Guidelines for Diagnostic Flexible Bronchoscopy in Adults: Joint Indian Chest Society/National College of Chest Physicians (I)/Indian Association for Bronchology Recommendations

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ABSTRACT

Flexible bronchoscopy (FB) is commonly performed by respiratory physicians for diagnostic as well as therapeutic purposes. However, bronchoscopy practices vary widely across India and worldwide. The three major respiratory organizations of the country supported a national-level expert group that formulated a comprehensive guideline document for FB based on a detailed appraisal of available evidence. These guidelines are an attempt to provide the bronchoscopist with the most scientifically sound as well as practical approach of bronchoscopy. It involved framing appropriate questions, review and critical appraisal of the relevant literature and reaching a recommendation by the expert groups. The guidelines cover major areas in basic bronchoscopy including (but not limited to), indications for procedure, patient preparation, various sampling procedures, bronchoscopy in the ICU setting, equipment care, and training issues. The target audience is respiratory physicians working in India and well as other parts of the world. It is hoped that this document would serve as a complete reference guide for all pulmonary physicians performing or desiring to learn the technique of flexible bronchoscopy.

KEYWORDS: Bronchoscopy, Evidence-based medicine, Guidelines, Lung cancer; Tuberculosis, Intensive care

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EXECUTIVE SUMMARY

Bronchoscopy suite setup and staff protection

Bronchoscopy suite setup

- Flexible Bronchoscopy should be performed in a suite or room dedicated for this purpose (3A)
- A bronchoscopy suite should have dedicated areas for patient preparation, performance of procedure, and postprocedure monitoring (3A)
- Every bronchoscopy suite should have all essential equipment required for patient monitoring and resuscitation (3A)
- A bronchoscopy suite should have dedicated areas for bronchoscope disinfection and storage of equipment (3A)
- Wherever feasible, bronchoscopy should be performed in a room with negative pressure design (3A)
- Bronchoscopy room should have minimum of 12–15 fresh air exchanges per hour with direction of airflow from room entrance to the back and outside (3A)
- If recirculation of air is unavoidable, direct exhaust air thrown outside should be away from patient-care areas, and high-efficiency particulate air (HEPA) filters must be used (3A).

Staff protection

- Personal protective equipment (PPE) should be worn by all health-care personnel in the bronchoscopy suite (3A)
- Use of N95 mask is recommended when there is either suspicion of mycobacterial infection or high risk of droplet infection (3A)
- Health personnel in proximity to the patient during bronchoscopy should ideally wear eye-shields (3A)
- Needles should not be used to remove biopsy specimens from forceps (3A)
- All staff should be vaccinated against hepatitis-B and receive annual influenza vaccine (3A)
- Impermeable surgical gowns should be worn by bronchoscopists and health personnel in proximity to the patient during the procedure (3A)
- Staff concerned with cleaning and disinfection of bronchoscopes should wear adequate PPE including gowns, gloves, masks, and proper eye-shields (2A)
- Latex or nitrile, powder-free gloves should be preferably used by persons engaged in disinfecting bronchoscopes (2A)
- Hand-hygiene practices should always be followed before and immediately after removing PPE (UPP)
- All health personnel exposed to disinfectants in the bronchoscopy unit should undergo a baseline clinical evaluation (3A)
- Baseline spirometry should be performed for all personnel exposed to disinfectants in the bronchoscopy unit (3A)
- All staff engaged in bronchoscope disinfection should undergo periodic clinical assessment and spirometry if required (3A).
- Bronchoscopy should be performed in patients with suspected TB who are unable to produce sputum or when sputum analysis is unyielding (2A)

Patient evaluation and safety issues during flexible bronchoscopy

Prebronchoscopy hematology evaluation

- Performing coagulation studies, platelet counts, and hemoglobin levels routinely before flexible bronchoscopy is not recommended (3B)
- Coagulation studies, platelet counts, and hemoglobin should be performed before bronchoscopy in patients with clinical risk factors for bleeding such as ongoing anticoagulation, bleeding diathesis, and chronic liver and kidney disease (UPP)
- We recommend a platelet count of at least 20,000 per mm^3 for performing bronchoalveolar lavage (BAL) (3B)
- We recommend a platelet count of at least 50,000 per mm^3 for performing endobronchial biopsy (EBB)/transbronchial lung biopsy (TBLB) (3B)
- BAL can be performed in patients with platelet count $<20,000$ per mm^3 if clinically indicated, after careful risk–benefit analysis. In patients with thrombocytopenia, oral route is preferred for performing bronchoscopy (UPP)

Antiplatelet and anticoagulation agents

- Clopidogrel, prasugrel, or ticagrelor should be discontinued at least 5 days before EBB and TBLB (2A)
- Low-dose aspirin can be continued in patients planned for TBLB/EBB (2A)
- Liaison with concerned specialist is recommended for the modification of antiplatelet therapy in patients on dual-antiplatelet agents and at high risk of thrombosis (UPP) [Appendix 1]
- Warfarin should be stopped at least 5 days prior to transbronchial needle aspiration (TBNA) or bronchoscopic biopsy and a preprocedure international normalization ratio (INR) of <1.5 should be ensured (3A)
- Newer oral anticoagulants (NOACs) should be stopped at least 2 days before TBNA or bronchoscopic biopsy (3A)
- We recommend bridging therapy with low-molecular-weight heparin (LMWH) in patients on anticoagulation and at high risk of thrombosis. LMWH, when indicated, should be started 2 days after stopping warfarin. The last dose of LMWH should be administered 24 h before the procedure (3A) [Appendix 2]
- BAL can be performed in patients on therapeutic anticoagulation after careful risk–benefit analysis, preferably via oral route (UPP)

Bronchoscopy in Asthma and Chronic Obstructive Pulmonary Disease (COPD)

- Bronchoscopy can be safely performed in patients with asthma and chronic obstructive pulmonary disease (COPD) (2A)
- Patient's asthma treatment should be optimized before bronchoscopy, especially when BAL is to be performed (2A)

- Treatment for COPD should be optimized before bronchoscopy (3A)
- Routine administration of bronchodilators before bronchoscopy is not recommended in patients with asthma or COPD who are adequately controlled (1A)

Antibiotic prophylaxis and good clinical practice points

- Routine use of prophylactic antibiotics is not recommended before flexible bronchoscopy to prevent procedure-related infections (1A)
- Patients should receive proper counseling and written advice regarding the management of postbronchoscopy fever (UPP)
- A fasting duration of at least 2 h for clear liquids and 4 h for light meals is recommended before bronchoscopy (3A)
- Written informed consent should be obtained from every patient (UPP)
- Patients should be enquired regarding known allergies, comorbidities, and drug history (including anticoagulants or antiplatelets) (UPP)
- Duration of fasting should be confirmed (UPP)
- In all patients, intravenous (IV) access should be obtained and maintained until the patient is deemed fit to be discharged (UPP)
- Routine vital signs such as blood pressure (BP), heart rate (HR), oxygen saturation (SpO_2), and respiratory rate should be recorded (UPP)

Patient monitoring during and after flexible bronchoscopy

- Flexible bronchoscopy should preferably be performed with the patient in supine position (2A)
- Nasal and oral routes are equally suitable for performing bronchoscopy (3A)
- Oral route should be preferred for larger size bronchoscopes, for therapeutic procedures such as foreign body removal, or in patients with thrombocytopenia (UPP)
- Routine oxygen supplementation is recommended for patients with risk factors for desaturation, low baseline oxygen saturation (SpO_2 <90%), or significant desaturation during procedure (>4% decrease from baseline or SpO2 <90% for >1 min) (3A)
- Continuous pulse oximetry, heart rate (HR), and continuous (or repeated) noninvasive BP monitoring are recommended during FB (3A)
- Continuous or repeated electrocardiography (ECG) monitoring should be performed during bronchoscopy in patients with known cardiac disease or arrhythmias (3A)
- All patients should be monitored for symptoms including dyspnea, chest pain, and hemoptysis after completion of bronchoscopy (3A)
- All patients should have vital parameters (including consciousness, HR, respiratory rate, SpO_2, and BP) recorded immediately after bronchoscopy and repeated as indicated (3A)
- Patients should be kept under observation until they achieve preprocedure level of consciousness and acceptable vital parameters (3A)

Premedication, sedation, and anesthesia

Premedication and sedation

- Anticholinergic premedication should not be administered before FB (1A)
- Dextromethorphan may be considered as an antitussive to optimize patient comfort prior to the procedure (2B)
- Administration of IV sedation should be considered to improve patient tolerance (2B)
- FB can also be safely performed without IV sedation (2B)
- Combination of midazolam or propofol with an opioid is preferred over either alone (1A)
- Choice of sedation (midazolam/propofol/dexmedetomidine/fentanyl) should be made depending on the operator preference and availability of anesthetists/trained medical personnel (UPP)
- IV sedation with midazolam or fentanyl can be safely administered by the proceduralist (2A)
- Propofol should be administered by an anesthetist or trained medical personnel (2A)
- Assessment of the depth of sedation, BP, HR, respiratory rate, and SpO_2 monitoring should be performed in all patients receiving sedation during bronchoscopy (3A)
- Sedation should be cautiously administered in high-risk groups (UPP)
- Minimum possible dose of sedative should be administered (UPP)
- A log of sedative dosage administered should be maintained for each patient (UPP)
- Use of a sedation scale is preferred to monitor the depth of sedation throughout bronchoscopy (UPP)

Topical anesthesia

- Topical anesthesia should be routinely used during bronchoscopy (1A)
- Lignocaine is the preferred agent for topical anesthesia (3A)
- 2% lignocaine gel is recommended for topical nasal anesthesia (1A)
- Use of topical vasoconstrictors is not recommended during nasal bronchoscopy (2A)
- Lignocaine spray (10% concentration) is recommended for pharyngeal anesthesia (2A)
- Three to five sprays of 10% lignocaine are recommended for pharyngeal anesthesia (UPP)
- Nebulized lignocaine is not recommended for topical anesthesia (1A)
- Either "spray-as-you-go" technique or cricothyroid injection is recommended for topical anesthesia of vocal cords and trachea (1A)
- Either spray catheter or working channel of bronchoscope may be used for administering lignocaine in the "spray-as-you-go" technique (UPP)
- 1% lignocaine should be used for "spray-as-you-go" administration (1A)
- Bronchoscopist should make an attempt to keep total administered lignocaine dose to the lowest possible levels, with a suggested upper limit of 8.0 mg/kg body weight (2A)
- Bronchoscopists should routinely record the cumulative

dose of lignocaine used and be aware of signs of lignocaine toxicity (UPP)

Bronchoscopic sampling

Bronchoalveolar lavage (BAL)

- In diffuse lung involvement, BAL should be performed either from the right middle lobe or the lingula (2A)
- In patients with suspected *Pneumocystis jirovecii or Cytomegalovirus (CMV) pneumonia* with diffuse lung involvement, BAL should be performed bilaterally from more than one lobe, including the upper lobe (2A)
- In focal/patchy lung involvement, the site of BAL should be guided by high-resolution computerized tomography (HRCT) thorax findings (2A)
- At least 100 ml of normal saline should be instilled while performing BAL and total quantity should not exceed 200 ml (2A)
- The required amount of fluid should be instilled in 2–5 aliquots, and smaller aliquots should be used in patients with COPD (UPP)
- Either manual suction or wall suction can be used for aspiration of fluid during BAL (2A)
- If manual aspiration is being performed, a tubing should be added to the handheld syringe (2A)
- If negative pressure is applied using continuous wall suction, the pressure should be kept <100 mmHg and adjusted to prevent airway collapse (3A)
- A minimum of 10% of fluid return should be achieved during BAL (2A)
- Postbronchoscopic sputum (PBS) examination should be performed in patients with sputum smear-negative pulmonary tuberculosis (PTB) undergoing bronchoscopy, in addition to other diagnostic bronchoscopic procedures (2A)

Bronchial washings (BW) and Bronchial brushings (BB)

- In suspected lung malignancy with visible endobronchial abnormality, bronchial washings and brushings should be routinely obtained in all patients (2A)
- In suspected malignancy with nonvisible or peripheral lesions, bronchial washings and bronchial brushings should be performed under fluoroscopic guidance, wherever facilities are available (2A)
- A minimum of 20 ml of fluid should be instilled for obtaining bronchial washings (UPP)
- For endobronchially invisible lesions, greater amount of saline may be instilled (UPP)
- Bronchial washings should be performed both before and after EBB to achieve maximal diagnostic yield (2A)
- Bronchial brushings should be performed before EBB for maximal yield (2A)
- A minimum of 2–4 bronchial brushings are needed to achieve optimal yield and minimize complications (3A)
- Liquid-based cytology (LBC) and cell block (CB) preparation of bronchoscopic samples are recommended in suspected lung cancer wherever facilities are available (3A)

Sequence of sampling procedures

- TBNA should be the first procedure followed by BAL, BW, BB, EBB, and post-biopsy washings (UPP)
- If endobronchial needle aspiration (EBNA) is planned, it should be taken before EBB (UPP)
- In diffuse lung diseases, if BAL is planned for cellular analysis, it should be the first procedure to be performed (UPP)

Transbronchial needle aspiration (TBNA)

- Conventional TBNA (c-TBNA) should be considered in patients with lymph node size of ≥1 cm in short axis at 4R (right lower paratracheal) or 7 (subcarinal) locations and size of ≥2 cm at hilar or interlobar nodal locations (10 [hilar]/11 [interlobar]) (2A)
- For lymph node size <1 cm in short axis at 4R or 7 locations and <2 cm in short axis at other locations, endobronchial ultrasound guided TBNA should be considered (2A)
- We recommend the use of 19G needle during c-TBNA to obtain either histology or cytology specimen (2A)
- We recommend performing 3–4 aspirates per node for optimum yield during c-TBNA (2A)
- Additional aspirations should be obtained if required for other necessary investigations (UPP)
- Rapid on-site evaluation (ROSE) should be used to reduce additional diagnostic bronchoscopy procedures during c-TBNA (2A)
- It is recommended to routinely apply vacuum suction during c-TBNA (UPP)
- The use of automatic aspiration is preferable to manual aspiration during c-TBNA (UPP)
- We recommend the use of endobronchial needle aspiration (EBNA) along with other bronchoscopic diagnostic modalities in patients with exophytic necrotic endobronchial lesions and submucosal lesions (SMLs) (2A)

Endobronchial biopsy

- Either cup or alligator forceps may be used to obtain EBB (3A)
- Fenestrated forceps may be preferred to reduce the frequency of crush artifacts (UPP)
- Routine instillation of topical hemostatic/vasoconstrictor agents to prevent bronchoscopic biopsy-related bleeding is not recommended (3A)
- Topical epinephrine or cold saline instillation or intratumoral tranexamic acid may be attempted to prevent bleeding in high-risk endobronchial lesions (e.g. lesions with increased superficial vascularity or spontaneously oozing) (UPP)
- For achieving optimum yield, at least 4–5 specimens should be obtained while performing EBB (3A)
- Additional samples for molecular testing and microbiological investigations should be obtained as and when indicated (UPP)
- EBB should be performed in addition to TBLB in all patients with suspected sarcoidosis (1A)

Transbronchial lung biopsy (TBLB)

- Alligator forceps may be preferred for performing TBLB (2B)
- At least 5–6 biopsy samples of moderate-to-large size should be obtained during TBLB (3A)
- For focal lung lesions, TBLB should preferably be performed from the bronchial segment with maximal radiological abnormality (UPP)
- In diffuse lung disease, TBLB should be performed from the basal segment(s) of the lower lobes (UPP)
- For diffuse lung disease, TBLB may be safely performed without fluoroscopic guidance (2B)
- TBLB with fluoroscopy guidance may be considered for focal parenchymal lesions, wherever available (2B)
- Float sign should not be used to ascertain the adequacy of TBLB specimens (3A)
- Routine chest radiograph is not essential in asymptomatic patients following TBLB. All symptomatic patients should undergo a chest radiograph to rule out pneumothorax (3A)
- Wherever feasible, bedside thoracic ultrasound may be used to exclude pneumothorax following TBLB (2B)

Bronchoscopy training

- We recommend that a structured program be implemented for basic bronchoscopy training (2A)
- For structured training program in basic FB, we recommend that virtual reality (VR) simulator or anatomical model-based training may be incorporated into the conventional apprenticeship model (3B)
- We recommend performing a minimum of 100 flexible bronchoscopy procedures (50 supervised and 50 independent) to attain basic competency (3A)
- We recommend performing a minimum of 25 flexible bronchoscopy procedures per year to maintain competency (3A)

Flexible bronchoscopy in the intensive care unit

Indications and monitoring

- Routine bronchoscopy-guided sampling for the diagnosis of ventilator-associated pneumonia (VAP) is not recommended (1A)
- Bronchoscopy may be considered in patients not responding to empirical antibiotic therapy, or an alternate diagnosis is being considered (UPP)
- The routine use of bronchoscopy for managing lung atelectasis or collapse in the ICU setting is not recommended (2A)
- Bronchoscopy can be used in the management of complete lung or lobar collapse, not responding to aggressive chest physiotherapy (UPP)
- Bronchoscopy guidance is recommended during percutaneous tracheostomy (2A)
- The minimum essential parameters that should be continuously monitored during and after bronchoscopy in the ICU are SpO_2, cardiac rhythm using ECG, and BP (UPP)

Flexible bronchoscopy in patients on mechanical ventilation

- During bronchoscopy in intubated patients, the diameter of the endotracheal tube (ETT) should be at least 2.0 mm more than the outer diameter (OD) of the bronchoscope (UPP)
- Use of flexible bronchoscope with minimum working channel of 2 mm is preferable for bronchoscopy in endotracheally intubated patients (UPP)
- During bronchoscopy in mechanically ventilated patients, the FiO_2 should be increased to 100% at least 5–10 min before the procedure and continued till the immediate recovery period or as necessary thereafter (3A)
- The ventilator should be adjusted to a mandatory mode (3A)
- The tidal volume (Vt) may be increased by 100–150 ml (UPP)
- Pressure limits/inspiratory pressures should be increased to ensure adequate tidal volume (3A)
- Positive end-expiratory pressure (PEEP) should be kept at minimum possible while allowing adequate oxygenation (3A)

Noninvasive ventilation in flexible bronchoscopy among hypoxemic patients

- Bronchoscopy in mild-moderate ARDS should be performed with noninvasive ventilation (NIV) assistance(1A)
- NIV-assisted bronchoscopy should be performed by an experienced operator (UPP)
- While performing bronchoscopy with NIV, backup facilities for invasive ventilatory support should be readily available (UPP)

Equipment disinfection

Scope cleaning and disinfection

- We recommend that flexible bronchoscopes should be cleaned and disinfected in specific, separate designated areas (3A)
- Precleaning and cleaning of flexible bronchoscopes should be performed using either nonenzymatic or multienzymatic detergent solutions containing at least four enzymes (2A)
- Leak testing should be performed ideally after every bronchoscopy procedure (3A)
- Disinfection of flexible bronchoscopes may be performed either manually or using automated endoscope reprocessors (AERs) (2A)
- If resources permit, AER is preferred over manual disinfection in view of better safety profile to healthcare staff (UPP)
- The use of peracetic acid (PAA) is recommended for the disinfection of flexible bronchoscopes with a contact time of 5 min (3A)
- Glutaraldehyde (2%) and orthopthaldehyde (OPA, 0.5%) can be used as alternative disinfectant agents with contact time of 20 and 5 min, respectively (UPP)

- It is recommended that 70% alcohol purge be performed as the final step of bronchoscope disinfection (3A)
- It is recommended that reverse osmosis (RO) water/ sterile water be used for final rinse of the flexible bronchoscope after disinfection (3A)

Disinfection of accessories and scope storage

- Reusable accessories such as forceps should be thoroughly cleaned, disinfected, and sterilized after each use (3A)
- Cytological needles and cytology brushes should preferably be single use since they cannot be sterilized (3A)
- Bronchoscope cleaning brushes should preferably be used only for a single patient; in case re-used, they should be sterilized after each procedure (3A)
- Either manual methods or AER may be used for disinfection of bronchoscope accessories (3A)
- During storage, flexible bronchoscopes should be hung vertically without any valves attached (3A)
- Ventilated drying cabinets are preferred for storing bronchoscopes when not in use (3A)
- Alternatively, roomy, well-ventilated cabinets can be used to store bronchoscopes (3B)
- It is recommended to carry out periodic active bronchoscope infection surveillance, preferably at 1–3 months' intervals (3B)

INTRODUCTION

Clinical context and need for a guideline

Flexible bronchoscopy (FB) is an important diagnostic and therapeutic tool in respiratory medicine. Over the past few decades, the scope of bronchoscopy has been progressively expanding globally as well as in India. Although majority of respiratory physicians in India perform bronchoscopy, a recent national survey revealed that the practices are highly variable with respect to various aspects of the procedure.[1] A strong need, therefore, was perceived to develop a comprehensive, evidence-based guideline, including the key aspects of bronchoscopy which could serve as a reference document for bronchoscopists, especially in the Indian context. The Department of Pulmonary, Critical Care and Sleep Medicine at the All India Institute of Medical Sciences (AIIMS), New Delhi, collaborated with the Indian Chest Society (ICS), National College of Chest Physicians of India (NCCP-India), and Indian Association for Bronchology (IAB) to form an Expert Working Committee with an aim to develop guidelines for basic diagnostic flexible bronchoscopy.

