Therapeutic Whole-Lung Lavage for Pulmonary Alveolar Proteinosis

A Procedural Update

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Summary: Pulmonary alveolar proteinosis is a disease caused by increased accumulation and impaired clearance of surfactant by alveolar macrophages. This narrative review summarizes the role of therapeutic whole-lung lavage in the management of pulmonary alveolar proteinosis. We describe the preprocedural evaluation, indications, and anesthetic considerations, along with step-by-step technical aspects of the procedure, postoperative recovery, potential complications, and long-term outcomes.

Key Words: whole-lung lavage, pulmonary alveolar proteinosis, GM-CSF, interstitial lung disease

Pulmonary alveolar proteinosis (PAP), first described more than 50 years ago, is a disease of increased accumulation and impaired clearance of surfactant constituents by alveolar macrophages.1 It is extremely rare, with an estimated prevalence of 6.2 cases per million worldwide.2,3

In the past 15 years, inhaled or subcutaneous granulocyte-monocyte colony stimulating factor has been used effectively for medical management of PAP. More recently, responses to the chimeric anti-B-cell monoclonal antibody, rituximab, have been reported in patients with autoimmune PAP.4,5 However, effective treatment of PAP for many years has relied on whole-lung lavage (WLL) for relief of impaired gas exchange. Here we review the WLL and its implications for the patient, anesthesiologist, pulmonologist, and intensivist.

THERAPEUTIC WLL

The earliest descriptions of lung lavage involved catheter placement in the dependent lung in awake patients. In a series of publications from 1963 to 1965, Ramirez-Rivera and colleagues described subtle modifications to this technique that led to the modern WLL procedure.6,7 By 1965, a technique for lavaging the lung with a double-lumen endotracheal tube (DLT) under local, and then subsequently under general anesthesia, had been developed.8 However, the modern technique of WLL as practiced today was not described until 1994.9

WLL VERSUS BRONCHOALVEOLAR LAVAGE (BAL)

Lavage by multiple segmental BAL procedures is sometimes used when WLL is not available or the patient is deemed too ill for WLL; however, its effectiveness is not well established. WLL differs from BAL in that the latter uses much less lavage fluid and targets 1 pulmonary segment or subsegment at a time. The BAL procedure involves instilling 25 to 60 mL aliquots (up to a maximum of 300 mL) of saline through a flexible bronchoscope wedged into a distal airway, usually under local anesthesia.10 In contradistinction, WLL entails washing out 1 whole lung at a time either a few days apart or sequentially in 1 session. It is usually performed with a double-lumen endotracheal tube under general anesthesia (Fig. 1). The volume of saline used for WLL generally about 10 to 15 L and can be up to more than 50 L per lung. Nevertheless, BAL, has found favor as a therapeutic method in pediatric patients where there may be technical difficulties with securing the airway with a DLT and isolating the lungs.11-13

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INDICATIONS FOR WLL

Initially, WLL was used as a therapeutic maneuver to treat bronchiectasis, chronic bronchitis, lung abscess, and other debilitating syndromes in the setting of chronic respiratory failure. Currently therapeutic WLL is used for treating PAP. The prognosis of PAP improved dramatically with the advent of WLL, such that it remains the first-line therapy for PAP. In a substantial proportion of patients, the requirement for WLL may be so sporadic (or even necessary only once), that it is preferred versus medical options. However, there are no distinct determinants as to when to perform a WLL procedure in PAP patients. This is further complicated by the fact that spontaneous remission of PAP has been reported. The decision regarding when to perform a WLL remains a clinical one, although the usual criteria for considering WLL are the presence of substantial respiratory limitation or oxygen desaturation with or without exercise. Other data that may corroborate the severity of PAP include pulmonary function tests (PFTs), and serum markers such as lactate dehydrogenase, surfactant protein D, or Krebs von Lundgren factor 6 (KL-6). In clinical practice, patient symptoms,
desturation, radiographic findings, and PFTs are generally used in combination to determine the need for WLL.

