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STUDY TITLE: Safety of bronchoscopy in patients with interstitial lung disease: A prospective, observational, multicentre, international study.

STUDY CODE: SaBrILD

RATIONALE:

Bronchoscopy is a minimally invasive, diagnostic and therapeutic technique, commonly performed in the management of respiratory diseases, ranging from airway disease, parenchymal or interstitial abnormalities, to mediastinal disorders[1].

In the context of interstitial lung diseases (ILDs) bronchoscopy is widely used for diagnostic purposes to perform bronchoalveolar lavage (BAL), bronchial and transbronchial lung biopsy, transbronchial lung criobiopsy and intrathoracic lymph node sampling[2,3]. However, patients with ILDs refer to medical attention in a wide range of clinical conditions from mild functional impairment, with absent or mild respiratory symptoms, to severe lung involvement with low exercise tolerance and/or chronic respiratory failure. In these patients, a balance between benefits and risk, i.e. between the safety and the diagnostic utility of bronchoscopy, should be always carefully evaluated.

In the follow-up of patients with ILD, bronchoscopy may also be useful to diagnose lower respiratory tract infections, suspected lung cancer/pulmonary metastases or in the diagnostic work-up of patients with haemoptysis[1-3].

Furthermore, patients with ILDs may show an acute respiratory worsening in the context of the appearance of new lung abnormalities (ground-glass opacities, consolidations or both) at the CT scan, that may be related to acute exacerbation of ILD and/or lower respiratory trait infections. In this context, the rapid detection of an infective agent, (e.g. may mandatory to start and the most adequate antibiotic treatment, that can radically modify the disease natural history. Moreover, the absence of micro-organisms identification in case of acute ILD may support the diagnosis of idiopathic AE-ILDs[2,3].

Bronchoscopy is a relatively safe endoscopic technique, but it may show complications. Adverse events can occur during, few hours later, several days or even weeks after the procedure. In most cases adverse events are mild and self-limiting but they can require hours to days for resolution or lead patient to death. The most common reported complications include oxygen desaturation during procedure, mild and self-limiting bleeding, hypotension, hypertension, new onset arrhythmias, bronchospasm and post-procedural fever. Less common but more severe events may include pneumothorax, acute pulmonary oedema, major bleeding needing embolization, major acute cardiac events (MACEs) and pneumonia. However, there is a wide variability in the type and rate of adverse events depending on the diagnostic technique/procedure performed during bronchoscopy[1].

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BAL is a useful sampling technique in the first diagnosis of patients with many fibrotic and non-fibrotic ILDs. BAL findings may lead to the definite etiological diagnosis (e.g. in case of eosinophilic pneumonia), narrow the differential diagnosis and/or rule out other lung diseases mimicking ILDs (e.g. infections or malignancies)[4-6]. Transbronchial biopsies with forceps and cryoprobes are the most used techniques to obtain an histological diagnosis in diffuse parenchymal lung diseases while endosonographic techniques with needle aspiration (i.e. endobronchial ultrasounds transbronchial needle aspiration, EBUS-TBNA and endoscopic ultrasound with bronchoscope fine needle aspiration, EUS-B-FNA) and with cryoprobes, are usually employed in the diagnosis of ILD with hilar and /or mediastinal lymph nodes involvement (i.e. sarcoidosis)[5-11].

Despite its crucial utility, only limited data are available in the literature on the safety of bronchoscopy in patients with ILDs at the time of the first diagnosis and during the follow-up, and limited data are retrievable on the utility and safety of this sampling technique in patients with AE-ILDs.

One monocentric, retrospective study which aimed at evaluating the complication rate associated with fiberoptic bronchoscopy with bronchoalveolar lavage in a group of patients with interstitial lung diseases, reported the safety of BAL in patients with ILDs. In this study, 281 procedures were performed in 141 patients enrolled. During the study 12 complications occurred, with a rate od adverse events lower than 5%. Only minor complications were identified and none significantly compromised patient care; no major complication occurred. The most frequently experienced complication was fever after BAL that occurred in seven patients (2.5%) and resolved without therapy. However, this study did not include patients with suspected or confirmed AE-ILDs[12]. More recently, Molyneaux et al. reported a 2.7% rate of adverse events at 30 days in a cohort of 223 patients with IPF who underwent BAL for diagnostic purposes[4].

Arcadu et al.[13] in a retrospective, monocentric study, described a 13% diagnostic yield of bronchoscopy in patients with ILD admitted with respiratory failure for discriminating between infection and acute exacerbation, but the exact rate of complications was not reported.