Target audience of the guideline

This guideline is primarily aimed at respiratory practitioners in India; however, it may be equally relevant to other healthcare facilities around the world. The document is intended to provide evidence-based information regarding all aspects of basic diagnostic bronchoscopy, including the requirements for setting up a bronchoscopy facility, procedural and sampling techniques, patient monitoring, equipment care and disinfection, bronchoscopy in the intensive care unit (ICU) setting, and training issues.

Scope of the guideline

This guideline was formulated following a systematic search to extract relevant literature pertaining to various aspects of bronchoscopy which were deliberated in multiple prior discussions. Topics covered in the guideline include:

- Setting up of a bronchoscopy unit
- Indications, complications, and contraindications of flexible bronchoscopy
- Patient monitoring
- Sedation, premedication, and anesthesia for flexible bronchoscopy
- Diagnostic procedures during flexible bronchoscopy: Bronchial washings (BW), bronchial brushings (BB), bronchoalveolar lavage (BAL), transbronchial needle aspiration (TBNA), endobronchial biopsy (EBB), and transbronchial lung biopsy (TBLB)
- Equipment disinfection and staff safety
- Flexible bronchoscopy in the ICU
- Training in flexible bronchoscopy

Topics not covered in the guideline

- Advanced diagnostic and therapeutic bronchoscopy
- Bronchoscopy in specific clinical conditions
- Rigid bronchoscopy
- Specific steps in technique of various diagnostic modalities
- Bronchoscopic endotracheal intubation
- Pediatric bronchoscopy.

METHODOLOGY

This guideline is based on the appraisal of the available evidence after extensive literature search. Questions were formulated after a series of discussions among the Working group with special emphasis on the Indian scenario. These questions were incorporated into specific domains that encompassed all major aspects of flexible bronchoscopy.

Systematic searches were performed in the electronic databases (PubMed, EMBASE, and Cochrane) to identify potentially relevant studies. Existing guidelines or recommendations made by other major international associations in respiratory medicine, such as the British Thoracic Society (BTS) and the American Thoracic Society (ATS), were also reviewed in detail.

The literature search process began in January 2017 and continued up to November 2017. Searches were saved, and monthly e-mail alerts were configured to identify newly published literature. The search strategy included a combination of MESH indexed terms and free text terms

and was limited to publications in English language only. All screened articles were categorized as (1) definitely relevant, (2) possibly relevant, or (3) not relevant to the project. All articles were categorized according to the topics listed above in the "Scope of the guidelines." Initially, a detailed appraisal of the evidence was presented within the department where studies were further selected based on relevance, and a provisional grading of the recommendations was formulated. Subsequently, the relevant articles were mailed to all experts as per their allotted domains, for appraisal and inputs. Regular e-mail communications were continued, the suggestions received were incorporated and the grading was revised accordingly. For questions wherein evidence was lacking, expert opinion was used to formulate the consensus recommendations.

A 2-day meeting was held in December 2017 at AIIMS, New Delhi, with the participation of all expert committee members. Initially, the evidence pertaining to each question was presented in detail to the expert faculty of each domain separately in five parallel break-away groups moderated by a group chair and recorded by rapporteurs. All recommendations were formulated based on the level of evidence, as well as local issues of cost and availability due to diverse healthcare resources. After discussions and appropriate modifications, the recommendations were presented to the joint working group and finalized by consensus.

The modified Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system was used to classify the quality of available evidence as 1, 2, 3, or usual practice point (UPP: defined as important practical points lacking research evidence) [Table 1].[2] The strength of recommendation was graded as A or B depending upon the level of evidence. Grade A recommendations in the guidelines should be interpreted as "strong recommendation to do (or not to do), where benefit clearly outweighs the risk (or vice versa)," and the Grade B recommendations in the guidelines should be interpreted as "weak recommendation, where risk and benefits are more closely balanced or uncertain." The strength of recommendation was made after considering factors such as available volume of evidence, consistency in the evidence, applicability and generalizability to the target population, and practicality for implementation.

A draft guideline document was circulated to all group members, and their suggestions were incorporated after online deliberations. It was also proposed to revise and update the guidelines after 5 years.

Table 1: Quality of evidence and recommendations[2]

Quality of evidence	Level
Evidence from ≥1 good-quality and well-conducted RCTs or meta-analysis of RCTs	1
Evidence from at least 1 RCT of moderate-quality, or well-designed clinical trial without randomization; or from cohort or case-controlled studies	2
Evidence from descriptive studies, or reports of expert committees, or opinion of respected authorities based on clinical experience	3
Not backed by sufficient evidence; however, a consensus reached by the working group, based on clinical experience and expertise	UPP
Strength of recommendation	**Grade**
Strong recommendation to do (or not to do) where the benefits clearly outweigh the risk (or vice versa) for most, if not all patients	A
Weak recommendation, where benefits and risk are more closely balanced or are more uncertain	B

UPP: Useful practice point, RCT: Randomized controlled trial

BRONCHOSCOPY SUITE SETUP AND STAFF PROTECTION

The area where flexible bronchoscopy is performed must meet certain specific requirements and prerequisites. In addition, the optimal utilization of bronchoscopy also requires adequate technical understanding on part of the personnel. Appropriate airborne infection control measures are also essential while setting up a bronchoscopy unit. In certain countries, specific recommendations exist for designing a bronchoscopy suite and are bound by legal provisions. However, in resource-limited settings such as India, recommended standards need to be balanced with feasibility along with economic and organizational constraints.

Should bronchoscopy be performed in a dedicated room?

For proper infection control and patient safety, bronchoscopy should be performed in a dedicated bronchoscopy room. A survey from North America in 1991 found that only 17% of bronchoscopies were performed in a dedicated suite, as compared to 28% in the United Kingdom.[3,4] In a recent survey from Germany, 54% of the hospitals had a dedicated bronchoscopy lab.[5] Bronchoscopy surveys from India show an increase in the use of a dedicated bronchoscopy suite for performing bronchoscopic procedures, from 22.6% in 1994 to 79.8% in 2017.[1] Currently existing bronchoscopy guidelines also recommend that a dedicated bronchoscopy suite be used for performing bronchoscopy.[6]

Evidence statement

- Surveys conducted on bronchoscopy practices have shown an increasing trend of performing bronchoscopy in a dedicated suite
- A dedicated bronchoscopy suite is desirable for performing bronchoscopy to optimize patient safety, ease of procedure, and airborne infection control.

Recommendation

- Flexible bronchoscopy should be performed in a suite dedicated to this purpose (3A).

What are the minimum essential requirements for setting up a bronchoscopy suite?

Requirements of a bronchoscopy suite depend upon the complexity of procedures planned and requirement of general anesthesia. Even for awake diagnostic bronchoscopy, certain essential requirements should be met for optimal outcomes and airborne infection control.

Minimum essential requirements of a bronchoscopy suite include adequate space for prebronchoscopy preparation of the patient, area for performing the bronchoscopy procedure, postbronchoscopy area to observe and monitor the patient, space for storage of bronchoscopy-related equipment, and a separate area for cleaning and disinfection of the equipment. Necessary monitoring devices and resuscitation cart are also considered essential requirements of a bronchoscopy suite.[7] To minimize the risk of cross-contamination, workflow from dirty to clean area with adequate separation of each area has been recommended.[8]

Evidence statement

- The minimum requirement for setting up a bronchoscopy suite includes adequate prebronchoscopy patient preparation area, space for performing the procedure, adequate postprocedure monitoring area, and space for storing bronchoscopy-related equipment, resuscitation cart, and drugs.

Recommendation

- A bronchoscopy suite should have dedicated areas for patient preparation, performance of procedure, and postprocedure monitoring (3A)
- Every bronchoscopy suite should have all essential equipment required for patient monitoring and resuscitation (3A)
- A bronchoscopy suite should have dedicated areas for bronchoscope disinfection and storage of equipment (3A).

What should be the ventilation requirements for a bronchoscopy suite?

Cough during bronchoscopy may create a high-risk scenario for spread of airborne pathogens. This necessitates the use of airborne infection isolation rooms to prevent spread of infections via airborne droplets. No comparative studies on room design including methods and frequency of air exchange are possible due to ethical issues.

The American Institute of Health Architects and Centre for Disease Control (2003) guidelines recommend that all cough-inducing procedures (e.g., bronchoscopy) should be performed in rooms with high-efficiency particulate air (HEPA) filters, direct air exhaust to the external environment, and minimum of 12 air exchanges per hour with exhaust flow rate of 50 cfm and differential pressure of 2.5 Pa.[9,10] According to the Indian guidelines issued by the Ministry of Health and Family Welfare, bronchoscopy suites should have at least 15 air exchanges per hour, with directional air flow along with local exhaust ventilation, and air exhausted at least 2 m from any open window. Utilization of air cleaning methods such as ultraviolet germicidal irradiation or HEPA filtration has also been suggested subject to availability.[11]

Evidence statement

- A bronchoscopy suite should have optimal ventilation to ensure adequate airborne infection control. This can be achieved via negative pressure design, prespecified number of air exchanges per hour, and directional airflow from the outside adjacent spaces into the room.

Recommendation

- Wherever feasible, bronchoscopy should be performed in a room with negative pressure design (3A)
- Bronchoscopy room should have minimum of 12–15 fresh air exchanges per hour with direction of airflow from room entrance to the back and outside (3A)
- If recirculation of air is unavoidable, direct exhaust air thrown outside should be away from patient-care areas, and HEPA filters must be used (3A).

What personal protective measures should be adopted by operators performing routine and high-risk bronchoscopies?

Staff working in bronchoscopy suite are exposed to various occupational hazards, such as skin and mucus membrane irritation due to disinfectant fumes, transmission of airborne infections from patients during procedure, injuries related to needle stick, biopsy forceps, hypodermic needles, and radiation.[8] Consequently, vaccination against hepatitis and influenza has been recommended for healthcare personnel.[6,12] Use of needles to retrieve specimens from biopsy forceps may increase risk of needle stick injuries.

Airborne infections, especially tuberculosis (TB), remain an important hazard to healthcare personnel. Exposure to an index case of smear-negative culture-positive pulmonary TB (PTB) was documented to cause tuberculin conversion in 31% hospital staff, with higher rate in bronchoscopy staff as compared to others. Using the volume of the bronchoscopy room and number of tuberculin converters, infectiousness of the air was calculated; index case was estimated to have generated at least 249 infectious units per hour.[13] A study observed that tuberculin skin test conversion was higher in pulmonary fellows than infectious disease fellows, despite approximately equal exposure to TB.[14] It has also been reported that 4.6% of patients without an initial suspicion of TB had an unexpected diagnosis of TB after bronchoscopy, thereby demonstrating the risk of healthcare exposure to *Mycobacterium* in otherwise unsuspected cases in countries with intermediate TB incidence, and potential utility of N95 or better respirators for infection control.[15]

Various international guidelines have emphasized the importance of personal protective equipment (PPE), safe needle handling practices, and vaccination for bronchoscopy personnel. Particulate respirator masks (N95) have also been recommended in suspected TB or other infections with high risk of droplet infection.[6,8,16-18]

Evidence statement

- Appropriate use of PPE during bronchoscopy can protect operators from harmful infectious exposure. These include full barrier clothing (gowns, gloves,

masks, and goggles or eye-shields), following needle stick precautions, and immunization against influenza and hepatitis B.

Recommendation

- Personal protective equipment should be worn by all personnel in the bronchoscopy suite (3A)
- Use of N95 mask is recommended when there is suspicion of mycobacterial infection or high risk of droplet infection (3A)
- Health personnel in proximity to the patient during bronchoscopy should ideally wear eye-shields (3A)
- Needles should not be used to remove biopsy specimens from forceps (3A)
- All staff should be vaccinated against hepatitis-B and receive annual influenza vaccine (3A)
- Impermeable surgical gowns should be worn by bronchoscopists and health personnel in proximity to the patient during the procedure (3A).

What personal protective measures should be adopted by personnel who disinfect bronchoscopes?

Glutaraldehyde-based disinfectants are commonly used for sterilization and disinfection of heat-sensitive medical devices such as bronchoscopes, endoscopes, and surgical instruments. However, the disinfectants used in bronchoscopy room can be hazardous to staff as they produce irritating and sensitizing vapors and can cause toxic effects such as severe dermatitis, conjunctivitis, sinusitis, and asthma.[19]

Glutaraldehyde exposure is associated with significantly increased risk of dermatologic and respiratory symptoms.[19] Peak glutaraldehyde concentrations demonstrate positive correlation with nasal symptoms and work-related chronic bronchitis among hospital employees.[20] A causal relationship of glutaraldehyde with occupational asthma by specific bronchial challenge testing has also been demonstrated.[21] In a questionnaire-based study involving 173 institutions, 53.8% of healthcare personnel reported symptoms during scope sterilization and disinfection work. Importantly, although more than 50% of respondents used gloves, they seldom used mask and glasses.[22]

Allmers *et al*.[23] showed that elimination of powdered natural rubber latex (NRL) gloves was useful in reducing aerogen NRL allergen loads. As it has been shown that the disinfectant orthopthaldehyde (OPA) permeated vinyl gloves more rapidly than nitrile gloves, the latter should preferably be adopted by healthcare workers handling OPA.[24] Major international guidelines suggest that staff concerned with cleaning and disinfection of bronchoscopes should receive proper education regarding PPE and should wear adequate equipment including gowns, masks, and eye-shields.[25]

Evidence statement

- Proper use of PPE reduces adverse health effects in persons engaged in disinfecting bronchoscopes. Powder-free gloves reduce the incidence of occupational asthma and dermatitis.

Recommendation

- Staff concerned with cleaning and disinfection of bronchoscopes should wear adequate PPE including gowns, gloves, masks, and proper eye-shields (2A)
- Latex or nitrile, powder-free gloves should be preferably used by persons engaged in disinfecting bronchoscopes (2A)
- Hand-hygiene practices should always be followed before and immediately after removing PPE (UPP).

How should health status of personnel exposed to disinfectants in bronchoscopy unit be monitored?

Healthcare personnel exposed to disinfectants continue to face several health hazards in their workplaces during bronchoscopy. However, evidence is lacking regarding appropriate methods and the benefits of monitoring the health status of bronchoscopy staff. Major international guidelines recommend that for all bronchoscopy staff, a medical history regarding pre-existing asthma, skin sensitivities, and pre-employment baseline lung function should be elicited, and immunization against hepatitis-B should be ensured. Subsequently, a regular program for monitoring occupational lung health, including annual spirometry, is advised.[6,25]

Evidence statement

- Personnel exposed to disinfectants in the bronchoscopy suite need baseline and periodic monitoring for early identification of occupational health hazards.

Recommendation

- All health personnel exposed to disinfectants in the bronchoscopy unit should undergo a baseline clinical evaluation (3A)
- Baseline spirometry should be performed for all personnel exposed to disinfectants in the bronchoscopy unit (3A)
- All staff engaged in bronchoscope disinfection should undergo periodic clinical assessment and spirometry if required (3A).

Should sputum examination be always performed in a patient with suspected tuberculosis before bronchoscopy?

Sputum examination is a simple, noninvasive, and cost-effective method for diagnosing PTB.[26] Bronchoscopy, though important in the diagnosis of sputum smear-negative PTB, remains a procedure with high risk of airborne infection spread. In a recent retrospective study, 56.4% of patients with suspected PTB did not have sputum tested before bronchoscopy.[27] Thus, sputum examination is often overlooked by bronchoscopists in many cases leading to dual risk, both to the patient and healthcare personnel.

Induced sputum is another useful method for diagnosis of PTB. Successful induction has been reported in 76%–100% of cases, with a pooled sensitivity of 75% for diagnosis

of culture-positive PTB.[28,29] Prospective studies have shown that induced sputum is more cost-effective and has similar diagnostic yield as BAL for detecting TB.[30,31] A randomized controlled trial (RCT) of 100 subjects reported that although BAL had a higher yield as compared to induced sputum (65% vs. 45%), sputum examination was still useful and cost-effective.[32]

Sputum or induced sputum examination has been recommended by the international guidelines before bronchoscopy in suspected TB.[6,33] The Indian Airborne Infection Control guidelines recommend that if BAL is planned for diagnostic purposes, the patient should have at least two sputum smears negative for TB before the procedure.[11]

Evidence statement

- Sputum or induced sputum examination, when performed before bronchoscopy, reduces the need for bronchoscopic procedures required for diagnosis of TB.

Recommendation

- Bronchoscopy should be performed in patients with suspected TB who are unable to produce sputum or when sputum analysis is unyielding (2A).

INDICATIONS, CONTRAINDICATIONS, AND COMPLICATIONS OF FLEXIBLE BRONCHOSCOPY; PATIENT MONITORING AND SAFETY ISSUES

The following section describes the indications, contraindications, complications, evaluation, and safety issues of patients undergoing bronchoscopy.

What are the indications, contraindications, and complications of flexible bronchoscopy?

Bronchoscopy is an essential procedure in pulmonary medicine and is done for a wide range of diagnostic and therapeutic indications. In large retrospective studies, the most common indications for flexible bronchoscopy were suspected infections, malignancy, hemoptysis evaluation, and interstitial lung disease.[34-38] The common indications for therapeutic bronchoscopy are for removal of retained secretions and foreign body, with complication rates <1%, and the most common complications being laryngospasm, hemorrhage, and pneumothorax.[35,36,38]

There is limited literature especifically addressing contraindications for flexible bronchoscopy. Each patient must be individually assessed based on the risk–benefit ratio before the procedure. Bronchoscopy should be avoided in certain situations such as arrhythmia, recent myocardial infarction or unstable angina, uremia, bleeding diathesis, and uncontrolled hypertension.[39-41] Table 2 enumerates the absolute and relative contraindications of FB.

