Published in final edited form as:

Curr Pulmonol Rep. 2018 June ; 7(2): 56–62. doi:10.1007/s13665-018-0199-y.

Air Travel-Related Spontaneous Pneumothorax in Diffuse Cystic Lung Diseases

Nikolai Wajda, MD¹ and Nishant Gupta, MD, MS¹

¹Division of Pulmonary, Critical Care, and Sleep Medicine, University of Cincinnati, 231 Albert Sabin Way, MSB Room 6053, ML 0564, Cincinnati OH 45267

Abstract

Purpose of review: Spontaneous pneumothorax (SP) is a common manifestation of patients with diffuse cystic lung diseases (DCLDs) such as lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH) and Birt-Hogg-Dubé syndrome (BHD). Air travel may pose an additional risk for the development of SP. Here, we summarize the literature pertaining to air travel related SP in DCLDs in order to assist patients and clinicians in appropriate decision-making with regards to air travel.

Recent Findings: Several recent studies have estimated that the per-flight risk of SP in patients with DCLDs is approximately 1%, with disease-specific risk estimates of 1.1-2.6% in LAM, 0-0.63% in BHD, and 0.37% in PLCH.

Summary: In general, it should be safe for most patients with DCLDs to undertake air travel. Patients should be counseled to seek medical attention and not board the airplane in the presence of sudden/new onset chest pain and/or dyspnea prior to boarding the plane.

Keywords

Air travel; Birt-Hogg-Dubé syndrome; Diffuse cystic lung disease; lymphangioleiomyomatosis; pulmonary Langerhans cell histiocytosis; spontaneous pneumothorax

Introduction

3.8 billion passengers undertook air travel in 2016, a number that has increased substantially over the past decade [1]. The majority of passengers tolerate air travel without medical complications, even in those with chronic lung diseases [2–5]. Although flying at much higher altitudes, aircrafts are pressurized to maintain adequate oxygen environment. Federal Aviation Administration regulations specify that aircrafts maintain a cabin environment pressurized to an altitude of 8,000ft (2,438m) above sea level [6,7]. At an altitude of 8,000ft,

Corresponding Author: Nikolai Wajda, M.D., Division of Pulmonary, Critical Care, and Sleep Medicine, University of Cincinnati 231 Albert Sabin Way, MSB Room 6053, ML 0564, Cincinnati, OH 45267. wajdani@ucmail.uc.edu.

Conflict of Interest

Nishant Gupta and Nikolai Wajda declare no conflict of interest.

Compliance with Ethical Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

alveolar oxygen tension falls to 65mm Hg [6]. In this hypoxic environment, it is not surprising that respiratory complaints account for 2.3-12.1% of in-flight emergencies [2,3], however spontaneous pneumothorax (SP) is an uncommon in-flight emergency. There was no reported case of SP in two large studies evaluating in-flight emergencies among the general population that included over 22,000 passengers between the two studies [2,3]. This suggests that in the general population, the occurrence of air travel related pneumothorax is either extremely low, or unrecognized and therefore unreported.

Studies evaluating patients with general pulmonary disorders have failed to report an association between air travel and the risk of SP. In a prospective observational study in patients with chronic obstructive pulmonary disease (COPD), diffuse parenchymal lung disease, asthma, bronchiectasis or sarcoidosis, 18% of the patients in the study who undertook air travel experienced respiratory distress while flying, but there was no reported occurrence of SP [4]. In an effort to estimate the risk of air travel related SP in chronic pulmonary disorders, Taveira-DaSilva et al. reviewed the medical records and imaging studies of patients who travelled to the National Institutes of Health (NIH) and found no episodes of SP in 76 idiopathic pulmonary fibrosis (IPF) or 92 sarcoidosis patients who took 159 and 121 air trips, respectively [5].

SP is a common manifestation of diffuse cystic lung diseases (DCLDs) such as lymphangioleiomyomatosis (LAM), Birt-Hogg-Dubé Syndrome (BHD) and pulmonary Langerhans cell histiocytosis (PLCH). SPs in patients with DCLDs occur at a much higher frequency than the general population and are often recurrent, with some patients experiencing greater than 10 episodes of SP [8]. The hypobaric environment encountered during air travel is thought to lead to the development of SP in these patients through the rupture of cysts and bullae [9–11]. In this article, we will briefly discuss the physiology of development of SP during air travel, and critically appraise the available literature pertaining to the safety of air travel in patients with DCLDs. Finally, we make recommendations for appropriate counseling and management of patients with DCLDs who are planning air travel.