In patients with fibrotic ILDs (e.g. IPF) undergoing bronchoscopy, a rate of 3-4% of acute exacerbations were described. In a retrospective, monocentric study, Sakamoto et al[14] assessed the acute exacerbation rate after bronchoscopy with bronchoalveolar lavage in a cohort of 112 patients with IPF. 4 AE-IPF cases occurred during the study period with a rate of 3.5%. The risk of AE-IPF was significantly elevated within 30 days after BAL (rate ratio = 4.12; 95% CI = 1.03-12.2). The relative risk of developing AE after second or later BAL procedures was estimated to be considerably higher (rate ratio = 9.10; 95% CI = 2.27-26.98)[14].

Abe et al.[15,] in another monocentric study retrospectively analyzed the data of 155 patients with suspected IPF who had undergone BAL for diagnostic purpose. BAL-related AE was defined as the development of AE within 30 days after

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the procedure. During the study period 5 (3.2%) patients developed AE within 30 days after BAL. The average duration from BAL to AE onset was 7.8 days (2–16 days). Several risk factors for post-BAL AE were described: PaO2 < 75 mm Hg (p = 0.036), neutrophil content in BAL ≥ 7% (p = 0.0061), %DLCO < 50% (p = 0.019) and Gender-Age-Physiology (GAP) stage III (p = 0.034).

Transbronchial lung biopsy (TBLB) with forceps is a common procedure for obtaining histopathological samples in patient with pulmonary lesions and ILD as well. Neenu et al[16] conducted an observational, prospective, monocentric study to assess diagnostic yield, and safety of TBLB in ILD. During the study period 68 patients with ILD (including hypersensitivity pneumonitis - HP, sarcoidosis and idiopathic interstitial pneumonitis – IIP) underwent bronchoscopy with TBLB. Pathological diagnosis of ILD was obtained in 54.41%. A total of 11 (16.2%) patients had complications with no mortality after procedure, including: hemoptysis (5.9%), pneumothorax (7,4%), one case of acute exacerbation of underlying ILD, and one arrhythmia. None had severe bleeding requiring intervention. Complications rate was significantly higher in IIP patients than in non-IIP patients and in possible UIP radiological pattern vs non-UIP cases[16].

Recent studies investigated the role, diagnostic yield and safety of transbronchial lung criobiopsy (TBLC) in patients with ILD[17-23]. TBLC has been increasingly incorporated into the diagnostic work-up of ILDs and is currently considered an acceptable alternative to surgical lung biopsy in selected patients with fibrotic ILD and in centers with appropriate expertise[11,22]. Indeed, it allows the retrieval of larger and better-preserved tissue samples compared with conventional forceps biopsy, while maintaining a less invasive profile than surgical lung biopsy[11,22].

Procedural adverse events are frequent in TBLC, although most are minor[23]. The most frequent adverse events are pneumothorax and mild bleeding. In a systematic review on TBLC, overall complication rate was 23.1% (95% CI not reported; based on 31 studies), with summary incidence of pneumothorax of 9.4% (95% CI 6.7–12.5%) and summary incidence of moderate–severe bleeding of 14.2% (95% CI 7.9–21.9%). Summary incidence of mortality within 30 days was 0.3% (95% CI not reported; based on 33 studies)[24].

Aburto et al.[25] analysed 257 TBLC procedures, with mild complications in 15.2%, and 5.4% requiring hospital admission on the day of the procedure. In the 30 days following the TBLC, rates of readmission and mortality were 1.3% and 0.38% respectively. Variables significantly associated with hospital admission were modified Medical Research Council dyspnoea score ⩾2, FVC <50% and Charlson Comorbidity Index ⩾2.

Endosonography is a safe procedure in patients with sarcoidosis, the ILD most frequently associated with hilar and mediastinal lymph adenopthies. Crombag et al., in an international, randomized controlled trial, described, in 306 patients with a final diagnosis of sarcoidosis who underwent EBUS-TBNA and/or EUS-B-FNA, a rate of complication of 0.3% (medistinitis)

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To our knowledge, no studies evaluated the overall safety of bronchoscopy in patients with ILD at the time of the first diagnosis and during follow-up

STUDY ENDPOINTS

Primary endpoint:

- To assess the overall rate of complications occurring 30 days after bronchoscopy in patients with ILDs undergoing the endoscopic examination