**PREPROCEDURAL EVALUATION**

The most important step in performing this procedure is proper patient selection by carefully confirming the correct diagnosis, considering whether the disease is sufficiently severe to warrant WLL. Next is establishing that symptoms or desaturation are most likely due to PAP, ruling out the possibility that there is a concomitant disease process contributing to the symptoms (eg, infection, other interstitial lung diseases, significant fibrosis, cardiac), and discussing the alternative therapeutic options with the patient.

**PREANESTHESIA EVALUATION**

Preanesthetic evaluation should be performed in the usual manner, with special attention to the baseline PFTs, and chest radiography (Figs. 2A, B). Also, if this is a repeat procedure, details of the airway management and anesthetic record should be reviewed.

**PREOPERATIVE POLYCYTHEMIA**

Chronic hypoxemia is present in up to 30% of PAP patients. Secondary polycythemia may occur, which may potentially increase the risk of perioperative thromboembolic complications. Therefore, preoperative therapeutic phlebotomy may be considered in severe cases.

**PERSONNEL**

The team that performs WLL differs substantially between different centers. Although many models have proved successful, at the authors’ center, the WLL team consists of the following 3 different integral components:

1. Pulmonology team: to perform patient evaluation, confirm diagnosis, devise a management plan, and determine whether WLL is indicated. This team will also provide longitudinal follow-up.
2. Proceduralist: an intensivist-anesthesiologist with special training to perform the WLL and supervise immediate postoperative care in collaboration with the postanesthesia care unit (PACU) team.
3. Anesthesiologist-led anesthesia team: to provide general anesthesia services including management of airway, ventilation, fluid balance, and other medical issues.

**ANESTHESIA FOR WLL**

A left-sided DLT is preferred due to the relative technical ease of placement, as well as the desire to avoid blocking the right upper lobe bronchus takeoff with a right-sided DLT. Proper placement of DLT should be verified by flexible bronchoscopy.

We usually place a radial arterial catheter to help with blood pressure monitoring, as patients may become hypotensive and require vasopressor support during the second lung lavage as a part of sequential (same setting) bilateral WLL.

Total intravenous anesthesia (TIVA) is the more frequently used anesthetic technique for a WLL. TIVA is useful because the anesthesia team can be certain of continued delivery of the anesthetic to the patient, and it also avoids operating room contamination with the inhalational anesthetic during the periods when flexible bronchoscopic examination and/or suctioning of the airway is needed. We typically use an infusion of propofol. In selected cases, however, we have successfully used inhalational anesthetic during the first lung lavage phase of the procedure. Complete muscle relaxation should be maintained throughout the procedure to facilitate single lung ventilation and avoid coughing, which may cause desaturation or dislodgement of the DLT. Use of the Bispectral index monitor (BIS Monitor) (Covidien, Dublin, Ireland) or some form of brain-hypnosis monitoring is helpful to maintain adequate depth of anesthesia when TIVA is used.

Patient positioning is not standardized. Although a full lateral position may decrease the likelihood of spillage into the nondependent ventilated lung, we have found that maintaining the supine position for the entire procedure affords the opportunity to perform sequential lung lavage, where both lungs are lavaged in the same setting. The supine position reduces the risk of DLT displacement and is not associated with any perceived reduction in lavage success.

For fluid replacement, it is adequate to replace the fasting deficit, however maintenance fluids should be kept to a minimum, with the use of colloids preferred when there is a need to maintain intravascular volume. The WLL procedure can be associated with absorption of variable quantities of lavage fluid into the circulation that may result in volume overload in some cases. This can be easily treated by administering a dose of intravenous furosemide.
PROCEDURE DETAILS