Physiology and Development of Spontaneous Pneumothorax

Boyle's Law states that at a constant temperature, an inverse relationship exists between pressure and volume for a gas in enclosed space. As a plane gains altitude, the cabin pressure will be reduced while the volume of air within enclosed spaces, such as cysts, sinuses, or Eustachian tubes will increase. This can be easily visualized by the "bag of chips" analogy put forth by Baumann where the bag will become distended as the flight increases in altitude [12]. The volume of cysts has been predicted to increase by up to 38% during a flight, thus predisposing DCLD patients to increased risk of cyst rupture and the subsequent development of SP [11].

Lymphangioleiomyomatosis (LAM)

LAM is a rare neoplastic DCLD that can occur sporadically or as part of Tuberous sclerosis complex (TSC). Sporadic LAM (S-LAM) occurs almost exclusively in women with a

prevalence of 3.4-7.8 per 1,000,000 women [13]. Common presenting clinical complaints of S-LAM include SP, dyspnea, chest pain and cough [14]. Typical radiological findings in LAM include the presence of diffuse bilateral pulmonary cysts, renal angiomyolipomas, abdominal lymphangiomyomas and chylous pleural effusions [14]. TSC-LAM occurs in both males and females as part of an autosomal dominant multi-organ system process characterized by the formation of hamartomas in the brain, skin, heart, kidney, lungs and liver. TSC occurs in 1 in 5,800 live births [15] with cystic changes characteristic of LAM occurring in 26-49% of women [16–19]. In patients with TSC, the risk of development of LAM increases with age; in a study by Cudzilo et al., 27% of TSC patients <21 years old had LAM, whereas 81% of TSC patients >40 years old had HRCT evidence of cystic lung disease characteristic of LAM [20]. The typical cysts in LAM are round, uniform, thin-walled and distributed throughout both lungs with size varying from a few millimeters to 2 cm [21–23].

SP occurs in 55-73% of LAM patients [8,14, 24-27], with recurrent episodes reported in 73% of patients [25]. Air travel related SPs were reported 4.8% of LAM patients in the National Heart, Lung, and Blood Institute (NHLBI) LAM Registry data [14]. Three further studies have evaluated the occurrence of air travel related SP in LAM patients [5, 28, 29].

Taviera-DaSilva et al. evaluated the risk of air travel related SP in 281 LAM patients who had traveled to the NIH [5]. Fourteen patients with LAM who had traveled by air were found to have a pneumothorax on arrival. Six patients were documented as having a ‘new’ pneumothorax as imaging at the preceding visit to the NIH did not document a pneumothorax being present. The remaining 8 patients were documented as having a chronic pneumothorax, as prior imaging revealed the presence of a pneumothorax before boarding the air plane. The frequency of new air travel related SP was 2.9% per patient, or 1.1 per 100 flights. Of the patients diagnosed with ‘new’ pneumothorax, none reported symptoms during the flight and none had preflight imaging to document absence of pneumothorax prior to boarding. In this study, LAM patients with both acute and chronic pneumothorax had lower FEV1 (62 +/-6%) compared to patients with no history of pneumothorax (75 +/-2%) ($p<0.01$). All 6 patients with a new pneumothorax had an average cyst size greater than 1cm, suggesting that increasing cyst size may be a risk factor for developing air travel related SP. Patients with chronic pneumothoraces had preflight CT scans compared to CT scans after landing revealing limited change to the volume of chronic pneumothoraces following air travel.

Two additional questionnaire-based assessments of LAM patients have been conducted to evaluate the risk of SP related to air travel in patients with LAM. Pollock-BarZiv et al. conducted a survey of 327 LAM patients, of whom 276 had travelled by air at least once, for a combined total of 454 flights [28]. There were 10 air travel associated SPs reported in this study, with an air travel related SP defined as a pneumothorax that happened during air travel or soon after landing. The risk of SP was calculated as 2.2% per flight, and 3.6% per patient. Of the patients who developed an air travel related SP, 80% had experienced a prior pneumothorax, suggesting that prior SP is a risk for this complication during air travel. Of note, 5 out of the 10 patients who reported an in-flight pneumothorax had symptoms consistent with a SP that began before the flight occurred, thus suggesting that these patients

may have boarded the plane with an existing SP rather than developing a SP due to air travel. More recently, Gonano et al. performed a survey of 145 patients with LAM and found that the SP risk per flight was 2.6% and that the incidence per patient was 6.5%. The definition of air travel related SP in this study was different from the previous studies, with any SP reported within 30 days of air travel being considered related to air travel [29].