Bronchoscopy is generally a well-tolerated procedure that can be performed safely on an outpatient basis, and serious adverse events are extremely rare. Several factors influence the risk of complications including patient characteristics, sedation practice, and sampling procedures employed.[35] In a large retrospective series (n = 20,986), serious complications occurred in 1.08% of all procedures, with a mortality of 0.02%.[42] Hehn *et al.*[43] reported FB-related complications in 4.3% of 1358 procedures; among these, nonrespiratory complications occurred in 2.8%, with a mortality of 0.1%. The common adverse events include tachycardia or bradycardia, major and minor bleeding, bronchospasm, laryngospasm, cough, dyspnea, sore throat, desaturation, pneumothorax, and pulmonary edema. Bleeding complications have been reported in 0.19% of flexible bronchoscopy procedures.[42] Visual assessment of bleeding volume along with interventions required for hemostasis control [Table 3] needs to be considered for accurate grading of severity of bleeding after bronchoscopy.[6,44]

Evidence statement

- Suspected pulmonary infections, lung cancer, and evaluation of hemoptysis are the most common indications for diagnostic bronchoscopy
- Retained secretions and foreign body removal are the most common indications for therapeutic bronchoscopy
- Bronchoscopy is a safe procedure with serious adverse events of <1%
- Cough, hemoptysis, bleeding, hypoxia, and arrhythmia are the most common complications.

Is routine testing of coagulation profile, platelet count, and hemoglobin essential before performing bronchoscopy?

Bronchoscopy is associated with variable risk of bleeding which depends on patient-related factors as well as the

Table 2: Contraindications to flexible bronchoscopy

Absolute	Relative
Absence of informed consent	Lack of patient cooperation
	Recent myocardial infarction or unstable angina
Profound refractory hypoxemia	Respiratory insufficiency or failure
Severe bleeding diathesis uncorrectable before the procedure	Uncontrolled hypertension
Malignant cardiac arrhythmias	Unstable cardiac arrhythmias
	Uremia (for bronchoscopic biopsy)

Table 3: Classification of bleeding severity during bronchoscopy[6,44]

Bleeding	Description
No bleeding	Only blood traces, without any need for continuous suction. Spontaneous cessation of bleeding
Mild bleeding	Requirement of continuous suction
Moderate bleeding	Needs wedging of bronchoscope into bleeding segment for tamponade
	Requirement of intrabronchial adrenaline or cold saline for hemostasis
Severe bleeding	Needs placement of catheter, bronchial blocker or fibrin for hemostasis
	Requirement of fluid resuscitation, blood transfusion, intensive care, mechanical ventilation or death

sampling procedures performed. As per the recent Indian Bronchoscopy Survey by Madan *et al.*,[1] 26%–70% of respondents perform routine coagulation testing before bronchoscopy. Patients with coagulopathy (deranged prothrombin time or elevated International Normalized Ratio (INR), or elevated activated partial thromboplastin time [APTT]) are at increased risk of bleeding during bronchoscopy.[6] Currently, expert opinions vary regarding routine coagulation testing before FB.

The risk of bleeding is <1% in patients without coagulopathy but can increase up to 7.5% in subjects with deranged coagulation profile.[42] Among 104 patients undergoing TBLB, routine coagulation testing could not predict the risk of post-TBLB bleeding.[45] Similar results have been reported in other retrospective and prospective studies.[45,46] Risk factors for abnormal coagulation include anticoagulant therapy, evidence of liver disease, kidney disease, family history or physical evidence of bleeding tendency, or active bleeding.[6,47,48] Therefore, it is advised that patients with risk factors for abnormal coagulation undergo coagulation testing (PT/INR, APTT) before bronchoscopic biopsy.[6] The same evidence has to be extrapolated for EBB and TBNA due to lack of clinical evidence pertaining to these specific procedures.

Currently, there is no conclusive evidence demonstrating benefit of routine hemoglobin testing before bronchoscopy. In the recent Indian Bronchoscopy Survey, 52.7% of respondents routinely obtained hemoglobin levels before bronchoscopy.[1] In view of limited scientific evidence, the expert committee felt that recommendation on routine performance of these tests should be based upon cost-effectiveness and risk–benefit analysis.

Evidence statement

- Routine coagulation studies, platelet counts, and hemoglobin before flexible bronchoscopy do not predict the risk and severity of bleeding during the procedure.

Recommendation

- Performing coagulation studies, platelet counts, and hemoglobin levels routinely before bronchoscopy is not recommended (3B)
- Coagulation studies, platelet counts, and hemoglobin should be performed before bronchoscopy in patients with clinical risk factors for bleeding such as ongoing anticoagulation, bleeding diathesis, and chronic liver and kidney disease (UPP).

What should be the minimum platelet count for bronchoscopic sampling?

Thrombocytopenia has been conventionally considered as a risk factor for increased periprocedural bleeding during bronchoscopy; bleeding may occur in the bronchial mucosa during scope negotiation or after biopsy. Thrombocytopenic subjects are also at increased risk of nasal mucosal bleeding during this procedure.

There is scarce data on safety of bronchoscopy in patients with low platelet counts. Among 66 bone marrow-transplant patients undergoing bronchoscopy, platelet count <20,000 per mm^3 was not associated with increased bleeding risk after BAL.[49] In another prospective study evaluating safety of TBLB in 24 thrombocytopenic patients with a median platelet count of 30,000 per mm^3 (range 7000–60,000 per mm^3), the incidence of post-TBLB bleeding was reported to be as high as 25%, with a mortality of 4%. However, BAL could safely be performed in all subjects.[49,50] International guidelines recommend a minimum platelet count of 20,000 per mm^3 and 50,000 per mm^3 for safely performing BAL and TBLB, respectively.[6]

Evidence statement

- There is a higher risk of bleeding in patients with thrombocytopenia undergoing TBLB
- A platelet count of 50,000 per mm^3 for performing TBLB/EBB and 20,000 per mm^3 for BAL is considered safe.

Recommendation

- We recommend a platelet count of at least 20,000 per mm^3 for performing BAL (3B)
- We recommend a platelet count of at least 50,000 per mm^3 for performing EBB/TBLB (3B)
- BAL can be performed in subjects with platelet count <20,000 per mm^3 if clinically indicated, after careful risk–benefit analysis. In patients with thrombocytopenia, oral route is preferred for performing bronchoscopy (UPP).

Should antiplatelet agents be discontinued before bronchoscopy?

Bronchoscopic airway inspection and BAL are generally considered to be safe in patients on antiplatelet agents. However, antiplatelet agents are considered to increase periprocedural bleeding risk in patients undergoing TBNA or biopsies. Majority (53.7%) of bronchoscopists withheld both aspirin and clopidogrel before bronchoscopic biopsy in the Indian Bronchoscopy Survey; only 22.4% of respondents stopped clopidogrel only, which was in compliance with the international guidelines.[1]

Herth *et al.*[51] compared the incidence of post-TBLB bleeding in patients receiving aspirin as compared to those not on antiplatelet agents and found that overall bleeding incidence was similar in both groups (3.5% in aspirin arm and 5% in control arm). In another cohort of patients undergoing TBLB, postprocedure bleeding occurred in all subjects who were on dual antiplatelet (aspirin and clopidogrel), 88% of those on clopidogrel alone, and 3.4% of those on no antiplatelets. Of note, severe bleeding occurred in 50% in dual-antiplatelet group and 27% patients in clopidogrel group, with no mortality.[44] Thus, low-dose aspirin appears to be safe during bronchoscopic biopsy in terms of risk of bleeding, whereas dual antiplatelets are associated with higher risk. However, no clinical

evidence is available regarding the optimum of duration of cessation of antiplatelet drugs before bronchoscopic biopsy. International guidelines recommend modification of antiplatelet therapy based on invasiveness of procedure and risk of thrombosis.[6,52] Normalization of platelet function is expected to occur 5–7 days after withdrawal of clopidogrel.[53] This may be extrapolated to clinical practice, to derive a reasonable duration for cessation of clopidogrel and other antiplatelet agents (e. g., prasugrel or ticagrelor) before bronchoscopy.

Evidence statement

- Use of low-dose aspirin alone does not significantly increase the bleeding risk after TBLB
- Clopidogrel or dual-antiplatelet therapy (with clopidogrel and aspirin) is associated with significant increase in the risk of bleeding after TBLB.

Recommendation

- Clopidogrel, prasugrel, or ticagrelor should be discontinued at least 5 days before EBB and TBLB (2A)
- Low-dose aspirin can be continued in patients planned for TBLB/EBB (2A)
- Liaison with a concerned specialist is recommended for the modification of antiplatelet therapy in patients on dual-antiplatelet agents and at high risk of thrombosis (UPP) [Appendix 1].

In patients receiving anticoagulation, how should the therapy be modified before flexible bronchoscopy?

Therapeutic anticoagulation, in general, is associated with increased bleeding risk after endoscopic procedures. Withholding anticoagulation, on the other hand, predisposes the patient to potentially life-threatening thrombotic events. There are no dedicated studies which address the issue of modifying anticoagulation in patients undergoing bronchoscopy. International guidelines also differ in their recommendations.

No studies specifically pertaining to the above question were identified during the literature search; hence, various published guidelines were reviewed. International bronchoscopy guidelines recommend discontinuation of warfarin at least 5 days before bronchoscopy.[6] However, according to the recent endoscopy recommendations, warfarin and newer anticoagulants (NOACs) may be continued in case of low-risk procedures, keeping a target INR of 2–3. For procedures with high risk of bleeding, anticoagulation needs to be modified based on risk of thrombosis. In low-risk patients, warfarin should be stopped 5 days before procedure, and INR below 1.5 should be achieved.[52] Invasiveness of procedure along with risks of bleeding and thrombosis was considered to formulate recommendations.

With regard to optimal duration for stopping newer anticoagulants, the half-life of drugs was taken into consideration; the half-life of NOACs (apixaban, rivaroxaban, edoxaban, and dabigatran) ranges from 9 to 15 h, and stopping these drugs 1–2 days before the procedure can minimize bleeding risk.[54,55]

The evidence was also reviewed for initiating bridge therapy with heparin in patients at high risk of thrombosis if anticoagulation is stopped before bronchoscopy. Data from cardiovascular studies showed that warfarin interruption in atrial fibrillation increases the risk of thromboembolic events, and bridging therapy does not prevent such events; in fact, low molecular-weight heparin (LMWH) increases the risk of major perioperative bleeding.[56,57] In a recent meta-analysis of 25 studies (n = 35,944), bridging therapy did not reduce thromboembolic events and actually led to increased risk of overall and major bleeding.[58] Thus, bridging therapy with LMWH seems to be efficacious only in patients at high risk of thrombosis.

Keeping in view the nonavailability of studies assessing modification of anticoagulants before bronchoscopy, the expert committee considered available bronchoscopy and endoscopy guidelines to derive at consensus for recommendations. The proposed modification of anticoagulation including bridging therapy is elaborated in Appendix 2.

Evidence statement

- Anticoagulation is associated with increased risk of bleeding during bronchoscopy. There is lack of evidence regarding dose modification of anticoagulants before bronchoscopic procedures.

Recommendation

- Warfarin should be stopped at least 5 days prior to transbronchial needle aspiration (TBNA) or bronchoscopic biopsy and a preprocedure INR of <1.5 should be ensured (3A)
- Newer anticoagulants should be stopped at least 2 days before TBNA or bronchoscopic biopsy (3A)
- We recommend bridging therapy with LMWH in patients on anticoagulation and at high risk of thrombosis. LMWH, when indicated, should be started 2 days after stopping warfarin. The last dose of LMWH should be administered 24 h before the procedure (3A)
- BAL can be performed in patients on therapeutic anticoagulation after careful risk–benefit analysis, preferably via oral route (UPP).

How safe is bronchoscopy in patients with Asthma and Chronic Obstructive Pulmonary Disease?

Bronchoscopy may aggravate symptoms and cause transient decline in lung function in patients with pre-existing airway obstruction. Performing BAL may further exacerbate bronchospasm. Thus, the safety of this procedure in patients with airway obstruction needs careful consideration.

Studies in asthmatics have shown that bronchoscopy and BAL can be safely performed without compromising forced expiratory volume at 1 s (FEV1).[59] Moore *et al*.[60]

demonstrated that with preprocedural nebulization, the fall in FEV1 was similar in the severe asthma group compared to other groups. Similarly, no reduction in arterial SpO_2 or peak expiratory flow rate has been observed after this procedure.[61] The most common complication in all studies was bronchospasm which was managed without further clinical deterioration. The safety of bronchoscopy in COPD patients with adequate bronchodilatation has also been demonstrated. Chechani[62] performed FB in 26 hypercapnic patients with baseline pulse SpO_2 <90% and partial pressure of carbon dioxide (pCO_2) >45 mmHg, with oxygen supplementation, and found no major complications; 27% of patients had periprocedural desaturation and 62% had postbronchoscopy wheezing requiring inhaled bronchodilator therapy. Baseline FEV1, pCO_2, and FiO_2 could not predict risk of complications. However, patients with COPD and pulmonary hypertension have greater post-FB desaturation and those with severe disease are more likely to develop minor respiratory complications.[63,64] International guidelines recommend that asthma and COPD control should be optimized before bronchoscopy, especially when BAL is likely to be performed, and caution must be exercised while administering sedation.[6]

Evidence statement

- Bronchoscopy is a reasonably safe procedure in patients with COPD and bronchial asthma. The most common complication is bronchospasm, which may require treatment with inhaled bronchodilators.

Recommendation

- Bronchoscopy can be safely performed in patients with asthma and COPD (2A)
- Patient's asthma treatment should be optimized before bronchoscopy, especially when BAL is to be performed (2A)
- Treatment for COPD should be optimized before bronchoscopy (3A).

Should prebronchoscopy-inhaled bronchodilators be administered to all patients with obstructive airway disease?

Flexible bronchoscopy causes bronchospasm in patients with obstructive airway disease, especially when BAL is performed.[60] The administration of preprocedure-inhaled bronchodilators has been tried to reduce bronchospasm, facilitate ease of procedure, and minimize adverse effects.

In a case–control study comparing BAL sampling in 80 COPD patients with 40 controls, Stolz *et al*.[65] found no utility of prebronchoscopy bronchodilatation in reducing postprocedure symptoms or FEV1 decline. Similarly, Mohan *et al*.[66] found no beneficial effect of prebronchoscopic-inhaled salbutamol on symptoms or on FEV1 decline in subjects with obstructive airway disease undergoing bronchoscopy.

In various bronchoscopy surveys, 76.2%–97.2% of bronchoscopists routinely administered preprocedure bronchodilators to patients with asthma.[1] Van Vyve *et al*.[67] found similar fall in SpO_2 and FEV1 after BAL or bronchoscopic biopsy in asthmatics as compared to controls. Similarly, Elston *et al*.[68] found BAL and bronchoscopic biopsy to be safe with routine preprocedure nebulization with bronchodilators. However, none of the studies have assessed safety of bronchoscopy in controlled asthmatics without preprocedural bronchodilation.

Evidence statement

- Prebronchoscopy-inhaled bronchodilators do not reduce postprocedure symptoms or decline in lung function (FEV1) in patients with chronic obstructive airway disease and asthma
- Large prospective studies of bronchoscopy in asthma have routinely used preprocedure bronchodilators.

Recommendation

- Routine administration of bronchodilators before bronchoscopy is not recommended in patients with asthma or COPD who are adequately controlled (1A).

Is antibiotic prophylaxis required for bronchoscopy?

The incidence of postbronchoscopy fever is reported in 0.9%–2.5% of procedures, with transient bacteremia occurring in up to 6.5% of cases.[35] The fever is usually transient and self-limiting in majority of subjects.

Park *et al*.[69] evaluated the effect of antibiotics on the incidence of postbronchoscopy fever in 143 subjects and found no difference between the treatment and control groups. Similar findings were reported by Yamamoto *et al*.[70] using azithromycin in 153 patients. In contrast, Kanazawa[71] showed reduction in the incidence of fever after azithromycin, particularly in patients with abnormal bronchoscopy findings. The current international guidelines do not recommend the routine use of antibiotic prophylaxis to prevent postbronchoscopy fever. However, the importance of patient education regarding possibility of postbronchoscopy fever and assurance about its self-limiting nature has been emphasized.[6] In addition, appropriate counseling and written advice regarding management of postbronchoscopy fever have been recommended.[6]

Evidence statement

- Although transient bacteremia (0%–6.5%) and fever (0.9%–2.5%) have been reported after bronchoscopy, available evidence does not support the routine use of prophylactic antibiotics to prevent postbronchoscopy fever.

Recommendation

- Routine use of prophylactic antibiotics is not recommended before bronchoscopy to prevent procedure-related infections (1A)
- Patients should receive proper counseling and written advice regarding the management of postbronchoscopy fever (UPP).

What should be the optimum duration of fasting before flexible bronchoscopy?

Fasting is essential to prevent aspiration of gastric contents during bronchoscopy. However, there is no literature specifically addressing this aspect; most evidence is extrapolated from surgery and procedures under general anesthesia.

A Cochrane review and recent systematic review on fasting times for surgery found no significant increase in postoperative risk of aspiration or regurgitation if patients received fluids 2–3 h before surgery.[72] Anesthesia guidelines recommend fasting for 2 h for clear liquids, 4 h for milk, 6 h for light meals, and 8 h for full meal;[73] whereas bronchoscopy guidelines have recommended a minimum of 4 h limit for light meals.[6]

Evidence statement

- Fasting for a prespecified duration is needed before bronchoscopy to reduce risk of aspiration and periprocedural complications.

Recommendation

- A fasting duration of at least 2 h for clear liquids and 4 h for light meals is recommended before bronchoscopy (3A).

What are the other good clinical practices regarding patient preparation before flexible bronchoscopy?

Bronchoscopy is an invasive procedure and hence requires proper patient preparation. It is mandatory to obtain informed written consent from all patients or their caregivers after explaining the procedure in detail, including the likelihood of potential complications. Patients must be advised to take their regular medications the night before the planned procedure and should be kept nil per mouth as per the currently existing guidelines, i.e., 2 h for liquids and 4 h for solid food.[6,73] Any history of drug allergy must be elicited and mentioned; preprocedure vitals should be noted and must be stabilized if abnormal. An IV cannula should be secured and sedation may be offered if clinically feasible to improve the patient's tolerance for the procedure.[6]

Recommendation

- Written informed consent should be obtained from every patient undergoing bronchoscopy (UPP)
- Patients should be enquired regarding known allergies, comorbidities, and drug history (including anticoagulants or antiplatelets) (UPP)
- Duration of fasting should be confirmed (UPP)
- In all patients, IV access should be obtained and maintained until the patient is deemed fit to be discharged (UPP)
- Routine vital signs such as BP, HR, SpO_2, and respiratory rate should be recorded prior to the procedure (UPP).

What should be the preferred position of patients during bronchoscopy?

Bronchoscopy may be done in supine or sitting position. Most operators perform the procedure with the patient in the supine position. A few studies have attempted to compare the risk of complications depending on patient position during FB. van Zwam *et al.*[74] showed that bronchoscopy in sitting position was associated with higher incidence of SpO2 decline and periprocedural desaturation as compared to supine bronchoscopy. Similarly, bronchoscopy in sitting position was associated with higher frequency of desaturation (97%) as reported by Maranetra *et al.*[75]

Evidence statement

- Sitting position is associated with significant oxygen desaturation as compared to supine position during bronchoscopy, with no change in patient's comfort level.

Recommendation

- Bronchoscopy should preferably be performed with the patient in supine position (2A).

What should be the preferred route of insertion of bronchoscope?

Bronchoscopy may be done by either oral or nasal route. The oral route is associated with retch reflex and risk of biting the bronchoscope. Nasal route has the advantage of precise control of the instrument and ability to inspect the upper airway. However, there is considerable geographical difference in preferred route of scope insertion. In a Japanese Bronchoscopy Survey, >70% of respondents preferred oral bronchoscopy, whereas 94% of respondents from an Indian Survey utilized the nasal route.[1,76]

Randomized trials have reported that oral bronchoscope insertion of ≥6 mm external diameter was associated with significantly shorter time to pass vocal cords, lesser discomfort, dyspnea, cough, insertion site bleeding, lower total lignocaine dose, and greater willingness to return for repeat procedure as compared to nasal route.[77,78]

Evidence statement

- In nonsedated patients, oral insertion of bronchoscope is associated with lesser time to crossing vocal cords, more willingness to return, and better patient comfort
- There is no effect on diagnostic yield with either route of scope insertion.