At the authors’ institution, bilateral WLL (sequential at the same setting) is performed under general anesthesia in the main operating room (video, Supplemental Digital Content 1, http://links.lww.com/LBR/A119). In addition to standard monitoring, a Foley catheter is essential to monitor urine output during this lengthy procedure and PACU stay. Operating room arrangement can be seen in the schematic Figure 3, and during an actual case in Figure 4. We prefer to start with the most affected lung [as determined by radiographic imaging (Figs. 2A, B)]. After ensuring that the patient can tolerate single lung ventilation (the healthier side ventilated), the most affected lung is then lavaged with warmed normal saline in 0.5 to 1 L aliquots. It is important to use warmed fluid to avoid deleterious consequences of inadvertent hypothermia from the large instilled volumes. After each aliquot, the lung is allowed to drain with gravity. Chest percussion either with an oscillating vest device or pneumatic hand percussion is typically used, to facilitate agitation and mixing of the proteinaceous material and the lavage fluid. Drainage of the instilled fluid commences immediately after instillation, due to concern that use of a dwell time may result in excessive prolongation of the already lengthy procedure, and absorption of more of the lavage fluid into the circulation. We have found that immediate emptying after filling results in satisfactory removal of the proteinaceous material. The total lavage fluid recovered is continuously monitored. There has been a notion that changing the patient’s position from supine to prone position using specialized operating room tables, like the Jackson table, may help clear up the abnormal proteins (personal correspondence with Dr Bruce Trapnell of the University of Cincinnati). However, that is not without the added potential risks of patient injury due to imperfect bed rotation, and/or malpositioning of the DLT or even accidental extubation. Thus, the risks and benefits of such maneuvers should be considered carefully.

Initial lavage return usually appears as copious milky, proteinaceous material
characteristic of the disease, depending on severity, the efficiency of the percussion, and the lavage process. Subsequent lavages are progressively clearer such that by the final lavage, returned fluid is usually clear. The patient is then allowed to ventilate with both lungs. The lavaged lung is actively suctioned to remove any remaining fluid not drained by gravity. The procedure is then repeated on the other lung, after a rest period of bilateral lung ventilation (of individualized length depending on the clinical situation). The lavaged lung “wet lung” is generally very stiff immediately after the lavage. This rest period allows for interstitial lung fluid mobilization, more suctioning of residual alveolar lavage fluid, and recruiting more alveoli.

Typically, lavaging the second lung is more challenging because the patient has poor compliance and impaired ventilatory exchange. Initiating lavage on the second lung using this already compromised lavaged lung as the sole ventilatory medium for the patient may lead to frequent varying degrees of desaturation along with unfavorable ventilatory parameters. Thus, the procedure requires the skills of an experienced anesthesiologist and supportive team to overcome any instability using lung recruitment maneuvers, ventilator adjustments, and judicious handling of fluids, diuretics, and vasopressors.

At the end of the procedure, the DLT is changed to a single lumen tube, as it is not expected that the patient will be extubated easily in the operating suite. The presence of the residual lavage fluid and proteinaceous material results in a frothy airway that makes any attempt at reintubation very challenging. Thus, we recommend the use of an airway exchange catheter to accomplish this step. Subsequent to this, the patient is admitted to the PACU for further monitoring and weaning from mechanical ventilation.

**Lavage Techniques and Fluid Volume**

The goal should be a WLL technique wherein the highest gain in terms of protein removal can be achieved by the lowest possible instilled volume. Paschen and colleagues studied kinetics of WLL in adults and children. They concluded, that corrected for body weight, the same volume of about 250 mL/kg is used on average in both age groups of patients.

A modified lavage technique (MLT) has been described in a 36-year-old female with severe PAP unresponsive clinically to conventional lavage (CLT). The authors in this case based the observed increased protein clearance on ventilation of partially fluid-filled lung areas that allowed better reopening of closed airspaces and more efficient removal of the proteinaceous material. Bonella et al have studied an almost similar MLT as reported above albeit on a larger scale utilizing optical density monitoring to quantify the protein content of the recovered lavage fluid. In their study of adult PAP patients, 110 conventional WLLs were performed in 33 patients and 70 modified technique WLLs were performed in 9 patients. In all patients, they performed a lavage on each lung on a different day separated by 10 ± 3 days. CLT consisted of standard double-lumen ventilation, lung isolation, irrigating the collapsed lung with 1000 ± 200 mL saline solution at body temperature, and recovering the lavage fluid in repeated cycles. These cycles were continued until the optical density of the recovered fluid was <0.4 or a plateau was reached in terms of the clarity of the return fluid. In the MLT group, after an optical density target of 0.4 was reached initially using the conventional technique, controlled manual ventilation with 300 mL of room air using a bag 5 times was applied after instilling the first 500 mL of saline solution. Then, after recovering the first 500 mL of instilled saline solution, the rest of the fluid (500 mL) of this cycle was instilled and recovered, and the next cycle was started. Subsequently, the lavage was continued until the target OD value of 0.4 was reached for the second time. The median (range) amount of lavage fluid instilled in the CLT was 15 L (4 to 40) compared with 40 L (21 to 71) for the MLT. The median protein amount removed was 13,780 mg (350 to 32,015) in conventional versus 22,580 mg (2920 to 26,860) in modified lavage (P = 0.0001). The MLT had a significantly longer time before another lavage was required [225 ± 151 d vs. 84 ± 168 d (P = 0.011)].