Birt-Hogg-Dubé syndrome (BHD)

BHD is an autosomal dominant disease due to inactivating mutations in the *Folliculin* (*FLCN*) gene that result in characteristic skin lesions caused by hair follicle tumors (fibrofolliculomas), renal cancers, cystic lung disease and recurrent pneumothoraces [30]. Unlike LAM and PLCH, BHD does not typically progress to chronic respiratory failure. Depending on the referral population, the prevalence of SP associated with BHD is 22.5–76% [31–35] with a high rate of recurrence (75–82%) [32, 35]. Cysts in BHD are thin-walled, round to lentiform-shaped and of various sizes. Cysts are most commonly located in a basilar and subpleural distribution [30].

There have been three survey-based studies to evaluate air travel related SP in patients with BHD. Hoshika et al surveyed 48 patients with BHD, 40 of whom had flown for a combined total of 2142 flights in which there were no reported cases of SP [36]. Johannesma et al. performed a survey of 145 patients with BHD who had flown for a combined total of 2,528 flights and found 13 patients developed a pneumothorax within one month of air travel. Two patients experienced two episodes and one patient experienced three episodes of air travel related SP [33]. They calculated a pneumothorax risk of 0.63% per flight, and 9.0% per patient. Air travel related SP was the first episode of SP for five of the 13 patients. For the patients where the air travel related SP represented a recurrent episode, eight patients had not previously undergone pleurodesis while three patients had previously undergone pleurodesis. Most recently, Gupta et al. conducted a survey of 104 BHD patients in an effort to estimate the risk of air travel related SP. 99 out of the 104 patients had flown at least once, with the total number of estimated flights being 8,920. The investigators found 11 occurrences of SP in 8 patients either during or within 24 hours of the flight duration [35]. They calculated a lower risk per flight of SP at 0.12%, and 8% per patient. Gupta's study included 4 patients who had taken more than 1000 flights each. When these patients were excluded from analysis, the prevalence of flight-related pneumothorax decreased to 7.4% per patient and the risk per flight increased to 0.27%. For 3 patients, flight-related pneumothorax was their initial SP. Of the 8 other flight-related SPs, 7 occurred in patients who had not previously undergone pleurodesis, suggesting a statistically significant decrease in the overall risk of flight-related SP following pleurodesis ($p=0.02$).

Pulmonary Langerhans cell histiocytosis (PLCH)

PLCH is a rare disease that most commonly affects young smokers and results from the infiltration of histiocytes into airways and other organs. Invasion of these cells into the airways results in the development of inflammatory nodules that may cavitate resulting in the formation of cysts. Occurring as an isolated pulmonary process or as part of multi-organ system disease, the spectrum of pulmonary disease in PLCH can range from asymptomatic

to severe progressive respiratory failure with the common presenting respiratory symptoms of dyspnea, cough, chest tightness and SP [37]. The cysts that develop in PLCH have a predilection for the upper lung fields and characteristically spare the bases. Cysts may be thick or thin walled, irregularly shaped and can vary from several millimeters to 2cm in diameter [37–39]. 15-20% of patients with PLCH experience at least one SP in their lifetime [37]. Recurrence of pneumothorax is common with 58% of patients experiencing ipsilateral recurrence [40].

There is limited data with regards to air travel related SP in PLCH patients. Preliminary analysis from a current study by Singla et al. revealed that among a total of 61 patients with PLCH, 54 had flown at least once for an estimated total of 538 flights, with two reported episodes of SP either during or within 24 hours of air travel. The rate of air travel related SP was estimated to be 3.7% per patient and 0.37% per flight [41]. The study is ongoing (NCT03052101, www.clinicaltrials.gov), and will provide disease-specific information regarding the risk of air travel related SP in patients with PLCH.

Lack of recommendations regarding air travel and spontaneous pneumothorax

Available data suggests that while the overall frequency of air travel related SP in DCLDs is low, it is almost certainly higher than the general population. Despite this increased risk for SP, there is no consensus about the general safety of air travel in DCLD patients from which general practitioners and pulmonologists can make recommendations to their patients about the safety of air travel. This is demonstrated by patients with DCLDs reporting having received varied recommendations from their clinicians on their safety for flying, ranging from no specific guidelines to being told to avoid air travel all together.

In Gupta's survey of patients with BHD, 56% of patients reported receiving no recommendations regarding the safety of air travel following an episode of SP. Almost one-fourth of the patients in this cohort changed their flight frequency after receiving a diagnosis of BHD, with the majority (70%) of these patients deciding to avoid air travel altogether, mostly due to the perceived risk of SP during air travel [35]. Similarly, in another study, 35% of patients with LAM had been told by their clinicians to completely avoid air travel. Almost 80% of these patients had experienced a prior episode of SP thus suggesting that the perceived risk of recurrent SP related to air travel was the major driving force behind this recommendation [28].