Secondary endpoints:

To assess:

- Rate and type of complications occurring during single endoscopic procedure or endoscopic procedures combination (i.e. bronchoscopy with BAL and TBLB, etc)
- Rate and type of complications occurring within 24 hours after bronchoscopy (single procedure and procedures combination)
- Rate and type of complications occurring during the endoscopic procedure, within 24 hours and 30 days after bronchoscopy, at the time of the first ILD diagnosis Vs. during the follow-up
- Rate and type of complications occurring during the endoscopic procedure, within 24 hours and 30 days after bronchoscopy in case of suspected/diagnosed AE.
- Difference in rate and type of complications among non-exacerbated fibrotic Vs. non-fibrotic ILD
- Difference in rate and type of complications analysed for sampling techniques (i.e. BAL, endobronchial biopsy, transbronchial biopsy (with forceps and cryoprobes, endosonography) and related to the timing of bronchoscopy (diagnosis and follow-up)
- Rate and type of complications related to the respiratory support (i.e. low flow oxygen, high flow nasal cannulas, venturi mask, non-invasive and invasive mechanical ventilation) and type of sedation (conscious, deep sedation, general anaesthesia)
- Overall complications rate in patients <80 years old Vs ≥80 years old
- Comparison of complications rate between patients with and without chronic respiratory failure with ILD who underwent bronchoscopy.

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- Comparison of complications rate between patients with FVC <80% and ≥80% (measured at the time of bronchoscopy)
- Comparison of complications rate between patients with DLCO <50% and ≥50% (measured at the time of bronchoscopy)
- Rate and type of complications occurring during the endoscopic procedure when used for therapeutic purposes in patients with ILD;
- Need for respiratory support escalation following bronchoscopy.
- Diagnostic yield of bronchoscopy in patients with ILD, i.e. number of patients for whom bronchoscopy has provided a definite diagnosis of specific ILD or alternative diagnosis (e.g. lower respiratory tract infection or malignancy).
- Comparison of complications rate between patients with Eastern Cooperative Group Performance Status (ECOG-PS) <2 and ≥2 with ILD who underwent bronchoscopy.
- Hospitalization and 30-days mortality rate in patients with ILD following bronchoscopy.
- The main clinical, demographic, functional, radiological and procedural variables related to the presence of complications.

STUDY DESIGN

Observational, prospective, multicentre, international study on adult patients with ILD requiring bronchoscopy as diagnostic tool. The study protocol is designed, and it will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

The study will be registered on Clinicaltrials.gov

STUDY POPULATION

Patients ≥18 years old with interstitial lung disease who need to undergo bronchoscopy for diagnostic purposes, at the time of the first diagnosis or during follow-up (included in the work-up of an acute exacerbation). During the study period, individual patients may undergo more than one bronchoscopic procedure (e.g., for initial diagnostic purposes or for subsequent clinical indications such as disease exacerbation). Therefore, each procedure will be considered as a separate observation for safety analysis.

STUDY PERIOD

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Patients will be consecutively enrolled starting from May 2026. The estimated time required to complete data collection and analysis is approximately 2 years.

INCLUSION CRITERIA:

- Consecutive adult (≥18 years old) patients with suspected or confirmed ILD who need to undergo bronchoscopy as part of their routine clinical practice,
- Patients able to understand and sign an informed consent

EXCLUSION CRITERIA:

- Patients who refused the study partecipation;
- Patients with contraindications to bronchoscopy

PARTECIPATING CENTRES

The study will be conducted at the following clinical centers:

- Respiratory Unit, ASST Santi Paolo e Carlo, Milan (Coordinating Centre);
- Service de Pneumologie Allergologie et Transplantation, Centre Constitutif du Centre de Référence des Maladies Pulmonaires Rares, FHU INFIRE, Paris, France
- Respiratory Unit and Adult Cystic Fibrosis Center, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico Milan, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy.
- Respiratory Unit – IRCCS San Gerardo dei Tintori Foundation, Monza
- Division of Respiratory Diseases, Ospedale Luigi Sacco, Polo Universitario, ASST Fatebenefratelli-Sacco
- Respiratory Unit, Medicine Department, ASST Papa Giovanni XIII, Department of Health Science, University of Milan, Bergamo, Italy.
- Respiratory Unit, IRCCS Humanitas Research Hospital, Department of Biomedical Sciences, Humanitas University, Milan, Italy.
- Respiratory Unit, Santa Maria alle Scotte University Hospital, Siena
- Respiratory Unit – Legnano Hospital