Recommendation

- Nasal and oral route are equally suitable for performing bronchoscopy (3A)
- Oral route should be preferred for larger size bronchoscopes, for therapeutic procedures such as foreign body removal, or in patients with thrombocytopenia (UPP).

Is oxygen supplementation routinely required during flexible bronchoscopy?

Bronchoscopy is associated with oxygen desaturation that is mostly transient but more likely in patients with poor lung

reserve. The utility of oxygen supplementation routinely for all flexible bronchoscopy procedures was reviewed. Milman *et al*.[79] reported that all patients undergoing bronchoscopy without oxygen supplementation had significant periprocedural desaturation. During BAL procedures, instillation of 200 ml saline was associated with higher frequency of desaturation as compared to 100 ml instillation (15% vs. 7%; $P < 0.05$).[80] It has also been shown that desaturation is more likely in patients with poor pulmonary reserve, i.e., FEV1 <1 L, and majority of them require oxygen supplementation.[81,82]

International guidelines recommend that patients should be monitored by continuous pulse oximetry during bronchoscopy and oxygen administered when desaturation is significant (SpO_2 fall >4% or SpO_2 <90%) and prolonged (>1 min) to reduce the risk of hypoxemia-related complications.[6]

Evidence statement

- Bronchoscopy is associated with significant oxygen desaturation, particularly in patients with low FEV1 and when BAL is performed.

Recommendation

- Routine oxygen supplementation is recommended for patients with risk factors for desaturation, low baseline SpO_2 (<90%), or significant desaturation during procedure (>4% decrease from baseline or SpO_2 <90% for >1 min) (3A).

Which vital parameters should be monitored during bronchoscopy?

Bronchoscopy is associated with several cardiopulmonary physiological alterations such as increased HR, increased BP, and hypoxia, which may precipitate arrhythmia and may even be life-threatening. Studies showed incidence of arrhythmia during FB ranging from 0.02% to 10%. Factors associated with increased risk of cardiac complications include pre-existing cardiac disease, recent myocardial infarction, and pre-existing rhythm disorders.[34,38,42]

In a small prospective study including 45 subjects, all cases had significant BP elevation during bronchoscopy while tachycardia and ST changes were reported in 15.6% and 8.9% of cases, respectively.[83] Other prospective studies have also shown that this procedure is associated with significantly increased HR and cardiac output along with oxygen desaturation.[84-86]

Evidence statement

- Bronchoscopy is associated with increase in HR and BP
- Overall risk of arrhythmias during bronchoscopy is low; risk of arrhythmias ranges from 0.02%–10%
- Sinus tachycardia and atrial or ventricular premature contractions are the most common arrhythmias associated with FB.

Recommendation

- Continuous pulse oximetry, HR, and continuous (or repeated) noninvasive BP monitoring is recommended during bronchoscopy (3A)
- Continuous or repeated ECG monitoring should be performed during bronchoscopy in patients with known cardiac disease or arrhythmias (3A).

How should the patients be monitored after flexible bronchoscopy?

Postprocedure monitoring after bronchoscopy is an important aspect to ensure patient safety and early identification and management of complications. No clinical studies comparing various modalities of monitoring or reporting clinical outcomes were available for consideration. Therefore, the international guidelines on the topic were reviewed.[6,7] The expert committee framed the recommendations to ensure optimal postprocedure care and more intensive monitoring for sedated patients.

Evidence statement

- Postprocedure monitoring in a predesignated space by trained personnel is important for early identification and prompt management of complications after bronchoscopy.

Recommendation

- All patients should be monitored for symptoms including dyspnea, chest pain, and hemoptysis after completion of bronchoscopy (3A)
- All patients should have vital parameters (including consciousness, HR, respiratory rate, SpO_2, and BP) recorded immediately after bronchoscopy and repeated as indicated (3A)
- Patients should be kept under observation until they achieve preprocedure level of consciousness and acceptable vital parameters (3A).

PREMEDICATION

Should anticholinergic premedication (atropine or glycopyrrolate) be administered before flexible bronchoscopy?

Anticholinergics such as atropine and glycopyrrolate have been used as premedication agents before bronchoscopy to reduce airway secretions and prevent reflex bronchoconstriction and vasovagal reactions such as bradycardia and syncope.[6] However, evidence regarding their benefit has not been demonstrated.[87,88] In a large placebo-controlled RCT including 1000 subjects, although anticholinergic premedication with intramuscular atropine or glycopyrrolate reduced airway secretions during the procedure, they did not reduce cough, patient discomfort, oxygen desaturation, or procedure duration.[89] In fact, the use of anticholinergics, particularly atropine, led to greater hemodynamic fluctuations.

Other agents such as clonidine, labetalol, atenolol, fenoterol, and 1% menthol have also been evaluated

for premedications before flexible bronchoscopy. Bronchoscopy may be associated with increase in HR and BP along with episodes of oxygen desaturation.[79,85] Clonidine is a centrally acting antihypertensive that diminishes stress-induced sympathoadrenal response such as elevation in BP and HR.[90] The role of clonidine as a premedication agent was evaluated in two RCTs; oral clonidine was found to attenuate hemodynamic response to bronchoscopy without causing excessive hemodynamic depression and sedation, while IV clonidine provided better hemodynamic profile but no improvement in patient comfort.[91,92]

Beta-blockers such as atenolol and IV labetalol also do not provide significant benefits in hemodynamics or patient tolerance of FB.[93] Fenoterol as a premedication agent was associated with reduced cough and requirement of topical anesthesia.[94] However, administration of 1% menthol did not provide similar benefits.[95] It was noted that majority of the above studies had methodological limitations and small sample size, thus limiting their generalizability.

Evidence statement

- Administration of anticholinergic premedication before bronchoscopy is not associated with reduction in secretions, cough, or procedure duration and may be associated with greater hemodynamic fluctuations.

Recommendation

- Anticholinergic premedication should not be administered before flexible bronchoscopy (1A).

Should antitussives be administered before flexible bronchoscopy?

Suppression of cough during bronchoscopy can enhance patient comfort. Administration of dextromethorphan was associated with lesser cough, shorter procedure time, and lesser sedative requirement during the procedure.[96] Schwarz *et al*.[97] reported that subjects who received dextromethorphan (along with sedation) had significantly fewer requirements of topical anesthesia and sedation, achieved better analgesia, were more cooperative, had less unpleasant sensation and cough, and produced less sputum at the end of the procedure.

Codeine and levodropropizine have also been evaluated as antitussive agents for bronchoscopy. Subjects who received codeine premedication required lesser dose of supplemental local anesthesia.[98] Similarly, the use of levodropropizine in 16 subjects with COPD undergoing FB was associated with lower requirement of supplemental local anesthesia; however, the study was limited by its small sample size and included only patients with COPD in hypersecretory phase.[99]

Evidence statement

- Administration of oral antitussives before bronchoscopy has been evaluated only in a few studies with small sample size
- Dextromethorphan premedication in setting of bronchoscopy performed under sedation is associated with reduction in cough, shorter procedure duration, lower topical anesthesia requirement, and less sedative dosage
- Codeine phosphate premedication is associated with reduction in topical anesthetic requirement before bronchoscopy.

Recommendation

- Dextromethorphan may be considered to optimize patient comfort before bronchoscopy (2B).

Should intravenous sedation be routinely administered to patients undergoing flexible bronchoscopy?

Use of preprocedure sedation may help in improving the tolerance of patient. Since bronchoscopy may be associated with cough, sensation of asphyxiation, pain, and unpleasant experiences, many bronchoscopists prefer giving sedation during bronchoscopy. However, no-sedation bronchoscopy is also performed at many centers.

The feasibility of performing bronchoscopy without sedation has been demonstrated in various studies. Survey data have shown that 59.4% of the bronchoscopists in India perform bronchoscopy without administration of sedation, while 36.1% of bronchoscopies in Japan are done using IV sedation.[1,76] Hatton *et al*.[100] reported that sedation with midazolam improved ease of FB (for the proceduralist) although comfort of procedure (assessed by doctor/nurse/patient) and willingness to return for repeat bronchoscopy was similar as in patients where sedation was not administered. In contrast, no-sedation bronchoscopy is also well tolerated and can be performed using topical lignocaine within the amount of recommended dosage, although acceptance of repeat bronchoscopy may be lower.[101]

Various agents such as diazepam, midazolam, lorazepam, propofol, and fospropofol have been compared with placebo, and it has been consistently demonstrated that administration of sedation is beneficial for patient comfort and tolerance without causing significant hemodynamic disturbance.[100,102-107] A meta-analysis of nine studies evaluated the safety and efficacy of moderate sedation during bronchoscopy and found that the willingness to return for repeat procedure was greater in the sedation group and duration of procedure was shorter, while hypoxic episodes were comparable in both groups.[108]

Evidence statement

- "No-sedation" bronchoscopy is widely performed and is a well-tolerated procedure
- Judicious administration of IV sedation in appropriate dose during bronchoscopy is associated with improved patient tolerance and comfort without significant alteration in hemodynamics.

Recommendation

- Administration of IV sedation should be considered to improve patient tolerance during bronchoscopy (2B)
- Bronchoscopy can also be safely performed without IV sedation (2B).

Which agents can be used for sedation during flexible bronchoscopy?

Several benzodiazepines (e.g., midazolam, diazepam, and lorazepam) have been used as sedatives during bronchoscopy. Midazolam, however, is preferred in view of its short half-life and rapid onset of action. Propofol also is a rapidly acting agent but has a narrow therapeutic window and can cause respiratory depression. Similarly, fentanyl and alfentanil are short-acting μ-opioid receptor agonists and cause sedation, analgesia, and cough suppression. Dexmedetomidine is a selective alpha 2-agonist with dual-sedative and analgesic properties; it is administered by infusion and causes only mild respiratory depression even at high dose. Several RCTs have compared various sedative agents with each other, such as midazolam with propofol, midazolam with dexmedetomidine, and midazolam with alfentanil/fentanyl, and it was found that propofol and dexmedetomidine provide superior patient comfort and tolerance during bronchoscopy.[109-114]

The utility of dual-agent sedation has also been studied. It is reported that the combination of benzodiazepine with opioid is superior to benzodiazepine alone. In studies which compared midazolam alone with midazolam plus alfentanil/hydrocodone/fentanyl, it was found that combined sedation provided superior patient tolerance without causing significant side effects.[115-117] Similarly, Schlatter *et al.*[118] reported improved cough scores with propofol plus hydrocodone versus propofol-only.

Comparisons between dexmedetomidine and propofol–opioid (fentanyl) combinations have shown better hemodynamic stability with dexmedetomidine and higher incidence of desaturation in propofol–fentanyl group, without any difference in patient satisfaction levels.[119] Dexmedetomidine–fentanyl combinations showed higher mean SpO_2 and better hemodynamic stability as compared to dexmedetomidine–propofol; however, there was no difference in cough, discomfort score, sedation level, or requirement of topical anesthesia.[120]

Evidence statement

- Midazolam, propofol, dexmedetomidine, all improve patient comfort and improve tolerance of bronchoscopy. Among these, propofol and dexmedetomidine have been found to be superior to midazolam in terms of quality of sedation, comfort, and tolerance
- Combined administration of midazolam or propofol with opioid results in improved patient comfort, cough, and lower midazolam or propofol requirement compared to either agent alone
- However, use of propofol has been restricted for use by an anesthesiologist or trained technician in many countries, and dexmedetomidine has to be administered by IV infusion 15–20 min before bronchoscopy and continued throughout the procedure which may be cumbersome for short procedures such as BAL or airway inspection.

Recommendation

- Combination of midazolam or propofol with opioid is preferred over either alone (1A)
- Choice of sedation (midazolam/propofol/dexmedetomidine/fentanyl) should be made depending on the operator preference and availability of anesthetists/trained medical personnel (UPP).

Can sedation be safely administered by proceduralist?

Two prospective studies have demonstrated that sedation could be safely administered by a nonanesthesiologist without increased risk of complications.[121,122] In a survey done in Switzerland among 229 pulmonologists, it was found that in 84% of bronchoscopies, propofol was administered without anesthesiologist and sedation-related morbidity and mortality were low.[123] Although propofol administered by a trained physician has been found to be safe, it must be remembered that it is a respiratory depressant with a narrow therapeutic range and has no available reversal agent.[124] Thus, there is risk of inducing a too deep level of sedation, complicated by hypoventilation, apnea, or cardiovascular depression. Hence, it is advisable that propofol should be administered only by persons trained in the administration of general anesthesia. Furthermore, propofol has not been approved for use by nonanesthetists in many countries.[125,126]

Evidence statement

- Administration of sedation with midazolam and fentanyl is safe when performed by an experienced proceduralist
- Propofol has a narrow therapeutic window with increased risk of respiratory and cardiovascular depression

Recommendation

- IV sedation with midazolam or fentanyl can be safely administered by the proceduralist (2A)
- Propofol should be administered by an anesthetist or trained medical personnel (2A).

What precautions should be taken while administering intravenous sedation?

Administration of sedation may be associated with depression of respiratory and cardiovascular function, especially when combined agents are used. Use of midazolam alone or in combination with alfentanil results in increase in pCO_2.[115] Patients with liver or kidney disease and heart failure and older patients are considered at higher risk of adverse events and thus require dose modification of sedatives.[127] Various guidelines recommend that assessment of depth of sedation, blood pressure measurement, and pulse oximetry is required in all patients receiving IV sedation.

However, no consensus exists regarding the role of capnography.[128-130]

Evidence statement

- Administration of sedation during flexible bronchoscopy may be associated with depression of respiratory and cardiovascular functions necessitating close monitoring of vital parameters.

Recommendation

- Assessment of the depth of sedation, BP, HR, respiratory rate, and SpO_2 monitoring should be performed in all patients receiving sedation during bronchoscopy (3A)
- Sedation should be cautiously administered in high-risk groups (UPP)
- Minimum possible dose of sedative should be administered (UPP)
- A log of sedative dosage administered should be maintained for each patient (UPP).

How should the optimum depth of sedation be assessed?

Since the patients who receive sedation may be at increased risk of respiratory and cardiovascular depression, the depth of sedation should be monitored. Proceduralist-administered sedation should be carefully titrated by administrating drugs in small incremental doses to avoid over-sedation. Various tools have been developed for the assessment of depth of sedation (e.g., Modified Ramsay Sedation Scale [MRSS]; Modified Observer's Assessment of Alertness/Sedation score [MOAA/S]; American Society of Anesthesiologists Sedation Scale [ASASS]) [Appendix 3], and have been found to be useful to avoid over-sedation. In various studies, the depth of sedation has been targeted to MRSS scale of 2–3, MOAA/S scale 2–3, and ASASS depth of minimal-to-moderate sedation.[131-133] More recently, the bispectral index monitoring is being studied for monitoring depth of sedation, with mixed results in available studies.[134,135]

Evidence statement

- Various sedation scales have been used and have been found useful in the assessment and monitoring of the depth of sedation in patients undergoing bronchoscopy.

Recommendation

- Use of a sedation scale is preferred to monitor the depth of sedation throughout bronchoscopy (UPP).

Which is the preferred agent for topical anesthesia during flexible bronchoscopy?

Topical anesthesia is a cardinal component of optimizing patient comfort during bronchoscopy. Lignocaine is the most commonly used agent due to its favorable pharmacological profile, quick onset, short duration of action, and lesser toxicity compared with other agents. Other agents and available concentrations which have been used include cocaine (4%), benzocaine (20%), and tetracaine (1%).

Lignocaine spray at 2% concentration applied to the vocal cords and tracheobronchial tree has been shown to reduce cough and sedation requirements as compared to placebo in the setting of bronchoscopy performed with fentanyl and midazolam.[136] Benzocaine and tetracaine have narrow therapeutic index and are not widely used. Cocaine has additional vasoconstrictor properties but has been associated with risk of myocardial infarction.[137] Retrospective case series on local anesthetic adverse effects have reported more cases of methemoglobinemia with benzocaine and prilocaine than with lignocaine.[138,139] Comparative studies of different topical agents are limited by small sample sizes; two RCTs compared lignocaine with cocaine and prilocaine, and found them both to be as efficacious as lignocaine.[140,141]

Evidence statement

- Topical anesthesia using lignocaine reduces cough and sedation requirements during bronchoscopy. The risk of methemoglobinemia is least with lignocaine.

Recommendation

- Topical anesthesia should be routinely used during bronchoscopy (1A)
- Lignocaine is the preferred agent for topical anesthesia (3A).

What is the preferred method for nasal lignocaine administration?

Different formulations of lignocaine, including spray and 2% gel, have been used for nasal anesthesia during bronchoscopy. Small randomized trials comparing these methods with respect to efficacy of anesthesia by assessing patient comfort and ease of bronchoscope insertion have found them to be similar.[142-145] While both lignocaine spray and gel showed better anesthesia than eutectic mixture of local anesthetics cream or lignocaine swabs, the 2% lignocaine gel formulation was rated more pleasant compared to the spray.[143]

Evidence statement

- Both lignocaine 2% gel and spray are effective in providing nasal anesthesia for bronchoscopy. Lignocaine gel is preferred by patients compared to the spray formulation.

Recommendation

- 2% lignocaine gel is recommended for topical nasal anesthesia during bronchoscopy (1A).

What is the role of topical vasoconstrictor instillation before nasal bronchoscopy?

Use of nasal vasoconstrictors such as oxymetazoline, xylometazoline, and phenylephrine along with local anesthetics has not been adequately evaluated in bronchoscopy. One RCT comparing nasal phenylephrine with lignocaine–phenylephrine combination and cocaine found no difference in ease of bronchoscope insertion and patient or bronchoscopist assessment of discomfort of the procedure.[144] Studies on nasal intubation and nasal upper gastrointestinal endoscopy have also found that the use of

vasoconstrictors such as phenylephrine or oxymetazoline adds no benefit in reducing epistaxis, pain, or procedure discomfort.[146-148]

Evidence statement

- Topical vasoconstrictor administration during nasal bronchoscopy has no benefit in either reducing pain scores and epistaxis or facilitating bronchoscope insertion.

Recommendation

- Use of topical vasoconstrictors is not recommended during nasal bronchoscopy (2A).

What is the preferred method for pharyngeal anesthesia during bronchoscopy?

Pharyngeal anesthesia during bronchoscopy may be administered using several methods such as spray, gargles, or nebulization. The most widely adopted method is the administration of 4–5 actuations of 10% lignocaine spray. A volume of 2.5 ml of 4% lignocaine administered by nebulization contains 100 mg of lignocaine, while 4–5 sprays of 10% lignocaine contain 40–50 mg of lignocaine. A randomized comparison of 100 mg of lignocaine spray with 100 mg nebulized lignocaine found both to be similar in the prevention of cough, although spray formulation was rated as more unpleasant.[149] All received IV diazepam sedation and a further 100 mg of lignocaine solution through the bronchoscope onto the vocal cords and major airways during the procedure. Large RCTs in no-sedation bronchoscopy have been performed with pharyngeal anesthesia using lignocaine spray.[150,151]

Evidence statement

- Lignocaine spray and nebulization are equally effective in providing pharyngeal anesthesia during bronchoscopy although patients report lignocaine spray to be more unpleasant
- Large RCTs in no-sedation bronchoscopy have been performed with pharyngeal anesthesia using lignocaine spray with significantly less cumulative dose of lignocaine as compared to studies using nebulized lignocaine.