The only available recommendations regarding DCLD and air travel are in the 2011 British Thoracic Society (BTS) guidelines, which state "patients with lymphangioleiomyomatosis should be advised that they are at increased risk of pneumothorax and that any unusual clinical symptoms such as chest pain or breathlessness should preclude air travel until fully evaluated." [11]. Based on the current literature summarized above, this recommendation can be extrapolated to patients with other DCLDs such as BHD and PLCH.

Safety to fly after a pneumothorax

There are no studies on the safety of air travel following the resolution of pneumothorax in patients with DCLDs. In general, for all pneumothoraces, there is limited data regarding the safety and timing of air travel post resolution of pneumothorax. Cheatham and Safcsak performed an observational study of 12 patients who underwent management for a traumatic pneumothorax. 10 patients flew after waiting 14 days following radiographic resolution of their pneumothorax with none experiencing in-flight symptoms. One patient flew against medical advice before waiting 14 days of resolution of pneumothorax and developed symptoms in flight that resolved after her flight landed. This observation led the authors to conclude that patients should wait for 14 days following radiographic resolution of a traumatic pneumothorax before taking another flight [43]. In another prospective study involving 179 patients who underwent a total of 183 percutaneous transthoracic needle biopsies at the National Cancer Institute (NCI) and planned air travel within 14 days the investigators encountered 65 episodes of pneumothorax, 50 (77%) of whom travelled by air in less than 4 days. 1 patient developed mild shortness of breath and hemoptysis after landing and one patient who had chest pain prior to flight developed increasing chest pain and shortness of breath as the plane was landing. Based on this data, the authors concluded that patients with a post-procedure pneumothorax patients may be safe to undergo travel before the recommended two weeks [42].

The BTS and the International Air Transport Association (IATA) recommend waiting 7 days after radiographic resolution of SP and 14 days after radiographic resolution of traumatic pneumothorax before undertaking air travel [11, 44]. The IATA also recommends that air travel less than seven days post SP may be acceptable if a Heimlich valve is in place and the patient is accompanied by medical personnel [44]. The Aerospace Medical Association suggests that air travel be delayed for 2-3 weeks after drainage [45].

Limitations of current literature:

There are several limitations to the data that lead to difficulties in calculating the true frequency of air travel related pneumothorax, and the studies have design flaws that could lead to both an under- as well as overestimation of the actual risk of development of air travel related SP in patients with DCLDs.

There is no consensus definition for air travel related spontaneous pneumothorax. In the available studies the definition ranged from SP happening during the flight [28] to within 30 days of air travel [33]. The advantage of a shorter period is that it increases the likelihood of including SPs that are truly flight related. The disadvantage of shorter periods is that it might exclude SPs that take a longer duration to become clinically apparent [33,46]. SP is a common complication of these uncommon diseases and there is a risk of overdiagnosing air travel related SP if a longer duration is used.

Five out of the six studies included in this review were patient surveys, which suffer from both selection and recall bias. Patients who experienced a problem with air travel are more likely to complete the surveys than patients who have never experienced any issues.

Additionally, the questionnaires ask patients for the total number of flights, which is subject to recall bias and almost certainly a gross estimation rather than an exact number.

In the absence of chest imaging of patients before undertaking air travel, it is possible that some of the pneumothoraces were present in a subclinical manner prior to flights and only became symptomatic once the patient was exposed to the low pressure environment during the flight. In one study, five out of 10 patients diagnosed with a flight related SP reported symptoms consistent with a SP prior to boarding, raising the possibility that the SP happened at ground level and was not truly flight-related [28].

Lastly, none of the patients in the NHLBI cohort who were diagnosed with air travel related SP exhibited clinical symptoms of a SP [5] rather these patients were identified incidentally on routine chest imaging conducted as part of the medical evaluation. It is possible that these episodes represent preexisting pneumothoraces and that the actual risk of air travel related SP may be lower than what was estimated in this cohort. Alternatively, this study raises the possibility that air travel related SP is more common, and that certain episodes remain undiagnosed due to lack of symptoms or follow-up chest imaging.