Bonella et al were also the first to study the effects of consecutive (single lung—different day) WLL on protein kinetics. A subgroup of their patients (n = 9) underwent a total of 6 consecutive WLLs (6 CLT and 3 MLT). In these patients, the removed protein amount declined with consecutive WLLs (P = 0.04) but the instilled volume did not change (P = 0.2). They also noted that the median amount of removed protein was inversely related to the lung’s diffusing capacity, as well as PaO2.

In summary, the above findings point toward the potential benefits of the MLT as a means to increase protein removal. However, MLT may potentially lead to more pulmonary
edema due to the large fluid volumes required, as well as potential barotrauma. A confirmatory study would be useful before MLT becomes the standard of care for lung lavage patients.

Other methods to improve lavage return have also been investigated. Perez and Rogers performed an observational study in 6 consecutive (single lung—different day) WLLs in 5 patients. The lavage was performed in the following 3 stages: stage I, passive drainage; stage II, assisted clearance with manual chest percussion; and stage III, positional clearance with prone positioning. They performed high-volume lavages using 45 to 60 L of warm saline. They concluded that the most effective adjunct to lavage is manual chest percussion therapy. They also found improvement in drainage of proteinaceous material with prone positioning that appeared radiographically to make a difference in the clearing of the posterior segments. Manual chest percussion has been previously shown to be better than mechanical chest percussion in clearance of proteinaceous material. Again, additional studies will be necessary before widespread adoption of prone occurs.

OUTCOME DATA

In a comprehensive survey over a decade ago, Seymour and Presneill analyzed the literature, covering data from 1958 onwards, comprising 240 small case series and reports with a total of 410 patients in all. Those patients who had lavage at any time during the course of their disease (54%) had a superior 5-year survival rate of 94 ± 2% compared with 85 ± 5% for those not receiving such treatment \( (P = 0.04) \).

More recently, several authors have presented national outcome data based on retrospective and cross-sectional analyses. Bonella et al reported on a single-center cohort of 61 patients who were followed for 30 years with primary and secondary PAP. In their population, there was a 70% remission rate (43/61 patients). Whether WLL affects the likelihood of PAP remission cannot be determined by their data, but most of the patients who had a remission (40/43, 93% of those remitting) had WLL. The authors also found that the average number of bilateral WLL (each lung done at a different day) to reach remission was 3.9 ± 3 (mean ± SD) and time to remission was 3.7 ± 3.4 (y, SD).

At our institution, where we perform bilateral WLL during the same setting (same day, both lungs) we have also noticed the heterogeneity and an unpredictable pattern of recovery where some patients achieve full remission after the first WLL, whereas others require repeat lavage periodically. In the most aggressive cases, repeat WLL has been needed as often as every 2 to 3 months.

Somewhat similar data were published by Xu et al, who reviewed 241 cases of PAP in China. Both WLL and segmental BAL were performed in almost similar proportions in their cohort with similar favorable outcomes. They also reported that only 1 session of WLL or BAL was sufficient for most of their patients. However, Inoue et al reported slightly different outcome data from Japan. Their cohort was made up of 166 patients, with autoimmune PAP. They reported that 30% of the patients were treated with WLL therapy and 23% were treated with segmental BAL therapy using a bronchoscope. Their results showed an overall improvement in outcome in 30% of patients and a worsening of outcome for 28% with no change in the rest. They also observed no significant correlation between the clinical course/prognosis and age, sex, period from the onset of the disease, smoking status, or environmental/occupational exposure history.