Recommendation

- Lignocaine spray (10%) is recommended for pharyngeal anesthesia during bronchoscopy (2A)
- Three to five sprays of 10% lignocaine are recommended for pharyngeal anesthesia during bronchoscopy procedure (UPP)

Should nebulized lignocaine be administered for topical anesthesia during flexible bronchoscopy?

Nebulized lignocaine has been studied as a method of delivering topical anesthesia during bronchoscopy both in sedation and in no-sedation settings. Older RCTs with small sample sizes have demonstrated faster procedure times and less requirement of additional lignocaine when nebulized lignocaine was used.[152,153] Compared to saline placebo, lignocaine nebulization does not reduce cough, sedation requirements, or bronchoscopist's perception of ease of procedure.[154] In another RCT involving 150 subjects, it was concluded that additional lignocaine cannot be recommended to patients undergoing FB under combined IV sedation.[155] A specialized nebulization device called the Enk device which delivers nebulized lignocaine through the working channel of bronchoscope has also been studied. A comparison of lignocaine delivery either via the Enk device or via working channel of bronchoscope found that the mean duration of procedure was similar using either of the two techniques.[156] Administering topical lidocaine via nebulization using spray catheter allows lower requirement of the drug as compared to its delivery via a conventional syringe. In addition, lower doses of IV fentanyl were used with the spray catheter than with the syringe, although no differences in patient tolerance or safety were observed.[157] A recent RCT in the setting of no-sedation bronchoscopy also demonstrated no benefit of additional nebulized lignocaine over pharyngeal spray.[158]

Evidence statement

- RCTs show conflicting evidence regarding the role of nebulized lignocaine during bronchoscopy in reducing patient discomfort, cough rate, or sedation requirements
- Use of nebulized lignocaine results in a higher cumulative dose of the drug administered.

Recommendation

- Nebulized lignocaine is not recommended for topical anesthesia during bronchoscopy (1A).

What is the preferred mode of delivery of lignocaine to vocal cords and trachea?

The two most commonly employed modes of delivery of lignocaine to vocal cords and trachea in bronchoscopy are "spray-as-you-go" technique and cricothyroid injection method. A small randomized trial comparing both these methods in no-sedation bronchoscopy found shorter time to reach carina, less cough, and total dose of lignocaine in the cricothyroid group.[159] Visual analog scale (VAS) for patient discomfort was comparable in both groups. Drug administration via cricothyroid injection also found better VAS scores for ease of procedure and cough than spray-as-you go technique in sedation bronchoscopy.[160] Other studies have also reported similar results with cricothyroid injection, demonstrating faster procedure times[161] and better quality of anesthesia.[162] In a recent RCT, cricothyroid injection demonstrated superiority over the spray technique.[163] Another single small randomized study comparing two techniques of "spray-as-you-go," using a spray catheter compared against standard injection through working channel of bronchoscope during EBUS found less cough with spray catheter, though there was no difference in total lignocaine dose or sedative requirements.[164] Although cricothyroid injection is likely more effective in controlling cough, it is an invasive procedure that is not widely practiced and has a learning curve for achieving acceptable expertise.[161]

Evidence statement

- Cricothyroid injection demonstrates better efficacy in reducing cough, facilitating patient comfort, and ease of performing FB compared with "spray-as-you-go" technique
- However, cricothyroid injection is an invasive procedure, requires training to perform, and is not widely practiced.

Recommendation

- Either "spray-as-you-go" technique or cricothyroid injection is recommended for topical anesthesia of vocal cords and trachea (1A)
- Either spray catheter or working channel of bronchoscope may be used for administering lignocaine during "spray-as-you-go" technique (UPP).

What is the optimum lignocaine concentration for "spray-as-you-go" technique?

Lignocaine in different concentrations (1%, 2%, and 4%) has been evaluated for "spray-as-you-go" administration both in sedation and no-sedation bronchoscopy. During no-sedation bronchoscopy using nebulized lignocaine, use of 1% lignocaine provided similar pain rating and median VAS score for cough, with significantly lower cumulative lignocaine dose requirement. The median cumulative dose of lignocaine was significantly higher in the 2% group and 28% of patients in this group exceeded the maximum recommended dose (>8.2 mg/kg).[151] A comparison of 1% and 2% lignocaine (LIFE study, n = 500, none received nebulized lignocaine) in no-sedation bronchoscopy found no difference in cough or overall procedural satisfaction, although the cumulative dose of lignocaine used in 2% lignocaine group was greater.[150] Similarly, comparisons between 1%, 1.5%, and 2% lignocaine have shown similar tolerance to bronchoscopy in all three groups.[165] Two other smaller trials have also shown similar pain rating and cough severity using 2% versus 4% lignocaine and 1% versus 2% lignocaine.[166,167] A recent RCT comparing 1% versus 2% lignocaine for topical anesthesia during EBUS-TBNA also found 1% to be equally efficacious for the procedure.[168]

Evidence statement

- 1% lignocaine is as efficacious as 2% lignocaine in providing topical anesthesia for FB while significantly reducing the cumulative dose of lignocaine.

Recommendation

- 1% Lignocaine should be used for "spray-as-you-go" administration during bronchoscopy (1A).

What is the maximum permissible dose limit of lignocaine to be used?

Topical lignocaine has a favorable safety profile with varying systemic absorption rates. Peak serum concentration occurs after about 20–45 min of topical application.[169] Serum levels of lignocaine may be variable due to erratic absorption and effect of intermittent suctioning during bronchoscopy.[170] The cardiovascular side effects include slowing of sinus conduction, QRS widening, hypotension, shock, and asystole, while neurological side effects include seizures, dizziness, and euphoria. Ventricular tachycardia and collapse attributable to lignocaine toxicity have been reported even within the prescribed dose limits.[170] Conventionally, the safe upper limit for serum lignocaine concentration is considered to be 5 mcg/ml although a wide dose range has been evaluated in various studies. Among 154 patients receiving a mean lignocaine dose of 15.4 mg/kg body weight, 62% of the patients reported euphoria and dizziness although only one patient had serum drug concentration above 5 mcg/ml.[171] In contrast, FB using median dose of 9.6 mg/kg body weight of lignocaine led to subjective side effects in 92% of participants.[172] Smaller observational studies evaluating plasma lignocaine concentrations after topical lignocaine administration showed no toxicity with total dose of 8–11.6 mg/kg body weight.[172,173] Large randomized trials in no-sedation bronchoscopies have also been performed safely with lignocaine doses of 5–7 mg/kg body weight.[150,151] The suggested lignocaine doses according to route administered during FB is shown in Appendix 4.

Evidence statement

- Studies examining maximal tolerated dose of lignocaine have shown conflicting results with significant interpatient variability in lignocaine levels and side effect profiles
- Large RCTs even in no-sedation FB have demonstrated optimal operator satisfaction and patient comfort using total lignocaine doses of 5–6 mg/kg body weight.

Recommendation

- The bronchoscopist should make an attempt to keep total administered lignocaine dose to the lowest possible levels, with a suggested upper limit of 8.0 mg/kg body weight (2A)
- Bronchoscopists should routinely record the cumulative dose of lignocaine used and be aware of signs of lignocaine toxicity (UPP).

BRONCHOSCOPIC SAMPLING

Bronchoalveolar lavage (BAL)

Which lobe (s) are preferable for performing bronchoalveolar lavage in patients with diffuse lung disease?

Conventionally, BAL is performed from the right middle lobe or from the lingular lobe in conditions with diffuse parenchymal involvement.[174] It is postulated that the absence of or minimal collateral ventilation and more anterior location during supine position favors maximal fluid and cellular recovery from these lobes.[175,176]

Furthermore, the recovery of BAL fluid is significantly higher from middle and lingular lobes as compared to lower lobes among procedures conducted on healthy nonsmoking volunteers.[177] Results from observational

studies and RCTs comparing different techniques and suction methods for performing BAL have shown that the amount of fluid return from middle and lingular lobe was significantly higher compared to other bronchial segments.[178-180] In addition, BAL fluid aspirated from the middle and lingular lobes showed similarity in terms of total volume of fluid aspirated, percent of fluid return, total cellularity, and differential cell count.[181,182]

Performing bilateral and multilobar BAL is associated with significantly higher diagnostic yield in immunocompromised patients with diffuse lung involvement and suspicion of pneumocystis or *CMV pneumonia*.[183-185]

Performing BAL guided by HRCT abnormalities such as ground-glass opacities, tree-in-bud lesions, or focal consolidation is associated with higher diagnostic yield.[186-190] In interstitial lung disease (ILD), it is recommended that BAL should be performed from the lobes corresponding to areas of greatest abnormality visible on chest imaging.[180,191]

Evidence statement

- Right middle lobe and lingula are the preferred sites for performing BAL in diffuse lung disease
- The BAL fluid return from right middle lobe and lingula is significantly higher as compared to other sites
- In BAL performed in diffuse lung disease, significant correlation exists between the cellular characteristics of fluid obtained from the right middle lobe and lingular lobe
- In immunocompromised patients with diffuse lung involvement due to suspected *P. jirovecii or* CMV infection, BAL performed from more than one lobe is associated with higher diagnostic yield than BAL from single lobe alone
- Use of HRCT for selecting suitable area for BAL is associated with higher diagnostic yield
- The presence of ground-glass opacity, consolidation, or tree-in-bud appearance on HRCT scan of thorax significantly correlates with higher diagnostic yield on BAL.

Recommendation

- In diffuse lung involvement, BAL should be performed either from the right middle lobe or from the lingula (2A)
- In patients with suspected *P. jirovecii or CMV pneumonia* with diffuse lung involvement, BAL should be performed bilaterally from more than one lobe, including the upper lobe (2A)
- In focal/patchy lung involvement, the site of BAL should be guided by HRCT thorax findings (2A).

How much volume of saline should be instilled for performing bronchoalveolar lavage in adult patients?

BAL has been performed using a volume of fluid ranging widely from 100 to 550 ml. Instillations of smaller volumes may result in a more "bronchial" component dominating the cellular picture. Dohn and Baughman[192] reported that >240 ml fluid instillation is required to detect abnormal cellularity in patients of ILD. However, in an observational study including 55 patients with ILD, no difference in the cellular yield was observed by increasing the volume of instilled fluid to >100 ml.[193] Experimental studies have reported that 100–120 ml of fluid is adequate for sampling the distal airways.[194,195] In fact, larger volumes (>200 ml) are associated with higher rates of adverse events such as fever, hypoxemia, cough, and dyspnea.[80,196,197] The European Society of Pneumology and the ATS recommend instillation of 100–240 ml and 100–300 ml of fluid for performing BAL, respectively.[181,191] Usually, the required amount of fluid is instilled in 2–5 aliquots; however, no definite evidence exists regarding the exact number of aliquots to be used during BAL. In an observational study including 30 patients with mild COPD who underwent BAL with 100 ml fluid instillation, larger aliquots (2 × 50 ml) caused significantly more desaturation than smaller (5 × 20 ml) aliquots.[198]

Evidence statement

- At least 100 ml of fluid is required to be instilled to sample the distal airways
- No difference is observed in cellular and acellular components of BAL fluid at instilled volume of >100 ml
- Increasing the instilled volume beyond 200 ml significantly increases the likelihood of adverse events without affecting diagnostic yield
- The required volume of fluid is instilled in 2–5 aliquots, with larger aliquots causing significantly more desaturation in patients with COPD.

Recommendation

- At least 100 ml of normal saline should be instilled while performing BAL, and total quantity should not exceed 200 ml (2A)
- The required amount of fluid should be instilled in 2–5 aliquots and smaller aliquots should be used in patients with COPD (UPP).

What is the optimal method and pressure for suction application during bronchoalveolar lavage?

BAL fluid can be retrieved either using manual aspiration with a hand-held syringe or using a fixed negative pressure (usually ≤100 mmHg) with a wall suction apparatus. Application of a fixed negative pressure may result in airway collapse and reduction in amount of BAL fluid recovery.[199,200] It is usually suggested to limit the suction pressure to below 100 mmHg if wall suction is used and to adjust the applied pressure to avoid airway collapse.[181,191] A prospective nonrandomized study including 66 patients found no difference in volume and percentage of BAL fluid recovered or in diagnostic yield between BAL using manual suction (hand-held syringe) or using continuous negative wall suction.[179] Modification of the manual suctioning technique (by connecting a small rubber tubing attached to a syringe) provides higher percentage of BAL fluid recovery and higher diagnostic yield, with fewer complications compared to the conventional suction method.[178,180]

Evidence statement
- BAL fluid can be retrieved by application of a negative pressure either manually using the hand-held syringe or by using the wall suction apparatus
- Manual suction provides significantly higher percentage of BAL fluid return compared to wall suction, without affecting diagnostic yield
- Modified manual suction technique is superior to conventional suction method with regards to the percentage BAL fluid return and diagnostic yield, with fewer complications.

Recommendation
- Either manual suction or wall suction can be used for aspiration of fluid during BAL (2A)
- If manual aspiration is being performed, tubing should be added to the hand-held syringe (2A)
- If negative pressure is applied using continuous wall suction, the pressure should be kept <100 mmHg and adjusted to prevent airway collapse (3A).

What volume and percentage of bronchoalveolar lavage fluid return should be considered satisfactory?

The amount and percentage of fluid recovered during BAL depend on multiple factors, including sampled lobe, aliquot volume, method of suction, and patient-related factors (airway collapse in patients with COPD decreases fluid return).[201] The minimum percentage of fluid retrieved during BAL that is representative of distal airways should be at least 10% of the instilled volume.[199,200,202] Observations made from prospective and randomized trials have shown that a minimum return of 10% of the total instilled fluid is required for optimum diagnostic yield;[180,203] and retrieved fluid volume of <10% of the instilled amount may provide misleading cell differential counts.[191] Furthermore, inadequate fluid return is associated with adverse events such as pyrexia, hypoxemia, and cough.[204] According to the ATS guidelines, BAL procedure should be stopped either if <5% per aliquot is retrieved persistently, or if the volume of fluid instilled exceeds the amount retrieved by >100 ml.[191]

Evidence statement
- The minimum retrieved percentage of BAL fluid that represents the sampling of distal airways is 10% of the instilled fluid volume
- Minimum 10% fluid recovery of the instilled volume is associated with optimum diagnostic yield during BAL.

Recommendation
- A minimum of 10% of fluid return should be achieved during BAL (2A).

What is the role of postbronchoscopy sputum analysis following bronchoalveolar lavage?

Sputum samples can be sent for analysis in patients with suspected TB or lung cancer after performing various diagnostic bronchoscopic procedures such as BW, BAL, TBLB, or EBB. A number of prospective and retrospective studies have shown that the addition of postbronchoscopy sputum (PBS) to various other bronchoscopic specimens in patients with sputum smear-negative PTB is associated with increase in the diagnostic yield. PBS provides a diagnostic yield in 4.1%–38.8% cases and may be the only diagnostic specimen (excluding culture results).[205-216] A few older studies in patients with suspected lung cancer have shown that PBS adds to the diagnostic yield and was the only diagnostic sample in 2.8%–5.2%.[217-219] However, in prospective observational studies that included suspected patients of lung cancer, none showed PBS as the only diagnostic modality.[220,221]

Evidence statement
- Addition of PBS examination to routine diagnostic bronchoscopic procedures in patients with sputum smear-negative PTB increases the diagnostic yield by 4.1%–38.8%
- Addition of PBS examination to routine diagnostic bronchoscopic procedures in patients with suspected lung cancer increased the diagnostic yield by 2.8%–5.2%.

Recommendation
- PBS examination should be performed in patients with sputum smear-negative PTB undergoing bronchoscopy, in addition to other diagnostic bronchoscopic procedures (2A).

Bronchial washings (BW) and bronchial brushings (BB)

Bronchial washings (BW) and bronchial brushings (BB) are commonly used cytological modalities during FB. However, there is large variation in the combination of procedures performed by pulmonologists for the bronchoscopic sampling of an endobronchial lesion suspected as lung cancer.[1]

Should bronchial washings and bronchial brushings be routinely performed in all patients with suspected lung malignancy?

Bronchial washings and bronchial brushings are frequently combined with EBB for the diagnosis of lung cancer, and numerous studies have evaluated their utility and diagnostic yield in this clinical situation. In a series of 484 patients with suspected malignancy and endoscopically visible or central lesions, BW alone were positive in 76% and BB alone in 74%; when both were combined with EBB, the yield increased from 82% (with BB alone) to 94% (using all the three modalities).[222] Furthermore, BW and BB were the sole diagnostic modalities in 12% of cases. For endobronchially visible lesions, the diagnostic yield of BW and BB ranges from 28% to 76% and 47% to 80%, respectively.[223-225] Thus, BW and BB are complimentary to EBB in the evaluation of centrally located lesions suspected as lung cancer.

The use of fluoroscopy has been shown to further increase the yield. In a study of 200 patients with suspected lung

malignancy who underwent bronchoscopy, the yield of BB performed under fluoroscopic guidance was 78%.[226]

A meta-analysis of 35 prospective studies including 4507 patients have shown that in central lesions, the diagnostic yield of BW, BB, and EBB was 47%, 61%, and 74%, respectively, and the combined yield of all three modalities was 88%.[227] On the other hand, in peripheral lesions, the diagnosis achieved by TBLB, BW, and BB was reported as 57%, 43%, and 54%, respectively, with overall combined yield of 79%.[227]

Evidence statement

- The diagnostic yield of BW in suspected lung malignancy ranges from 28% to 76% in visible lesions and up to 66% for nonvisible lesions
- The diagnostic yield of BB in suspected lung malignancy ranges from 47% to 80% in visible lesions and up to 48% in nonvisible lesions
- The addition of both BW and BB to EBB increases the diagnostic yield in patients with suspected lung malignancy in visible as well as nonvisible lesions.

Recommendation

- In suspected lung malignancy with visible endobronchial abnormality, bronchial washings and brushing should be routinely obtained in all patients (2A)
- In suspected malignancy with nonvisible or peripheral lesions, BW and BB should be performed under fluoroscopic guidance, wherever facilities are available (2A).

How much saline should be instilled for obtaining adequate bronchial washings?

There is no consensus regarding the optimum amount of fluid to be instilled for obtaining maximum yield in BW. In patients with visible tumors, no difference in diagnostic yield was found between instillation of 20 ml or >20 ml of saline solution for BW. However, in nonvisible tumors, the diagnostic yield for BW performed with >20 ml of saline solution was higher (prebiopsy BW, 43%; postbiopsy BW, 52%) than when performed with only 20 ml (prebiopsy BW, 30%; postbiopsy BW, 38%).[228] On the other hand, Sompradeekul *et al*.[229] found no difference in the yield of BW for malignancy among the groups that used small (21–44 ml), moderate (41–60 ml), or large (>60 ml) amount of instilled fluid.

Evidence statement

- Instillation of saline volume >20 ml improves the diagnostic yield in nonvisible lesions but has no effect on yield in endobronchially visible lesions
- No difference in the yield of BW is found when >20 ml of fluid was used for cytological analysis.

Recommendation

- A minimum of 20 ml of fluid should be instilled for obtaining BW (UPP)
- For endobronchially invisible lesions, greater amount of saline may be instilled (UPP).

Should bronchial washings and brushings be performed before or after endobronchial biopsy?

No consensus currently exists as to what should be the optimal sequence of bronchoscopic sampling. Scriven *et al*.[230] observed that the yield of postbiopsy BW was significantly higher than the prebiopsy washings (64% vs. 47%, respectively). It has been postulated that the postbiopsy BW specimens may get contaminated with blood, thereby rendering the sample inappropriate for cytological analysis. However, among 75 patients with endobronchially visible lesions, although blood contamination was observed in 43.7% of postbiopsy washings compared to only 8.5% of prebiopsy washings, the difference in diagnostic yield was not statistically significant (53% in prebiopsy vs. 57% in postbiopsy groups).[231]

Similar results were reported by other studies which concluded that for endoscopically visible tumors, the diagnostic yield of BW does not differ whether performed before or after BB and biopsy.[228,232-234] However, a prospective randomized trial by Hou *et al*.[235] concluded that in endobronchial exophytic tumors, prebiopsy brushing appears to be superior to postbiopsy brushing.