Future Directions:

As mentioned above, different studies have used varying time points to define an air travel related SP. The varying definitions likely have significantly impacted the estimated rate of flight related SP. Consensus regarding the definition of air travel related SP will help mitigate this problem, and better enable future studies to refine the risk estimation in at-risk populations. Future studies should be aimed at establishing a more individualized, disease-specific risk profile for the development of air travel related SP in patients with DCLDs after taking into account clinical variables such as demographics, smoking status, cyst profusion, pulmonary function tests, prior history of SPs, and prior history of pleurodesis. Lastly, the timing of safe air travel following a SP is unclear and needs to be better established in future studies, for SPs in general, and especially for patients with underlying increased propensity for SPs such as patients with DCLDs.

Conclusions and Recommendations:

*Note: Please see the section titled “Electronic Supplementary Material” for a podcast recording of an interview between the author Dr. Nishant Gupta and Editor in Chief Dr. Shirin Shafazand.

Based on the available data reviewed here, patients with DCLDs are at an increased risk for air travel related SP compared with general population, although the overall risk per flight remains low (Table 1). In patients with LAM, the risk appears highest with calculated risk per flight being 1.1–2.6%. The frequency of SP in patients with BHD is estimated to be 0–0.63% per flight, while in PLCH, for which the least amount of data exists, the risk of air travel related SP is estimated to be 0.37% per flight.

Despite the paucity of high-level evidence, we put forth the following suggestions that may assist clinicians in guiding patients with DCLDs prior to air travel:

- 1) In general, it is safe for patients with DCLDs to undertake air travel. Patients with DCLDs should be educated and counseled about the risk of in-flight pneumothorax, however specific recommendations on whether it is safe to fly should be individualized taking into account individual health factors (larger cyst size, lower FEV1, prior pneumothoraces, prior pleurodesis, and other comorbidities) as well as individual patient concerns and values.
- 2) Patients with DCLDs should be educated about the presenting signs and symptoms of a spontaneous pneumothorax. Patients who experience acute onset of chest pain and/or new or worsening dyspnea prior to air travel should seek medical attention prior to boarding flight. Awareness of new symptoms may be of particular importance if the flight's destination is a location with limited medical resources or where a language barrier may exist.
- 3) For patients with DCLD who experience acute onset of chest pain or new/ worsening dyspnea during a flight or in the 24 hours following air travel, we recommend that they seek immediate medical attention, especially if further air travel is planned.
- 4) For patients with DCLD who experience an air travel related SP, we recommend evaluation for pleurodesis in order to reduce/prevent the risk of recurrence of further episodes of SP with and without air travel.
- 5) Patients with no known history of DCLD who experience air travel associated spontaneous pneumothorax should receive a HRCT chest to evaluate for the presence of underlying DCLD. In a recent study, the strategy of screening for DCLDs with HRCT followed by pleurodesis was determined to be cost effective in patients presenting with an apparent primary SP [47].
- 6) We suggest radiographic resolution of an acute spontaneous pneumothorax prior to boarding a flight. An additional waiting period of seven days following radiographic resolution of pneumothorax, in keeping with the BTS and IATA guidelines, should be sufficient for most patients before undertaking air travel.
- 7) Patients with chronic, loculated pneumothoraces do not appear to be at an increased risk of developing/worsening SP as compared to other DCLD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: N.G. received funding and support from the NIH, NIH grant number: U54HL127672, to conduct some of the research reported in this article.

References:

Papers of particular interest, published recently, have been highlighted as:

