to date looking at the management of surgical and nonsurgical AP fistula in patients using a synthetic hydrogel.

In conclusion, use of synthetic hydrogel with flexible bronchoscopy is a good therapeutic option for closing AP fistulas in most patients, regardless of the size, location, and etiology of the fistula, particularly in the patient who is not a good candidate for surgical intervention. Bronchoscopic interventions to seal AP fistulas are safe and relatively free from associated complications. Therefore, we believe that closure of AP fistula should first be attempted by application of a synthetic hydrogel, especially when further surgery would carry an extremely high risk for an adverse event. It is a reasonable, nonsurgical, minimally invasive intervention that may be appropriate for the treatment of prolonged air leaks in patients who are either operable or inoperable. Prospective trials are needed to further characterize the clinical circumstances in which this intervention may be most appropriate.

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