The overall diagnostic yield obtained by combining prebiopsy and postforceps biopsy BW and BB is higher than either alone. van der Drift *et al*.[228] showed that the combined yield of pre- and post-BW along with EBB was 94% and 56% for visible and nonvisible lesions, respectively. Similarly, Piaton *et al*.[232] concluded that the yield of fiberoptic bronchoscopy may reach close to 100% in the diagnosis and typing of centrally located, primary lung cancers by combining biopsies and pre–post-BW. These results have been supported by other studies as well.[229,231,233,235-237]

Evidence statement

- The diagnostic yield of prebiopsy and postbiopsy BW is similar; the yield of prebiopsy washings ranges from 31.6% to 84% and postbiopsy washings ranges from 31.6% to 79%
- The diagnostic yield of prebiopsy brushings is higher (41%) than postbiopsy brushings (31%) in patients with visible endobronchial lesions
- When combined, the overall yield of pre- and post-biopsy washings along with biopsy increases up to 94%–100%.

Recommendation

- Bronchial washings should be performed both before and after EBB to achieve maximal diagnostic yield (2A)
- Bronchial brushings should be performed before EBB for maximal yield (2A).

What is the minimum number of bronchial brushings to be performed for optimizing the diagnostic yield?

The optimum number of bronchial brushings to be obtained has not been not well defined. In 270 patients with pulmonary neoplasms, the combined diagnostic sensitivity of the first two brushings was 85.9%; this increased to 87.8% and 89.6% by including the third and fourth brushing, respectively.[238] No further improvement in sensitivity was observed by taking additional brush specimens risk of bleeding increased. The authors concluded that the diagnostic yield from BB improved up to four brush samples.

Evidence statement

- The diagnostic yield of bronchial brushings increases with the number of brushings performed
- No further increase in diagnostic yield occurs after four brushings (89.8%) and risk of bleeding increases.

Recommendation

- A minimum of 2–4 bronchial brushings are needed to achieve optimal yield and minimize complications (3A).

Should liquid-based cytology preparation and cell block be preferred over standard cytological technique in suspected lung cancer patients?

Conventional direct smear technique is conventionally used to prepare smears for microscopic examination. However, smear preparations have several shortcomings such as variable specimen thickness, nonuniformity of slides, preparation and fixation artifacts, overlapping cellular material, obscuring elements such as mucus, inflammation, and blood, and poor cellular preservation.[239] Recent advances in cytopathological techniques include the development of liquid - based cytology (LBC) and cell - block (CB) preparation. The diagnostic yield of LBC is considered either higher or at least comparable to the conventional smears. A recent comparison between smear and LBC has shown a diagnostic accuracy of 55% with LBC as compared to 50% with conventional smear with superiority in terms of cellularity and lesser number of unsatisfactory smears.[240] Similar results have been reported by other studies as well.[241-244]

Use of CB preparations may further increase the overall yield in addition to providing diagnostic material for immunohistochemical (IHC) and molecular studies.[245] Among bronchial washings, CB provided an exclusive diagnosis in 6.5%–14% over conventional smears and LBC.[245,246]

Evidence statement

- LBC of bronchoscopic specimens provides higher diagnostic accuracy than the conventional smear method and fewer unsatisfactory smears
- Preparation of CB along with LBC increases the diagnostic yield with an added advantage of allowing IHC and molecular testing on the specimens.

Recommendation

- LBC and CB preparation of bronchoscopic samples are recommended in suspected lung cancer wherever facilities are available (3A).

What should be the sequence of various bronchoscopic sampling procedures for visible endobronchial lesions?

No RCT has compared the sequence of different bronchoscopic procedures while acquiring specimens from endobronchial lesions, and only observational studies are available regarding this aspect. Ward *et al*.[247] compared the immunopathologic findings of BAL and EBB in clinically stable lung-transplant recipients, posttransplant bronchiolitis obliterans syndrome, and normal volunteers. BAL was the first procedure performed, followed by EBB and TBLB. Bleeding following EBB and TBLB may alter the cellular composition of BAL.

Hong *et al*.,[248] while evaluating the usefulness of EBUS-TBNA in the diagnosis of sarcoidosis, performed BAL followed by EBB and TBLB, and EBUS TBNA was the last procedure performed. However, Caglayan *et al*.[249] performed TBNA before the other procedures such as BB and BW.

Evidence statement

- No RCT has compared the sequence of different bronchoscopic procedures. In observational studies, c-TBNA or BAL has been the first procedure performed followed by brushings and biopsies. TBLB is usually the last sampling procedure to be performed.

Recommendation

- TBNA should be the first procedure followed by BAL, BW, BB, EBB, and TBLB (UPP)
- If endobronchial needle aspiration (EBNA) is planned, it should be taken before EBB (UPP)
- In diffuse lung diseases, if BAL is planned for cellular analysis, it should be the first procedure to be performed (UPP).

Transbronchial needle aspiration (TBNA)

Conventional TBNA (c-TBNA) is a bronchoscopic procedure in which specimens are obtained from beyond the confines of the endobronchial tree.[250] The most common indications for performing c-TBNA are for primary diagnosis or staging of bronchogenic carcinoma or to obtain specimens from submucosal lesions (SMLs) or exophytic, necrotic, or vascular lesions.

The diagnostic yield of c-TBNA varies from 20% to 90%.[251-257] The predictors of higher diagnostic yield by c-TBNA include larger lymph node size, subcarinal and right paratracheal location, use of TBNA histology needle, and level of experience of the bronchoscopist.[258]

Which nodal stations and nodal size should be considered for conventional transbronchial needle aspiration?

c-TBNA is more commonly described for aspiration of lymph nodes at station 4R (right lower paratracheal),

7 (subcarinal), 10 (hilar), and 11 (interlobar), and 4L (left lower paratracheal) according to the International Association for the Study of Lung Cancer mediastinal node map [Appendix 5].[259]

Majority of the studies that included patients with suspected lung cancer with mediastinal lymphadenopathy found significantly higher yield from stations 4R (right paratracheal) and 7 (subcarinal).[251,260-272] In a large retrospective study of c-TBNA that included 400 patients with mediastinal lymph node size of >1 cm, the diagnostic yield was maximum at stations 4R (84.9%) and station 7 (84.5%) and increased to 92.7% when both stations were sampled. No further increase in yield was obtained by sampling >2 stations.[261] Randomized trials have also demonstrated that for nodal stations 4 and 7, the diagnostic yield with c-TBNA is comparable to that obtained by EBUS-TBNA.[273-275] The use of rapid on-site evaluation (ROSE) with c-TBNA may be sufficient for diagnosis in up to 54.3% subjects, thus obviating the need for EBUS.[276] A systematic review that included 53 studies and 8000 patients reported that sampling from station 4R provided the highest diagnostic yield (70%), followed by station 7 (69%), 10/11 (67%), and 4L (60%).[258]

Lymph node size in short axis on computed tomography (CT) thorax is an important predictor for diagnostic yield of c-TBNA. Among 732 patients with unselected mediastinal lymphadenopathy, diagnostic yield of c-TBNA was 79% for lymph node size of >2 cm, 76% for size 1–2 cm, and 62% for size <1 cm.[263] Various other prospective and retrospective studies have reported significantly higher diagnostic yield for lymph node size >2 cm in short axis.[251] However, for lymph nodes between 1 and 2 cm size, the yield varies widely from 13.3% to 87.6% and is significantly lower for nodes <1 cm. On the other hand, a few studies have reported no correlation of nodal size with diagnostic yield during c-TBNA.[260,264,276,277] In a systemic review that evaluated the predictors of successful aspiration during c-TBNA, it was shown that lymph node size of ≥2 cm in short axis is a predictor of increased diagnostic yield.[258]

Evidence statement

- Most frequent nodal sites for aspiration using conventional transbronchial needle (c-TBNA) include lower right paratracheal (4R), subcarinal (7), and hilar or interlobar group of nodes (10/11)
- c-TBNA at nodal stations 4 and 7 is associated with higher diagnostic yield compared to other stations and is not significantly different from the diagnostic yield obtained by EBUS-TBNA at the same nodal stations
- The presence of lymph node size >2 cm in short axis diameter is a strong predictor of higher diagnostic yield during c-TBNA
- For lymph nodes between 1 and 2 cm size, the diagnostic yield of c-TBNA varies widely from 13.3% to 87%, with significantly lower yield, if lymph nodes are <1 cm.

Recommendation

- c-TBNA should be considered in patients with lymph node size of ≥1 cm in short axis at 4R or 7 locations and size of ≥2 cm at hilar or interlobar nodal locations (10/11) (2A)
- For lymph node size <1 cm in short axis at 4R or 7 and <2 cm in short axis at other locations, endobronchial ultrasound-fine needle aspiration (EBUS-TBNA) should be considered (2A)

What should be the optimum needle size for performing conventional transbronchial needle aspiration?

Various sizes of transbronchial aspiration needles are available for c-TBNA. Needles of size 20G–22G are usually used to obtain cytology specimens, while the larger (18G/19G) needles are needed to obtain a core of tissue for histology.[253,278]

Use of histology needle (19G/18G) provides higher yield than cytology needle (21G/22G).[253,263,279] In a prospective non-randomized trial that included 732 patients with mediastinal lymphadenopathy, the use of 19G needle gave 80% yield as compared to 66% with the 22G needle. However, no difference in the yield between both needle sizes was observed in lymph nodes larger than 2 cm.[263]

The effect of needle size on diagnostic yield in patients with suspected lung cancer has been variable. Two studies have demonstrated significantly higher yield with histology needle (19G) as compared to cytology needle of 21G (254) or 22G (283) without increase in complications.[251,280] In contrast, some studies observed that needle size did not influence diagnostic yield during c-TBNA.[260,272] In a systemic review aimed at identifying predictors of successful c-TBNA, it was reported that using a histology needle to obtain both histology and cytology specimens was associated with higher diagnostic yield as compared to cytology needles.[258] The World Association of Bronchology and Interventional Pulmonology have also suggested use of 19G needle during c-TBNA.[281]

Evidence statement

- Use of histology needle (19G or 18G) provides higher diagnostic yield without increasing the rate of complications compared to cytology needle (21G or 22 G) in patients with unselected mediastinal lymphadenopathy or suspected malignancy.

Recommendation

- We recommend the use of 19G needle during c-TBNA to obtain either histology or cytology specimen (2A).

What should be the minimum number of needle passes per node to achieve optimum yield?

The number of needle aspirates performed at each nodal site impacts diagnostic yield. However, the minimum number of aspiration required per target site for optimum yield is yet unclear and variable.

Several studies have evaluated the effect of number of needle passes on c-TBNA yield. In a prospective observational study of 245 patients with mediastinal lymphadenopathy, a yield of 95.5% was achieved with three needle passes, and no further increase with additional passes.[270] In patients with suspected lung cancer, no significant increase in diagnostic yield was achieved after four needle passes.[262] Some other studies, however, did not demonstrate any difference in yield with the number of needle passes.[277,282] In several instances, c-TBNA aspirates need to be sent for molecular analysis (multigene mutational analysis), GeneXpert, or other additional investigations.[283-285] However, no study has elucidated the optimum number of passes required to obtain adequate specimens for these investigations. In a prospective observational study of 94 patients with nonsmall cell lung cancer, at least four passes were taken from each site, of which the last two aspirates were analyzed for epidermal growth factor receptor (EGFR) mutations. Among the 58 patients finally diagnosed with adenocarcinoma, EGFR was detected in the aspirates of 23 patients (39.6%).[284]

Evidence statement

- Up to four passes per node is associated with increase in diagnostic yield of c-TBNA
- Additional aspirations may be required either if only one TBNA site is available for aspiration or if further investigations are required on the specimen.

Recommendation

- We recommend performing 3–4 aspirates per node for optimum yield during c-TBNA (2A)
- Additional aspirations should be obtained if required for other necessary investigations (UPP).

Should rapid on-site examination (ROSE) be routinely performed during conventional transbronchial needle aspiration?

ROSE provides immediate feedback regarding the adequacy of the obtained specimen. It may help in guiding the operator to modify the technique or obtain additional specimens in case of inadequate sampling.

The use of ROSE during c-TBNA has been shown to increase the diagnostic yield and reduce the number of additional diagnostic procedures.[262,286-288] Multiple RCTs have specifically evaluated the effect of adding ROSE during c-TBNA on diagnostic yield.[265,289-291] Of these, two studies included unselected patients with mediastinal lymphadenopathy and found no significant difference in diagnostic yield, percentage of adequate samples obtained, number of needle passes, or total procedure time.[265,289] However, Trisolini *et al*.[265] reported significant reduction in need of additional diagnostic procedures and procedure-related complications in the ROSE group. In another RCT including patients with suspected sarcoidosis, c-TBNA with ROSE was associated with higher yield (84% in ROSE group vs. 68% in the no-ROSE group).[290] In a recent meta-analysis of RCTs comparing c-TBNA with and without ROSE, no difference was observed in terms of diagnostic yield, number of needle passes, number of adequate samples, and procedure time.[292] However, the addition of ROSE was significantly associated with lesser number of complications; this was attributed to the lesser number of additional diagnostic procedures performed in ROSE group.

Evidence statement

- Performing ROSE during c-TBNA reduces the need of additional diagnostic procedures and related complications; increase in diagnostic yield has not been demonstrated.

Recommendation

- Rapid on-site evaluation (ROSE) should be used to reduce additional diagnostic bronchoscopy procedures during c-TBNA (2A)

What is the role of vacuum suction in conventional transbronchial needle aspiration?

During c-TBNA, vacuum suction is applied after the needle is completely inserted into the target site. However, sparse data are available regarding the preferred method of suction during c-TBNA. Suction can be applied manually using a simple syringe or using a modified technique by adding a plunger lock to the syringe (auto-aspiration). Addition of a plunger lock makes it easier to apply negative pressure.[293] In an observational study of c-TBNA in 24 patients, auto-aspiration technique provided significantly higher proportion of adequate specimens but with similar diagnostic yield.[293]

Evidence statement

- Use of automatic aspiration is associated with increase in percentage of adequate specimen acquisition during c-TBNA as compared to manual aspiration; diagnostic yield, however, is comparable. Suction can be applied during c-TBNA either manually using a handheld syringe or by auto-aspiration technique.

Recommendation

- It is recommended to routinely apply vacuum suction during c-TBNA (UPP)
- The use of automatic aspiration is preferable to manual aspiration during c-TBNA (UPP).

What are the indications of performing needle aspiration from endobronchial lesions?

Conventional sampling techniques may be unyielding, especially in patients with necrotic exophytic endobronchial lesions (EEL), submucosal lesions (SML), or visibly highly vascular lesions with high risk of bleeding. For such lesions, the addition of endobronchial needle aspiration (EBNA) to conventional diagnostic methods increases the diagnostic yield; in some situations, EBNA may be the sole diagnostic modality.[249,294-301]

In a prospective study that included 95 patients with visible EEL and SML, all patients underwent forceps

biopsy, BW, BB, and EBNA. It was found that EBNA was the sole diagnostic modality in 11 and 8 patients with EEL and SML, respectively, and the addition of EBNA to conventional techniques increased the diagnostic yield from 82.1% to 95.8%.[295] Furthermore, the use of EBNA reduced the need for additional or repeated diagnostic procedures as well as the overall cost.[298]

Evidence statement

- Addition of EBNA to conventional bronchoscopic diagnostic modalities in patients with EEL or SML is associated with increase in diagnostic yield
- Performing EBNA in addition to other bronchoscopic sampling modalities reduced the need for additional or repeated diagnostic procedures.

Recommendation

- We recommend the use of EBNA along with other bronchoscopic diagnostic modalities in patients with exophytic necrotic endobronchial lesions and SMLs (2A).

Endobronchial biopsy (EBB)

Endobronchial biopsy (EBB) is a commonly performed procedure during bronchoscopy wherein a tissue sample is obtained with the help of a biopsy forceps for pathological analysis. The most common indication for performing EBB is to diagnose bronchogenic carcinoma. Other indications include sarcoidosis, endobronchial TB, and endobronchial metastasis.

What type of forceps should be used for performing endobronchial biopsy?

The most widely available forceps for EBB include the cup forceps and the alligator forceps, with or without spike. They are available in a range of sizes which are compatible with bronchoscope channel sizes from 1.2 to 3.7 mm.[302] The size of the tissue obtained may be classified as small, moderate, and large based on whether the tissue is smaller than, just fills, or larger than the cup of the forceps, respectively.[303] Direct comparisons of the diagnostic yield of biopsies obtained using cup and alligator forceps or using spiked and nonspiked forceps have not been performed; however, Aleva *et al*.[304] compared the EBB specimen quality using three different sizes of fenestrated cup forceps: smallest spherical, elliptical, and spherical and found that the bigger forceps yielded larger specimens, whereas the elliptical forceps better preserved epithelial morphology than the spherical forceps.

Various authors have reported the diagnostic yield using different forceps for EBB. Popovich *et al*.[305] used cup forceps and achieved a 73% diagnostic yield for central tumors. On the contrary, Goyal *et al*.[306] reported a diagnostic yield of 75.8% from biopsies obtained from visible endobronchial lesions in sarcoidosis using alligator forceps. However, no study has directly compared different types of forceps with each other. Hence, no conclusive consensus has emerged regarding the type of forceps that provides the best diagnostic yield through EBB. Fenestrated forceps is usually considered less traumatic for the tissue and may help in better preservation of epithelial architecture.

Evidence statement

- Both cup and alligator forceps have been used for performing EBB
- Literature supporting superiority of one type of forceps over the other for yield or safety is lacking.

Recommendation

- Either cup or alligator forceps may be used to obtain EBB (3A)
- Fenestrated forceps may be preferred to reduce the frequency of crush artifacts (UPP).

Should topical hemostatic/vasoconstrictor agents be routinely instilled before endobronchial biopsy to reduce the risk of bleeding?

The incidence of bleeding during bronchoscopy varies from 0.26% to 5% depending upon the definition used, procedure performed, and underlying risk factors.[307] Massive bleeding is a rare occurrence during bronchoscopy, with an incidence of 0.06% and 0.03% and a mortality of 0.01% and 0.003% for therapeutic and diagnostic procedures, respectively.[308] Various topical agents such as tranexamic acid, epinephrine, and cold saline have been used to control bleeding after biopsy. However, head-to-head comparisons between different hemostatic agents are lacking. Prakash[309] opined that prebiopsy instillation of epinephrine or other vasoactive agents to prevent bleeding from high-risk endobronchial lesions (large, polypoid, fleshy, or vascular) is not likely to be effective. Furthermore, instillation of endobronchial epinephrine may leads to cardiac complications such as ventricular fibrillation and coronary vasospasm.[310,311] Nevertheless, the BTS guidelines recommend topical instillation of 1:10,000 epinephrine solution for persistent biopsy-related bleeding.[6]

Recently, it has been suggested that intratumoral injection of tranexamic acid (IIT) is a safe technique to control prebiopsy bleeding, and a prebiopsy injection can be considered for lesions with a high risk of bleeding.[312,313] However, current evidence is limited by small sample size; hence, the universal applicability of this technique, including the costs associated with the need of a separate needle for injection, should be considered.

Evidence statement

- Topical vasoconstrictors and antifibrinolytics have not been systematically evaluated for prevention of bronchoscopic biopsy-related bleeding
- Intratumoral injection of tranexamic acid (IIT) has been tried successfully for the prevention of bleeding, but further evidence is needed for recommending its routine use.