- Of importance

••Of major importance

- 1). International Air Transport Association (IATA). Annual Review 2017 IATA website. <http://www.iata.org/media/annual-report-2017/index.html> Accessed August 30, 2017.
- 2). Peterson DC, Martin-Gill C, Guyette FX, et al. Outcomes of Medical Emergencies on Commercial Airline Flights. *N Engl J Med*. 2013;368 (22):2075–2083. doi: 10.1056/NEJMoal212052. [PubMed: 23718164]
- 3). Sand M, Bechara FG, Sand D, Mann B. Surgical and medical emergencies on board European Aircraft: a retrospective study of 10189 cases. *Critical Care*. 2009; 13(1):R3 Doi: 10.1186/cc7690 [PubMed: 19154581]
- 4). Coker RK, Shiner RJ, Partridge MR. Is air travel safe for those with lung disease? *Eur Respir J*. 2007;30(6):1057–1063. DOI: 10.1183/09031936.00024707 [PubMed: 17690127]
- 5). Taveira-DaSilva AM, Burstein D., Hathaway OM, Fontana JR, Gochuico BR, Avila NA, and Moss J. Pneumothorax after air travel in lymphangioleiomyomatosis, idiopathic pulmonary fibrosis and sarcoidosis. *Chest*. 2009; 136(3):665–670. Doi: 10.1378/chest.08-3034. [PubMed: 19318672]
- 6). Cottrell JJ. Altitude exposures during aircraft flight. *Chest*. 1988; 92(1) 81–84. DOI: 10.1378/chest.93.1.81
- 7). Federal Aviation Administration. 14CFR25.841 (a). US Government Publishing Office Website. <https://www.gpo.gov/fdsys/pkg/CFR-1999-title4-voll/pdf/CFR-1999-title4-voll-sec25-841.pdf> Accessed August 30, 2017.
- 8). Steagall WK, Glasgow CG, Hathaway OM, et al. Genetic and morphologic determinants of pneumothorax in lymphangioleiomyomatosis. *Am J Physiol Lung Cell Mol Physiol*. 2007; 293:3:L800–808. Doi: 10.1152/ajplung.00176.2007 [PubMed: 17616646]
- 9). Hu X, Cowl CT, Baqir M, Ryu JH. Air travel and pneumothorax. *Chest*. 2014;145(4):688–694. Doi: 10.1378/chest.13-2363 [PubMed: 24687705]
- 10). Nicholson TT, Sznajder JJ. Fitness to Fly in Patients with Lung Disease. *Ann Am Thorac Soc*. 2014;11(10): 1614–1622. Doi: 10.1513/AnnalsATS.201406-234PS. [PubMed: 25393882]
- 11). Ahmedzai et al. British Thoracic Society Standards of Care Committee. Managing passengers with stable respiratory disease planning air travel. British Thoracic Society recommendations. *Thorax*. 2011; 66 (Suppl 1):i 1–i30. Doi: 10.1136/thoraxjnl-2011-200295. [PubMed: 20978027]
- 12). Baumann MH. Pneumothorax and Air Travel. Lessons Learned From a Bag of Chips. *Chest*. 2009; 136 (3): 655–656. doi: 10.1378/chest.09-0891. [PubMed: 19736183]
- 13). Harknett EC, Chang WY, Byrnes S, et al. Use of variability in national and regional data to estimate the prevalence of lymphangioleiomyomatosis. *Q J Med*. 2011;104(11): 971–979. Doi: 10.1093/qjmed/hcr116
- 14). Ryu JH, Moss J, Beck GJ, et al. The NHLBI Lymphangioleiomyomatosis Registry: characteristics of 230 patients at enrollment. *Am J Resp Crit Care Med*. 2006; 173(1): 105–111. Doi: 10.1164/rccm.200409-12980C [PubMed: 16210669]
- 15). Osborne JP, Fryer A, and Webb D. Epidemiology of tuberous sclerosis. *Ann NY Acad Sci*. 1991;615:125–127. [PubMed: 2039137]
- 16). Costello LC, Hartman TE, Ryu JH. High frequency of pulmonary lymphangioleiomyomatosis in women with tuberous sclerosis complex. *Mayo Clin Proc*. 2000; 75(6): 591–594. Doi: 10.4065/75.6.591 [PubMed: 10852420]
- 17). Moss J, Avila NA, Barnes PM, et al. Prevalence and clinical characteristics of lymphangioleiomyomatosis (LAM) in patients with tuberous sclerosis complex. *Am J Respir Crit Care Med*. 2001; 164(4): 669–671. Doi: 10.1164/ajrccm.164.4.2101154 [PubMed: 11520735]
- 18). Franz DN, Brody A, Meyer C, et al. Mutational and radiographic analysis of pulmonary disease consistent with lymphangioleiomyomatosis and micronodular pneumocyte hyperplasia in women with tuberous sclerosis. *Am J Respir Crit Care Med*. 2001;164(4) 661–668. Doi: 10.1164/ajrccm.164.4.2011025 [PubMed: 11520734]
- 19). Muzykewicz DA, Sharma A, Muse V, Numis AL, Rajagopal J, Thiele EA. TSC1 and TSC2 mutations in patients with lymphangioleiomyomatosis and tuberous sclerosis complex. *J Med Genet*. 2009;46(7):465–468. Doi: 10.1136/jmg.2008.065342 [PubMed: 19419980]