COMPLICATIONS

Hypoxemia

Oxygenation and ventilation vary during different stages of WLL. During filling up of the nonventilated lung with the lavage fluid, there is ipsilateral pulmonary capillary bed compression, resulting in diversion of blood flow toward the ventilated lung. This effect can temporarily decrease the shunt created by the 1 lung ventilation and help with oxygenation. Conversely, blood flow to the nonventilated lung increases during the drainage of the lavage fluid from the nonventilated lung. This increases the shunt and is deleterious to the already tenuous oxygenation status of the patient. If the patient is on some positive end-expiratory pressure at this stage, it should be decreased to a minimum as the applied positive end-expiratory pressure may divert blood flow away from the ventilated lung increasing the shunt fraction. Refractory hypoxemia and respiratory failure may result, leading to an unplanned intensive care unit (ICU) admission. In addition, lavage fluid absorption during lengthier procedures can lead to pulmonary edema and exacerbate respiratory insufficiency. Several alternative strategies of lung ventilation have been attempted with some success if such a situation arises. These include...
manual ventilation of partially fluid-filled lung, intermittent double-lung ventilation, and concomitant use of inhaled nitric oxide and almitrine. In extremely unstable patients, rescue strategies that have been reported include pulmonary artery occlusion of the nonventilated lung using a pulmonary artery catheter and finally use of hyperbaric oxygen and veno-venous extracorporeal membrane oxygenation. 

Loss of Lung Isolation

Leakage of lavage fluid to the nonlavaged lung can occur at any time during the procedure. This can be due to increased airway pressure in the lavaged lung and or displacement of the bronchial lumen cuff or the DLT as a unit secondary to the shear forces of the lavage fluid current. Observing lavage fluid in the endotracheal tube on the ventilated lung should prompt the team to stop the lavage and perform suctioning of the ventilated lung, and initiate a flexible bronchoscope examination to confirm/adjust location of the DLT. Integrity of the bronchial and tracheal lumen cuff should be confirmed.

Hydrothorax and Pneumothorax

Although rare, these can occur at any stage of the procedure. These complications are most likely caused by rupture of the excessively distended alveolar sacs by lavage fluid due to the use of large saline aliquots and/or stacking of aliquots because of suboptimal fluid drainage. The risks of these complications may be greater with the modified lavage, as discussed above.

POSTOPERATIVE PHASE

PACU Phase

In the PACU, we continue with sedation using IV propofol, while the respiratory therapist provides repeated endotracheal suctioning. With aggressive weaning of FiO₂ and ventilatory support, patients can be typically extubated within 1 to 4 hours from the end of the procedure.

Post-PACU Discharge

In our institution, the satisfactorily recovered post-WLL patient is admitted under the care of the pulmonologist. Supplemental oxygen is weaned off overnight, and a desaturation walk test is performed in the morning to determine the need for supplemental oxygen before home discharge. The patient’s recovery may vary from no longer needing the supplemental oxygen, to the need for 2 to 6 L per minute of oxygen supplement that is weaned off at home over the following few days as they mobilize some of the absorbed lavage fluid.

ICU Versus PACU Admission

ICU admission is rarely needed and is usually reserved for those patients who would require more than 4 hours of ventilatory support in the PACU; generally these patients may be extubated the following morning.

Follow-up

PAP patients after WLL procedures typically use portable home pulse oximetry to wean themselves off supplemental oxygen if they ended up using it postoperatively, and follow-up with their pulmonologists in 2 weeks for an assessment.

Smoking cessation and lifestyle modification may be important to maintain remission. Recently a single-center cohort study has shown smoking to be associated with an increasing number of WLL sessions to achieve remission.

Future Directions

In terms of the technical aspects of WLL, there are many unanswered questions. The rarity of the disease limits the number of the available patients, rendering the conduct of robust controlled research trials difficult. However, development of national and international registries and collaborations will likely lead to future advances in the care of PAP patients using WLL and novel medical therapies.

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