Recommendation

- Routine instillation of topical hemostatic/vasoconstrictor agents to prevent bronchoscopic biopsy-related bleeding is not recommended (3A)
- Topical epinephrine or cold saline instillation or intratumoral tranexamic acid may be attempted to prevent bleeding in high-risk endobronchial lesions (e.g., lesions with increased superficial vascularity or spontaneously oozing) (UPP).

What should be the minimum number of endobronchial biopsies for achieving optimum yield?

With the advent of mandatory genetic and molecular testing of malignant lesions, greater quantity of tissue in biopsy specimens is now required. The number of EBB specimens required to maximize diagnostic yield must be weighed against the risk of complications such as bleeding, hypoxia, procedure duration, and patient tolerability.

In a retrospective review of 271 patients, Gellert *et al*.[314] demonstrated that among patients with visible endobronchial growths, taking five biopsy samples increased the diagnostic yield to 96% as compared to 65.2% with only a single-biopsy specimen. In another study of 26 patients with visible endobronchial lesions from whom six biopsies were obtained, the maximum diagnostic yield was achieved with four biopsies.[305] In contrast, Shure and Astarita[315] obtained five biopsies each from 18 patients with endobronchial lesions and demonstrated that maximal diagnostic yield was achieved at three samples with no further increase in yield with additional samples. Guidelines from major societies have also acknowledged the lack of robust evidence and recommend a minimum of 3–5 biopsy specimens to be obtained during bronchoscopy.[6,227]

Similarly, no conclusive evidence exists regarding the optimum number of EBB specimens to be obtained in cases of benign lung disorders, such as sarcoidosis, wherein the endobronchial mucosa often appears normal. Majority of studies pertaining to sarcoidosis have performed at least four EBBs as part of their standard procedure.[290,306,316]

Evidence statement

- The diagnostic yield of EBB is variable depending on the number of specimens obtained. The yield with three samples ranges from 59.2% to 80.7%, four samples ranges from 65.4% to 88.4%, and five samples ranges from 75.4% to 88.4%.

Recommendation

- For achieving optimum yield, at least 4–5 specimens should be obtained while performing EBB (3A)
- Additional samples for molecular testing and microbiological investigations should be obtained as and when indicated (UPP).

Should endobronchial biopsy be routinely performed in patients with suspected sarcoidosis undergoing transbronchial lung biopsy?

Transbronchial lung biopsy (TBLB) is often combined with EBUS-TBNA for the diagnosis of sarcoidosis. Whether performing EBB routinely adds to the diagnostic yield of TBLB and EBUS-TBNA has been a subject of debate, especially in situations where the endobronchial mucosa is grossly unremarkable.

Bybee *et al*.[317] were the first to show in a retrospective review of 41 patients of sarcoidosis that EBB provides a diagnostic yield of 20% for demonstrating granulomas. In another study of 150 patients with a final diagnosis of sarcoidosis, TBLB and EBB were diagnostic in 64.5% and 71.4% subjects, respectively.[318] Furthermore, in 10.8% of cases, EBB was the sole diagnostic modality. No major complications were observed with EBB, whereas TBLB was associated with eight instances of minor bleeding and two pneumothoraces.

In sarcoidosis, even the normal-appearing mucosa may demonstrate pathological changes. Shorr *et al*.[319] performed six EBBs in all 34 patients with sarcoidosis, including two biopsies from the main carina and four biopsies from abnormal-appearing bronchial mucosa. The addition of EBB to TBLB increased the yield of demonstrating nonnecrotizing granulomas by 20.6%. Although the yield was higher in biopsies obtained from abnormal-appearing mucosa, 30% of normal-looking mucosa also revealed the presence of granulomas. Similarly, Armstrong *et al*.[316] reported that the yield of EBB for sarcoidosis in patients with abnormal mucosa was 91% compared to 37% in those with normal-appearing mucosa and that combining EBB with TBLB increased the overall yield from 73% to 88%. Gupta *et al*.[320] studied 38 consecutive patients of sarcoidosis and reported that the diagnostic yield of EBB was 54% in patients with abnormal mucosa and 20% in those with normal mucosa. EBB increased the diagnostic yield over TBLB by 10%. Goyal *et al*.[306] demonstrated that a combination of TBLB and EBB provided a superior diagnostic yield (81.4%) as compared to either TBLB (68.7%) or EBB alone (49.6%) in 151 patients of sarcoidosis. Other authors have also shown increase in diagnostic yield (ranging from 6% to 23.5%) by adding EBB to TBLB for diagnosing sarcoidosis.[321,322] The yield of EBB ranges from 54% to 91% in patients with visible bronchial abnormality, compared to 20%–40% in patients with normal-appearing mucosa.[316,319,320,323]

Evidence statement

- The yield of EBB in sarcoidosis ranges from 20% to 70%. In patients with visible endobronchial mucosal abnormality, the yield ranges from 54% to 91%; furthermore, 20%–40% of normal-appearing mucosa also demonstrates pathological abnormality on EBB
- The addition of EBB to TBLB increases the diagnostic yield by 6%–20.6%.

Recommendation

- EBB should be performed in addition to TBLB in all patients with suspected sarcoidosis (1A).

Transbronchial lung biopsy

Transbronchial lung biopsy (TBLB) is commonly performed for the diagnosis of parenchymal lung diseases, sarcoidosis, and bronchogenic carcinoma. The procedure requires a good understanding of the technique to minimize complications in the form of bleeding and pneumothorax.

What type of forceps should be used for transbronchial lung biopsy?

As for EBB, many types of forceps are available and have been used for TBLB, such as cup forceps and alligator forceps, with or without spike. Cup forceps may reach more peripheral areas of the lung but may be associated with higher risk of pneumothorax. The advantage of alligator forceps is the ability to obtain a larger biopsy sample.[324] Alligator forceps is considered to tear the lung to a greater degree than cupped forceps; thus, they may be associated with higher bleeding risk. Hence, pneumothorax and airway bleeding are the major concerns associated with TBLB.[324,325]

Studies which compared the overall diagnostic yield of TBLB using cup or alligator forceps have reported conflicting results. Curley *et al*.[326] showed that in 43 patients undergoing TBLB, alligator forceps retrieved larger pieces of tissue and was more likely to obtain diagnostic tissue than cup forceps, without any difference in the complication rate. On the contrary, a smaller study of 20 subjects reported higher tissue adequacy using large cup forceps than large alligator forceps.[327] No pneumothorax was detected and no difference in bleeding rate was observed. Other comparative studies found no difference in the yield of either cup or alligator forceps for TBLB.[328,329] Jabbardarjani *et al*.[329] reported three pneumothoraces, two with cup forceps and one with alligator forceps among 44 patients undergoing TBLB. A recent RCT conducted in 150 patients of sarcoidosis compared cup forceps versus alligator forceps for TBLB and demonstrated that both types of forceps provided similar diagnostic yield; however, the cup forceps was associated with a higher risk of pneumothorax, with four pneumothoraces in cup forceps group as compared to none in alligator forceps group.[303]

Evidence statement

- Diagnostic yield of TBLB using either cup or alligator forceps has been shown to be similar
- A single RCT has shown higher incidence of pneumothorax with the use of cup forceps for TBLB.

Recommendation

- Alligator forceps may be preferred for performing TBLB (2B).

What should be the adequate number of transbronchial lung biopsy samples?

The optimal number of samples to be taken during TBLB is uncertain and probably depends on the suspected underlying etiology. The need of optimum yield must be balanced against procedural safety.

Roethe *et al*.[330] performed TBLB under fluoroscopy guidance in 37 subjects with suspected sarcoidosis and demonstrated that up to ten biopsy samples may be required for stage 1 sarcoidosis, whereas five samples may be sufficient for stage 2–3 disease when obtained from the radiologically most affected lobe. A prospective study conducted by Descombes *et al*.[331] in 530 consecutive patients undergoing TBLB concluded that for localized lesions and stage 1 sarcoidosis, at least 7–10 specimens may be necessary for adequate yield, whereas 5–6 specimens may be adequate in subjects with diffuse parenchymal involvement. In subjects with localized lesions, obtaining more than four biopsy samples provided higher diagnostic yields than when up to four specimens were collected; however, for diffuse lung disease, obtaining more than four specimens did not increase the yield any further.[332] Curley *et al*.[326] evaluated the yield of TBLB for various clinical indications in 43 patients and showed that among the diagnostic specimens, the first two biopsy specimens provided diagnosis in 86.6%, which increased up to 100% by the fourth sample. Similarly, obtaining four specimens provided 90% yield and no further increase in yield with additional specimens in patients with suspected stage 2 sarcoidosis.[333] In subjects with peripheral pulmonary nodules, obtaining at least six samples provided higher diagnostic yield than four samples (70% vs. 50%, respectively).[305] International guidelines also recommend obtaining six TBLB samples for optimal yield.[227]

Evidence statement

- For diffuse lung disease, the yield of six or more TBLB samples is higher compared to five or less samples
- For localized disease, TBLB yield is higher if more than four samples are obtained (yield of ≤ 4 biopsies: 52%, >4 biopsies: 70%).

Recommendation

- At least 5–6 biopsy samples of moderate-to-large size should be obtained during TBLB (3A)

What should be the preferred lobe (s) for performing transbronchial lung biopsy?

TBLB has been performed from various lobes, and there are no studies comparing the diagnostic yield of sampling different sites. Factors which influence the decision of selecting the appropriate lobe for sampling include site (s) of radiological abnormality, ease of procedure, and risk of complications, especially pneumothorax and bleeding. The expert panel felt that radiological findings should be given due consideration when deciding the lobe from which biopsy is to be obtained, particularly in patients with localized lung lesions. Furthermore, TBLB should not be performed from both lungs in the same sitting. Lingula and middle lobe are best avoided in view of their proximity to fissures. Dependent lobes may be preferred to minimize the theoretical risk of spillage of blood from upper lobes into the major airways.

Evidence statement
- For focal lesions, TBLB is usually performed from the bronchial segment with the maximal involvement
- Data regarding differential yield of TBLB obtained from different bronchial segments in diffuse lung disease is lacking.

Recommendation
- For focal lung lesions, TBLB should preferably be performed from the bronchial segment with maximal radiological abnormality (UPP)
- In diffuse lung disease, TBLB should be performed from the basal segment (s) of lower lobes (UPP).

Does fluoroscopy guidance add to the yield and safety of transbronchial lung biopsy?

Biplanar fluoroscopy and CT-guided fluoroscopy can help in TBLB procedures by confirming the position of the forceps. However, it is associated with radiation hazard and cost constraints. Generally, comparative studies of TBLB performed with and without fluoroscopy have not demonstrated significant difference in the yield or the risk of pneumothorax. Puar *et al*.[334] reviewed the role of fluoroscopy in TBLB for sarcoidosis and found that the mean diagnostic yield of TBLB based on the demonstration of noncaseating granuloma was 75% (range, 50%–100%) using fluoroscopy and 80% (range, 56%–92%) without fluoroscopy. However, the occurrence of pneumothorax was similar in TBLB with or without fluoroscopy (3.28% and 3%, respectively).[333-341]

Anders *et al*.[342] reported that the diagnostic yield of TBLB was higher using fluoroscopy guidance than without, for neoplastic lesions (73% vs. 52.5%; $P < 0.05$) but not for sarcoidosis. Similarly, a retrospective review of 650 TBLB procedures showed that compared to no fluoroscopy use, the diagnostic yield of TBLB was better with fluoroscopy guidance for focal lesions (46.2% vs. 29.4%; $P = 0.008$) but not for diffuse disease (45% vs. 40%; $P = 0.289$).[343] A postal survey of 194 physicians found that the pneumothorax rate was significantly lower in procedures using fluoroscopy versus those without fluoroscopy.[344] On the other hand, a retrospective review of patients with HIV and diffuse lung infiltrates did not find any significant impact of adding fluoroscopy to TBLB on diagnostic yield or complication rate.[345]

Evidence statement
- The overall yield of TBLB is similar whether it is performed with or without fluoroscopy guidance. The yield without fluoroscopy ranges from 32.9% to 80% and with fluoroscopy ranges from 43.8% to 75%
- The yield of TBLB in focal lesions is higher with fluoroscopy guidance (46.2%–72%) as compared to without fluoroscopy (29.4%–52.5%); for diffuse lung disease, the yield of TBLB is similar with or without fluoroscopy (45% and 40%, respectively)
- The incidence of pneumothorax is comparable while performing TBLB with fluoroscopy (3.28%) or without fluoroscopy guidance (3%).

Recommendation
- For diffuse lung disease, TBLB may be safely performed without fluoroscopic guidance (2B)
- TBLB with fluoroscopy guidance may be considered for focal parenchymal lesions, wherever available (2B).

Should "float sign" be used to assess the quality of transbronchial lung biopsy specimen?

The quality assessment of TBLB specimens on site remains an important issue. While the sample quality is assessed pathologically by size, number of alveoli, and preservation of tissue architecture, similar criteria for "on-site" assessment during the procedure are lacking. The presence of "float sign" has been used to assess the sample quality by the operator.

In a prospective study of 18 patients of sarcoidosis, 74% of diagnostic samples floated compared to only 39% of nondiagnostic samples.[346] Furthermore, on pathological examination, samples which floated were more likely to contain alveoli compared to those which sank. On the other hand, Curley *et al*.[326] observed that TBLB specimens that floated were no more likely to be diagnostic or abnormal as compared to nonfloating specimens. A retrospective analysis of 209 patients of sarcoidosis who underwent TBLB found that the percentage of floating samples in the diagnostic and nondiagnostic group was comparable (93.5% vs. 91.9%, respectively).[347]

Evidence statement
- Positive float sign can be demonstrated in 73.7% of alveolar TBLB samples and 38.5% of nonalveolar TBLB samples
- There is no difference in the diagnostic yield or accuracy obtained between floating and nonfloating samples.

Recommendation
- Float sign should not be used to ascertain the adequacy of TBLB specimens (3A).

Should postprocedure chest radiograph be routinely performed following transbronchial lung biopsy?

The incidence of pneumothorax following TBLB varies from 1% to 6%. Pneumothorax may not be visible on radiographs until 1–2 h after the procedure and occasionally may be detected even several hours later.[348-350] Although widely performed, the utility of routine chest X-rays following TBLB is still unclear.

Frazier *et al*.[351] studied the role of routine chest roentgenograms in 305 patients who underwent fluoroscopy-guided TBLB and detected two pneumothoraces with the fluoroscope, both of which were missed by chest radiography; both subjects were symptomatic. Similarly, out of 454 TBLB procedures wherein routine postprocedure chest radiographs were done, only one pneumothorax was documented which was first suspected clinically and subsequently confirmed with chest radiograph.

Hence, to diagnose one pneumothorax, 454 routine chest radiographs were taken.[352] Izbicki *et al*.[353] assessed the safety of avoiding routine chest radiographs after transbronchial biopsy in 208 consecutive patients. Based on the symptoms, 16 radiographs were performed, which detected early-onset pneumothorax (at 2 h) in six patients and late-onset pneumothorax in two patients (at 26 h and 9 days postprocedure). In another study, when routine chest radiography was performed after 2 h in 350 TBLB procedures, pneumothorax was detected in 10 patients, of which seven were asymptomatic; the remaining three who were asymptomatic had mild pneumothoraces which resolved without intervention.[354] The authors thus concluded that chest radiograph needs to be obtained only in symptomatic patients following TBLB.

Evidence statement

- The incidence of pneumothorax after TBLB ranges from 1% to 6%
- Majority of patients with pneumothorax requiring intervention are symptomatic; asymptomatic pneumothoraces are infrequent
- Many routine chest X-rays are usually performed to detect a very small number of pneumothoraces.

Recommendation

- Routine chest radiograph is not essential in asymptomatic patients following TBLB. All symptomatic patients should undergo a chest radiograph to rule out pneumothorax (3A).

What is the role of thoracic ultrasound following transbronchial lung biopsy for excluding pneumothorax?

Thoracic ultrasound is a simple bedside tool which is increasingly being used to diagnose pneumothorax. Prompt and accurate diagnosis can be made in most cases using sonographic signs such as the absence of "lung slide" and presence of "lung point."[355] It has a high negative predictive value for excluding pneumothorax.[355] However, the utility of performing ultrasound routinely after TBLB to detect or exclude pneumothorax is not clearly defined.

Kreuter *et al*.[356] studied the diagnostic utility of thoracic ultrasound versus chest radiography in 1023 patients undergoing TBLB and found that ultrasound detected more pneumothoraces than chest radiograph. Thus, considering chest radiograph as the gold standard, the sensitivity of thoracic ultrasound for the detection of pneumothorax was 100% with a diagnostic accuracy of 99%. Shostak *et al*.[357] reported the sensitivity, specificity, and diagnostic accuracy of ultrasound for detecting pneumothorax following 48 TBLB procedures to be 88%, 97%, and 97%, respectively. In another series of 35 patients who underwent TBLB, only one patient developed pneumothorax; this was detected by both ultrasound and chest radiography, thereby giving an accuracy, sensitivity, and specificity of 100%.[358] Similar results were reported after 113 TBLB procedures, wherein the sensitivity, specificity, and diagnostic accuracy of ultrasound for postprocedure pneumothorax were 100% compared to sensitivity of 87.5% and specificity of 99.6% with chest radiograph.[359]

Evidence statement

- Thoracic ultrasound is a simple bedside tool with no radiation hazard for excluding pneumothorax
- The sensitivity of thoracic ultrasound is 88%–100% in ruling out pneumothorax after TBLB.

Recommendation

- Wherever feasible, bedside thoracic ultrasound may be used to exclude pneumothorax following TBLB (2B).

TRAINING IN FLEXIBLE BRONCHOSCOPY

Is there a need for a structured training program for basic flexible bronchoscopy?

Bronchoscopy training has undergone rapid changes over the past two decades, due to the increased complexity of diagnostic and therapeutic procedures that are now being performed. However, basic flexible bronchoscopy continues to remain the backbone of a pulmonary physician. Consequently, a robust and comprehensive bronchoscopy training schedule is essential for a Pulmonary Medicine program. There is a perceptible change in the attitudes around training with the focus moving from apprenticeship-based to competency-based learning based on skill acquisition. The mannequin models and, more recently, real-time bronchoscopy simulators are becoming increasingly popular. However, their role as a formal training modality is still under evolution.

In a randomized trial involving 13 pulmonary fellows across 3 years of training, Blum *et al*.[360] demonstrated that trainees who received instruction through a structured program using virtual reality (VR) simulator improved their skills at the time of their first bronchoscopy on a real patient as compared to those who did not train using the simulator. Other nonrandomized trials have also demonstrated efficacy of VR simulators in improving the overall performance, speed, and dexterity of bronchoscopy in fresh trainees and in some cases bringing it at par with individuals with considerable prior experience in bronchoscopy.[361,362]

A novel anatomical model called Dexter Endoscopic Dexterity Trainer has been found to be useful as an introductory tool to familiarize beginners with the airway anatomy.[363] Furthermore, a training program that combined manikin with classroom lectures and an educational CD-ROM helped improve performance of a batch of newly joined pulmonary and critical care residents on a simulator.[364,365] Recently, three-dimensional printer-based technologies have now made it possible to design customized anatomical models which replicate the airway anatomy of individual patients. These models have shown to improve performance of bronchoscopy in trainees.[366]

Didactic lectures have been an integral part of structured bronchoscopy training programs. In a randomized comparison of training using online curriculum or classroom teaching, it has been shown that both methods are equivalent in improving the cognitive knowledge of trainees in bronchoscopy when measured using a multiple-choice question-based assessment.[367]

Evidence statement

- There is need for a structured program on flexible bronchoscopy training. Various modalities are available such as VR simulator, anatomical models, lectures, or conventional apprenticeship.