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- Respiratory Unit – IRCCS Policlinico San Matteo Foundation, University of Pavia
- Unit of Respiratory Medicine "L. Vanvitelli", A.O. dei Colli, Monaldi Hospital, Department of Translational Medical Sciences, University of Campania Luigi Vanvitelli, Naples, Italy
- Interventional Pulmonology Unit, Department of Pulmonology, Oncology and Hematology, Antonio Cardarelli Hospital, Naples, Italy.
- Respiratory Unit – Center for Rare Lung Disease - Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy.
- Respiratory Unit, Azienda Ospedaliera-Universitaria IRCCS Policlinico di Sant'Orsola Malpighi, Bologna, Italy
- Unit of Pneumology, San Martino Policlinic Hospital, Genoa, Italy

DATA COLLECTED

Data collected during the study period:

- Demographic and functional data: age, gender, race, type of admission (outpatient, ward, ICU), peripheral oxygen saturation, presence of comorbidities (Charlson Comorbidity Index), PS-ECOG, indication for bronchoscopy, need for long-term oxygen therapy, last functional assessment before bronchoscopy; immunosuppressive treatment; antifibrotic treatment; 6MWT distance and 6MWT Nadir before bronchoscopy
- Indication for bronchoscopy: diagnosis of ILD, diagnosis of AE-ILD, suspected lower respiratory tract infection, diagnosis of malignancy, work-up of haemoptysis; therapeutic procedure
- Type of supportive strategy: no support, low flow oxygen therapy, HFNC, non invasive mechanical ventilation, invasive mechanical ventilation. Type of Sedation (conscious, deep sedationm general anesthesia) and drugs administered.
- Occurrence of adverse events: desaturation (i.e. SpO2< 90% for at least 10 seconds), severe desaturation (i.e. SpO2< 80%), need for procedure interruption, perioperative hypotension (systolic blood pressure <90 mmHg or a Systolic Blood Pressure <20% of the preoperative value), perioperative hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg or a Systolic Blood Pressure ≥20% of the preoperative value that lasts for more than 15 minutes) events, new onset of cardiac arrhythmias (specify the rhythm) or myocardial ischemia or electrocardiographic ST-alterations, neurological events (i.e. severe sensorium depression, psychomotor agitation, stroke), pneumothorax, acute pulmonary oedema, fever; bronchospasm; new haemoptysis onset (evaluated using Nashville Working Group Scale); pneumonia, acute exacerbation of ILD, mediastinitis.

- Severity of complications, assessed using version 6 of Common Terminology Criteria for Adverse Events (CTCAE) (MedDRA 28.0).
- Sampling technique during bronchoscopy: endobronchial biopsy (EBB), transbronchial biopsy (TBB), transbronchial criobiopsy (TBCB), endobronchial ultrasound-guided transbronchial Needle-Aspiration (EBUS-TBNA); endoscopic ultrasound with bronchoscope fine needle aspiration, EUS-B-FNA; ultrasound guided mediastinal cryobiopsy; peripheral transbronchial needle aspiration.
- Clinical outcomes: full recovery after complication; need for support escalation; need for admission to ward (for outpatient) or ICU (for outpatients and ward-admitted patient).
- Hospital stay length (in hospitalised patients)
- Rate of hospital readmission within 30 days after bronchoscopy
- Mortality rate at 30 days after procedure.

SAMPLE SIZE

The sample size was calculated to estimate the overall incidence of 30-day complications (safety endpoint). Based on the available scientific evidence[4,16,24,27], which reports complication rates ranging from 0.3% to 23% depending on the procedure (BAL, EBUS, TBB, cryobiopsy), a conservative expected value of 10% was assumed. Assuming a 95% confidence level and a margin of error of 3%, the estimated sample size was 384 patients. Accounting for an anticipated 10% rate of missing follow-up data, the final sample size was set at 427 patients.

STATISTICAL ANALYSIS

Data with a non-normal distribution will be evaluated using the Mann–Whitney test and will be reported as median and interquartile range, whereas those with a normal distribution will be analyzed using Student's t-test and will be describe as mean and standard deviation. Categorical variables will be presented as proportions and analyzed using the chi-squared or Fisher's exact test, as appropriate. A p-value <0.05 will be considered statistically significant. Analyses will be carried out with the Statistical software STATA.

FUNDING

The study does not involve any additional costs compared to current clinical practice. No commercial funding.

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