- 20). Cudziło CJ, Szczesniak RD, Brody AS, et al. Lymphangioleiomyomatosis screening in women with tuberous sclerosis. *Chest*. 2013;144(2): 578–585. Doi: 10.1378/chest.12-2813 [PubMed: 23539171]
- 21). Crausman RS, Lynch DA, Mortensen RL, et al. Quantitative CT predicts the severity of physiologic dysfunction in patients with lymphangioleiomyomatosis. *Chest*. 1996;109(1): 131–137. Doi: 10.1378/chest.109.1.131 [PubMed: 8549175]
- 22). Avila NA, Chen CC, Chu SC, et al. Pulmonary lymphangioleiomyomatosis: correlation of ventilation-perfusion scintigraphy, chest radiography, and CT with pulmonary function tests. *Radiology*. 2000;214(2):441–446. Doi: 10.1148/radiology.214.2.r00fe41441 [PubMed: 10671592]
- 23). Avila NA, Dwyer AJ, Murphy-Johnson DV, Brooks P, Moss J. Lymphangioleiomyomatosis: correlation of qualitative and quantitative thin-section CT with pulmonary function tests and assessment of dependence on pleurodesis. *Radiology*. 2002;223(1): 189–197. Doi: 10.1148/radiol.2231010315 [PubMed: 11930066]
- 24). Chu S, et al. Comprehensive evaluation of 35 patients with Lymphangioleiomyomatosis. *Chest*. 1999; 115(4): 1041–1052. Doi: 10.1378/chest.115.4.1041 [PubMed: 10208206]
- 25). Almoosa KF, et al. Management of pneumothorax in lymphangioleiomyomatosis: effects on recurrence and lung transplantation complications. *Chest*. 2006;129(5):1274–81. Doi: 10.1378/chest.129.5.1274 [PubMed: 16685019]
- 26). Young LR, Almoosa KF, Pollock-BarZiv S, Coutinho M, McCormack FX, Sahn SA. Patient perspectives on management of pneumothorax in lymphangioleiomyomatosis. *Chest*. 2006; 129(5): 1267–1273. Doi: 10.1378/chest.129.5.1267
- 27). Hayashida M, Seyama K, Inoue Y, Fujimoto K, Kubo K; Respiratory Failure Research Group of the Japanese Ministry of Health, Labor, and Welfare. The epidemiology of lymphangioleiomyomatosis in Japan: a nationwide cross-sectional study of presenting features and prognostic factors. *Respirology* 2007;12(4):523–530. Doi: 10.1111/j.1440-1843.2007.01101.x [PubMed: 17587419]
- 28). Pollock-BarZiv S, Cohen MM, Downey GP, Johnson SR, Sullivan E, and McCormack FX. Air travel in women with lymphangioleiomyomatosis. *Thorax*. 2007; 62(2): 176–180. Doi: 10.1136/thx.2006.058537 [PubMed: 17040934]
- 29). Gonano C, Pasquier J, Daccord C, and Lazor R. Risk of Pneumothorax due to air travel in pulmonary lymphangioleiomyomatosis. *Respiration* 2017;94:150 DOI: 10.1159/000474251
- 30). Gupta N, Vassallo R, Wikenheiser-Brokamp KA, McCormack FX. Diffuse cystic lung disease. Part II. *Am J Respir Crit Care Med* 2015; 192: 17–29. Doi: 10.1164/rccm.201411-2096CI [PubMed: 25906201]
- 31). Zbar B, Alvord WG, Glenn G, et al. Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dube syndrome. *Cancer Epidemiol Biomarkers Prev*. 2002; 11(4):393–400. [PubMed: 11927500]
- 32). Toro JR, Pautler SE, Stewart L, et al. Lung Cysts, spontaneous pneumothorax, and genetic associations in 89 families with Birt-Hogg-Dube syndrome. *Am J. Respir Crit Care Med*. 2007;175(10): 1044–1053. Doi: 10.1164/rccm.200610-14830C [PubMed: 17322109]
- 33). Johannesma et al. Risk of spontaneous pneumothorax due to air travel and diving in patients with Birt-Hogg-Dube syndrome. *Springerplus*. 2016; 5(1): 1506 Doi: 10.1186/s40064-016-3009-4. [PubMed: 27652079] • Survey-based study of 145 BHD patients estimating the risk of SP related to air travel in patients with BHD.
- 34). Furuya M, Yao M, Tanaka R, et al. Genetic, epidemiologic and clinicopathologic studies of Japanese Asian patients with Birt-Hogg-Dube syndrome. *Clin Genet*. 2016; 90(5):403–412. Doi: 10.1111/cge.12807 [PubMed: 27220747]
- 35). Gupta N, Kopras EJ, Henske EP, James LE, El-Chemaly S, Veeraraghavan S, Drake MG, McCormack FX. Spontaneous Pneumothoraces in Patients with Birt-Hogg-Dube Syndrome. *AnnAmThorac Soc*. 2017;14(5): 706–713. Doi: 10.1513/AnnalsATS.201611-886OC. • Survey of 104 BHD patients describing the risk of spontaneous pneumothorax attributed to air travel, as well as the burden of spontaneous pneumothoraces and the utility of pleurodesis in patients with BHD.

- 36). Hoshika Y, Kataoka H, Kurihara M, Ando K, Sato T, Seyama K, Takahashi K. Features of Pneumothorax and Risk of Air Travel in Birt-Hogg-Dube Syndrome. *Am J Respir Crit Care Med*. 2012; 185:A4438.
- 37). Vassallo R, Harari S, Tazi A. Current understanding and management of pulmonary Langerhans cell histiocytosis. *Thorax*. 2017;72(10) 937–945. Doi: 10.1136/thoraxjnl-2017-210125 [PubMed: 28689173]
- 38). Bonelli FS, Hartman TE, Swensen SJ, Sherrick A. Accuracy of high-resolution CT in diagnosing lung diseases. *AJR AM J Roentgenol*. 1998;170(6): 1507–1512. Doi: 10.2214/ajr.170.6.9609163 [PubMed: 9609163]
- 39). Hartman TE, Tazelaar HD, Swensen SJ, Muller NL. Cigarette smoking: CT and pathologic findings of associated pulmonary diseases. *Radiographics* 1997;17(2):377–390. Doi: 10.1148/radiographics.17.2.9084079 [PubMed: 9084079]
- 40). Mendez JL, Nadrous HF, Vassallo R., et al. Pneumothorax in Pulmonary Langerhans cell Histiocytosis. *Chest*. 2004;125(3):1028–1032. Doi:10.1378/chest.125.3.1028 [PubMed: 15006964]
- 41). Singla A, Kopras EJ, McCormack FX, Gupta N. Management of Spontaneous Pneumothorax and safety of air travel in patients with Pulmonary Langerhans Cell Histiocytosis. *Am J Respir Crit Care Med*. 2017;195: A1591.
- 42). Tam A, Sing h, Gupta S, et al. Air Travel after Biopsy-related Pneumothorax: Is it Safe to Fly? *J Vasc Interv Radiol*. 2011;22(5):595–602. Doi: 10.1016/j.jvir.2011.01.436. [PubMed: 21514516]
- 43). Cheatham ML, Safcsak K. Air travel following traumatic pneumothorax: when is it safe? *Am Surg*. 1999;62:
- 44). International Air Transport Association (IATA). IATA Medical Manual, 2 2017 IATA website <http://www.iata.org/publications/Documents/medical-manual.pdf> Accessed Sept 21, 2017.
- 45). Aerospace Medical Association Medical Guidelines Task Force. Medical guidelines for airline travel, 2nd ed. *Aviat Space Environ Med*. 2003;74(5 Suppl):A1–19.
- 46). Postmus P, Johannesma et al. In-Flight Pneumothorax: Diagnosis May be missed because of Symptom Delay. *Am J Respir Crit Care Med*. 2014; 190(6): 704–705. Doi: 10.1164/rccm.201404-0698LE. [PubMed: 25221882]
- 47). Gupta N, Langenderfer D, McCormack FX, Schauer DP, and Eckman MH. Chest Computed Tomographic Image Screening for Cystic Lung Diseases in Patients with Spontaneous Pneumothorax Is Cost Effective. *Ann of Am Thorac Soc*. 2017;14(1): 17–25. Doi: 10.1513/AnnalsATS.201606-459OC [PubMed: 27737563]

Table 1.

Summary of major findings from the studies evaluating air travel related spontaneous pneumothorax in patients with diffuse cystic lung diseases.

Study [Ref]	Disease	Type of study	Number of patients who had ever flown	Total number of flights	Total number of air-travel related SPs	Air travel related SP risk/patient	Air travel related SP risk/flight
Johannesma [33]	BHD	Patient survey	145	2,528	16	9.0%	0.63%
Gupta [35]	BHD	Patient survey	104	8,920	11	8%	0.12%
Hoshika [36]	BHD	Patient survey	40	2142	0	0	0
Pollock-BarZiv [28]	LAM	Patient survey	276	454	10	4%	2.2%
Gonano [29]	LAM	Patient survey	77	194	5	6.4%	2.6%
Taveira-DaSilva [5]	LAM	Retrospective chart review	204	536	6	2.9%	1.1%
Singla [41]	PLCH	Patient survey	54	538	2	3.7%	0.37%

Abbreviations: BHD = Birt-Hogg-Dubé Syndrome, LAM = lymphangioleiomyomatosis, PLCH = pulmonary Langerhans cell histiocytosis (PLCH), SP = spontaneous pneumothorax