Recommendation

- We recommend that a structured program be implemented for basic flexible bronchoscopy training (2A).

What is the preferred method for basic flexible bronchoscopy training?

Structured training programs are gaining widespread acceptance in teaching institutions across the world for imparting medical procedural skills. The major advancement which has made this paradigm shift possible is the advent of advanced simulators that facilitate training with high semblance to a real patient in a safe-learning environment.[368] This not just helps in better training of the doctors but also improves patient safety. The American College of Chest Physicians (ACCP) has also recommended a simulation-based approach toward competency-based bronchoscopy training.[369] A systematic evaluation of newer training modalities for bronchoscopy, however, is still lacking, and available literature consists of relatively small number of participants.

Ost *et al*.[370] demonstrated the efficacy of VR simulators over the conventional apprenticeship method in training new fellows and showed that the fellows trained on VR obtained a higher score during their first procedure on a real patient. Further, novices who trained on VR simulator had higher satisfaction levels than those who were trained using conventional apprenticeship method.[371] Similarly, Wahidi *et al*.[372] followed two cohorts of fresh trainees and found that the group that trained on VR simulator and online curricula scored higher on predefined milestones during flexible bronchoscopy in real patients compared to those who trained by conventional apprenticeship.

Evidence statement

- A structured program using simulator-based approach is better than the conventional apprenticeship model for training novices to achieve bronchoscopy competency
- No head-to-head trials exist to compare anatomical models with other methods, though in a resource-limited setting, it is a reasonable low-cost alternative.

Recommendation

- For structured training program in basic flexible bronchoscopy, we recommend that VR simulators or anatomical model-based training methods may be incorporated into the conventional apprenticeship model (3B).

What is the minimum number of procedures required to achieve and maintain basic flexible bronchoscopy competence?

There is scarcity of evidence regarding the number of procedures which are required to achieve basic bronchoscopy competence and the number of procedures, which must be performed to maintain this skill. Thus, recommendations are largely based upon expert opinion. Faber[373] opined that at least 50–100 endoscopic procedures are needed to become proficient in fiberoptic bronchoscopic technique. The American Board of Thoracic Surgery recommended in its Booklet of Information that its candidates were required to perform at least 25 bronchoscopy and esophagoscopy procedures per year.[374]

Dull[375] compared the diagnostic yields of BW and biopsies between three skilled operators and a trainee who performed 99 supervised procedures and subsequent unsupervised procedures. He demonstrated that there was no difference in the pathologic diagnostic yield of specimens obtained by skilled bronchoscopists who had performed at least 100 flexible bronchoscopy each and the unsupervised procedures that the trainee performed after initial 99 supervised procedures, suggesting that 100 procedures were sufficient to become proficient in bronchoscopy.

The ACCP performed a postal survey of 1700 members and reached the consensus that at least 50 procedures may be necessary to become competent in routine bronchoscopy, and at least 50 procedures per year may be necessary to maintain the competence level.[376] The results of a similar survey on 1000 practicing pulmonologists in 1995 conducted by the American College of Physicians concluded that to achieve and subsequently maintain competency in basic FB, the minimum number of procedures required are 50 and 24 per year, respectively.[377]

Despite the lack of robust evidence, previous guidelines have ventured to lay down recommendations to address the above question. The BTS 2001 guidelines recommend a minimum of 50 bronchoscopy procedures under direct supervision and 50 more under indirect supervision for attaining basic competence.[378] The ACCP Guidelines on Interventional Pulmonary Procedures states that trainees should perform at least 100 procedures in a supervised setting to attain basic bronchoscopy competence and a minimum of 25 procedures per year to maintain adequate competence levels.[369]

Evidence statement

- According to physician surveys and expert opinion, at least 100 flexible bronchoscopies should be performed to attain basic competency
- Similarly, it is opined that 25–50 flexible bronchoscopies per year should be performed to maintain competency.

Recommendation

- We recommend performing a minimum of 100 flexible bronchoscopy procedures (50 supervised and 50 independent) to attain basic competency (3A)
- We recommend performing a minimum of 25 bronchoscopy procedures per year to maintain competency (3A).

FLEXIBLE BRONCHOSCOPY IN INTENSIVE CARE UNIT (ICU)

The diagnostic and therapeutic utility of flexible bronchoscopy has expanded in the ICU setting in recent years. However, a clear understanding of the various pathophysiological changes, risks, and complications during bronchoscopy and the necessary steps required to prevent and manage procedure-related adverse events are essential to perform safe bronchoscopy in critically ill patients.

What are the indications of flexible bronchoscopy in intensive care unit?

Flexible bronchoscopy has been used for a wide range of diagnostic and therapeutic indications in critically ill patients in the ICU. Common diagnostic indications included bronchial sampling to investigate the etiology of focal or diffuse pulmonary infiltrates, acute ILDs, evaluation of hemoptysis, upper and lower airway inspection, investigation for failure to wean from the ventilator, evaluation of patency and position of tracheotomy or endotracheal tube (ETT), thoracic trauma, inhalational injury, injury of large bronchus, suspicion of fistula or tumor infiltration, tracheobronchial stenosis, assessment of the position and functioning of tracheal or bronchial stents, potential candidate as lung donor, and assessment after lung transplantation or other thoracic surgical procedures. Common therapeutic indications include bronchial toileting, management of atelectasis or lung collapse, endobronchial bleeding, removal of foreign bodies, bronchoscopic intubation, percutaneous tracheostomy, and bronchoscopy-guided local drug treatment.[379-390] In addition, TBLB and TBNA may be performed safely in critically ill patients.[384-387]

Evidence statement

The common diagnostic indications for bronchoscopy in the ICU include evaluation of lung infiltrates, airway inspection, and assessment of position of ETT or airway stents. The common therapeutic indications include management of acute lobar collapse, bleeding control, removal of foreign body, bronchoscopic intubation, and percutaneous tracheostomy.

Should bronchoscopy be used to diagnose ventilator-associated pneumonia?

Bronchoscopy is a widely used technique for diagnosis of VAP with intention to obtain lower respiratory tract samples. The utility of BAL in diagnosing VAP, however, has yielded conflicting results. An RCT by Fagon *et al*.[391] that included 413 patients and compared bronchoscopic protected brush/BAL with endotracheal aspirate, found earlier attenuation of organ dysfunction, lesser antibiotic use, and decreased mortality on day 14 in the bronchoscopy arm. However, a large RCT including 740 patients compared BAL with quantitative cultures and endotracheal aspiration with nonquantitative cultures and did not find any difference in rates of targeted therapy, days alive without antibiotics, maximum organ dysfunction scores, length of hospital or ICU stay, and overall antibiotic use in both groups.[392] A Cochrane review that compared invasive versus noninvasive methods for diagnosing VAP in 1367 patients did not find any evidence of reduction in mortality, number of days on mechanical ventilation, length of ICU stay, or antibiotic change using BAL or protected specimen brush compared to endotracheal aspirate.[393]

Evidence statement

- Among patients with suspected VAP, bronchoscopy-guided strategies do not significantly impact clinically important outcomes compared with nonbronchoscopy-guided techniques.

Recommendation

- Routine bronchoscopy-guided sampling for the diagnosis of VAP is not recommended (1A)
- Bronchoscopy may be considered in patients not responding to empirical antibiotic therapy, or an alternate diagnosis is being considered (UPP).

Should bronchoscopy be used for the management of lung atelectasis or collapse in intensive care unit patients?

Lung collapse or atelectasis is commonly observed among patients receiving mechanical ventilation through ETT. Bronchoscopy is an effective technique for managing lung atelectasis or collapse in critically ill patients. Milledge[394] performed 21 bronchoscopies in 17 patients and demonstrated improvement in air-entry after bronchoscopic toileting in all cases with lobar collapse due to retained sputum. Another prospective study demonstrated partial to complete re-expansion of collapsed lung in all except one out of 10 patients.[395] Tsao *et al*.[396] performed selective intrabronchial air insufflation through FB in 12 critically ill patients with collapsed lung and achieved re-expansion in all subjects. Several other studies have also shown the utility of bronchoscopy for atelectasis.[379,389,396] In contrast, the only RCT that has directly compared bronchoscopy with respiratory therapy alone in 31 patients with acute lobar collapse did not find any additional benefit of adding FB to conventional respiratory therapy with regard to restoration of volume or percentage resolution of volume loss.[397]

Evidence statement

- Although observational studies have demonstrated usefulness of flexible bronchoscopy for the management of pulmonary atelectasis/collapse in critically ill

patients, the addition of this procedure to respiratory therapy alone for acute lobar collapse has not been found beneficial in randomized trials.

Recommendation

- The routine use of bronchoscopy for managing lung atelectasis or collapse in the ICU setting is not recommended (2A)
- Bronchoscopy can be used in the management of complete lung or lobar collapse, not responding to aggressive chest physiotherapy (UPP).

What is the optimum size of bronchoscope and endotracheal tube for performing flexible bronchoscopy in intensive care unit patients?

The passage of a bronchoscope through the tracheal tube (TT)/ETT in patients on a ventilator can significantly affect ventilation. Hence, careful selection of a bronchoscope with optimum diameter is required to obtain the best diagnostic or therapeutic results, while ensuring adequate ventilation throughout the procedure.

Ricou *et al*.[398] compared the yield and side effects of adult (5.9 mm outer diameter, [OD]) and pediatric (3.4 mm OD) size bronchoscopes for BAL in 20 mechanically ventilated patients. Significant reduction in minute volume and Vt was observed while using the adult bronchoscope compared to the pediatric scope although BAL yield was similar. An experimental model study showed that maximum OD of flexible bronchoscope which can be passed down the TT lumen at clinically useful ventilatory settings was 7.3 mm for TT size 9 mm, 5.7 mm for TT size of 8 mm, and 2. 7 mm for TT size of 6.5 mm.[399] Another experimental model study demonstrated that bronchoscope size of 4 mm (or less) would allow safer procedures in patients with severe ARDS.[400] Similarly, Lawson *et al*.[401] proposed that the internal diameter of the ETT should be at least 2.0 mm larger than the external diameter of the bronchoscope to maintain adequate volume delivery and minimize the development of auto-PEEP.

Previously published guidelines on diagnostic bronchoscopy in the ICU did not make any specific recommendations regarding the optimum size of scope, although it was emphasized that the bronchoscope should be selected according to type and size of airway device.[6] It is useful to remember that since various accessories used during bronchoscopic procedures (bronchial biopsy, bronchial brush) have the external diameter of about 2 mm, it is advisable to use the bronchoscope with working channel of at least 2 mm in diameter.

Evidence statement

- The difference in the external diameter of a bronchoscope and diameter of ETT/TT is an important factor affecting ventilation during flexible bronchoscopy among patients on mechanical ventilation
- Small-sized scopes provide an advantage of causing lesser reduction in minute volume and expiratory Vt while minimizing the rise in respiratory rate, intratracheal pressure, and end-expiratory pressure
- An ETT/TT having inner diameter at least 2.0 mm more than the external diameter of the bronchoscope preserves the minute ventilation and prevents rise in end-expiratory pressure; bronchoscopes with OD of 4 mm (or less) allow safer bronchoscopic interventions in patients with severe ARDS.

Recommendation

- During bronchoscopy in intubated patients, the diameter of the ETT should be at least 2.0 mm more than the OD of the bronchoscope (UPP)
- Use of flexible bronchoscope with minimum working channel of 2 mm is preferable for bronchoscopy in endotracheally intubated patients (UPP).

What changes should be made in ventilator settings during flexible bronchoscopy in mechanically ventilated patients?

Insertion of the flexible bronchoscope into the ETT may result in physiological changes, such as decrease in airway lumen, increased airway resistance, hypoxemia, and hypercarbia. To overcome these, ventilator settings need to be adjusted during FB to ensure adequate ventilation.

There are limited data comparing the various ventilation strategies during FB in mechanically ventilated patients. Most authors recommend increasing pressure alarm limits to allow adequate tidal volume (Vt) and increase in FiO2 to 100% for 5 to 10 minutes before procedure to allow adequate oxygenation.[6] An alternative strategy is to limit the pressure alarm and allow reduction in Vt to avoid dynamic hyperinflation; this, however, increases the risk of inadequate ventilation and consequent hypercarbia. Lawson *et al*.[401] ventilated a lung model using ETTs of varying sizes and utilizing different modes and parameters of ventilation; they found that despite extremely high peak inspiratory pressures, pressure at alveolar levels remained low during bronchoscopic occlusion of the ETT. Furthermore, significant auto-PEEP was observed (0–41 cmH_2O) during bronchoscopy, with higher respiratory rate and lower peak inspiratory flows being associated with higher auto-PEEP. It has also been demonstrated that reduction of Vt by limiting peak pressure is well tolerated and protects the subject against hyperinflation.[402]

Evidence statement

- During bronchoscopy in ventilated patients, the preferred strategy is to use a mandatory ventilatory mode and increasing peak pressure alarm limit to ensure adequate expiratory Vts
- An alternative ventilation strategy that allows reduction of Vt by limiting pressure limit to avoid dynamic hyperinflation has also been recommended
- FiO_2 should be increased to 1.0 during the procedure.

Recommendation

- During bronchoscopy in mechanically ventilated patients, the FiO_2 should be increased to 100% at

least 5–10 min before the procedure and continued till the immediate recovery period or as necessary thereafter (3A)
- The ventilator should be adjusted to a mandatory mode (3A)
- The Vt may be increased by 100–150 ml (UPP)
- Pressure limits/inspiratory pressures should be increased to ensure adequate tidal volume delivery (3A)
- PEEP should be kept at minimum possible while allowing adequate oxygenation (3A).

What are the complications during flexible bronchoscopy in intensive care unit?

Patients undergoing bronchoscopy in the ICU are at high risk of periprocedural and postprocedural complications due to hemodynamic stress and alterations in lung mechanics. Various complications reported include oxygen desaturation (3%–65%), bleeding (2.4%–32.4%), arrhythmias (1.5%–5.7%), bronchospasm (1.9%–8.6%), pneumothorax (1.2%–23.6%), hypotension (2.5%–22%), increased intracranial tension (20%–81%), and death (0.8%–5.4%).[379,380,384-386,388,403-412] In a prospective evaluation of 107 critically ill patients who underwent bronchoscopy (73 on invasive mechanical ventilation, 28 on oxygen, 6 on NIV), 10 patients had reversible cardiorespiratory events and 13 patients had transient desaturation.[380] While performing endobronchial sampling in the ICU, complications such as oxygen desaturation, hemorrhage, arrhythmias, bronchospasm, and pneumothoraces have been reported.[388]

Bronchoscopy with combined BAL/TBLB in the ICU setting and in mechanically ventilated patients is associated with pneumothorax in 14.3%–23.6% subjects and bleeding in 6%–10.5% subjects.[384,385] Among 37 thrombocytopenic patients undergoing diagnostic bronchoscopy (33 BAL, 3 washing, and 5 TBLB), two deaths occurred and minor bleed was reported in 32% of procedures.[403]

Although various prospective and retrospective studies have reported increase in intracranial pressure after bronchoscopy in patients with head injury, postcraniotomy or intracranial masses, no neurological deterioration, or sequelae has been documented in the ICU setting.[404,405,412]

Although majority of the above-mentioned complications are mild and transient, deaths have also been reported. Therefore, FB in the ICU setting should be considered as a high-risk procedure and a careful risk–benefit assessment is essential.

Evidence statement

- The commonly reported complications during bronchoscopy in critically ill patients include oxygen desaturation, bronchospasm, hemodynamic instability, arrhythmia, airway bleeding, pneumothorax, transient fever, and raised intracranial pressures
- TBLB in mechanically ventilated patients is associated with increased risk of pneumothorax.

What are the minimum essential patient parameters to be monitored during flexible bronchoscopy in intensive care unit?

Patients undergoing bronchoscopy in the ICU need continuous monitoring owing to higher procedural risk. However, the minimum essential parameters that need monitoring are not clearly defined. No controlled trials have compared intensive or less intensive or no monitoring during bronchoscopy in critically ill subjects. Most authors have measured BP (invasive or noninvasive), SpO_2, and ECG among their study subjects,[380,413] while a few reports included arterial blood gas (ABG) and end-tidal CO_2 ($EtCO_2$) as additional monitoring parameters.[414-416]

Evidence statement

- The most commonly monitored physiological parameters during bronchoscopy in the ICU include cardiac rhythm by ECG, oxygenation using SpO_2, and hemodynamic status by BP measurements (noninvasive). Measurement of $EtCO_2$ and ABG analysis has also been reported.

Recommendation

- The minimum essential parameters that should be continuously monitored during and after bronchoscopy in the ICU are SpO_2, cardiac rhythm using ECG, and BP (UPP).

Should flexible bronchoscopy guidance be routinely used for performing percutaneous dilatational tracheostomy in the intensive care unit?

Percutaneous dilatational tracheostomy (PDT) is a widely utilized technique in the ICU and may be performed with or without bronchoscopic guidance. PDTs performed with bronchoscopic guidance are associated with major complications in 0.38% and death in 0.16% of patients.[417] However, two retrospective studies comparing PDT with or without bronchoscopic guidance found no difference in complication rates between both groups.[418,419] Beiderlinden *et al*.[420] found low rate of complications (0.7%) during PDT with bronchoscopic guidance in 136 patients. In contrast, a retrospective analysis found higher complication rates during PDT with bronchoscopy compared to without bronchoscopy (11.9% vs. 1.9%). The complications encountered included tracheal stenosis, hoarseness, dysphagia, and need to abort the procedure.[421]

In patients on mechanical ventilation, PDT with bronchoscopic guidance results in fewer complications than without FB (13.3% vs. 60%, respectively).[422] Simon *et al*.,[423] in their systematic review, analyzed the adverse outcomes associated with PDT among studies published from 1985 to April 2013 and identified 71 deaths. Airway-related complications, i.e., cannula outside the tracheal lumen, were the second most common cause of lethal complication; all of these occurred in procedures done without FB guidance. In 2015, the Danish Guidelines for PDT in the ICU suggested that bronchoscopy guidance may be used for guiding PDT.[424] However, the Evidence-based Iberic and Pan-American

Federation of Societies of Critical and Intensive Therapy Care Tracheostomy Guidelines made no recommendation regarding the use of bronchoscopy during PDT stating lack of sufficient evidence.[425]

Evidence statement

- Use of bronchoscopy during PDT may reduce the rate of complications (cuff rupture, posterior tracheal wall damage, inaccurate extubation, accidental decannulation, cannula misplacement, and possibly death) compared to PDT without bronchoscopic guidance.

Recommendation

- Bronchoscopy guidance is recommended during percutaneous tracheostomy (2A).

What is the utility of noninvasive ventilation in flexible bronchoscopy among hypoxemic patients in intensive care unit?

Insertion of bronchoscope in airways is associated with decrease in airway lumen, increased resistance to airflow and work of breathing, decrease in PaO_2 by 10–20 mmHg, and decreased end-expiratory lung volume due to use of suction during procedure. NIV is a safe and effective method of recruiting alveoli and augmenting ventilation, thereby ameliorating hypoxemia in patients with acute respiratory failure and facilitating the performance of bronchoscopy in hypoxemic patients.[426]

Two randomized trials comparing FB with continuous positive airway pressure (CPAP) or oxygen via face mask or via venture mask in hypoxemic patients have shown better oxygenation and lesser need for intubation in the CPAP group.[427,428] A comparative trial of NIV with high-flow nasal cannula in ARDS patients during bronchoscopy showed significantly higher pO_2 levels in the NIV group.[429] Subsequently, a systemic review reported that majority of studies have demonstrated improvement in SpO_2 following the application of NIV during bronchoscopy in hypoxemic patients, thereby implying that FB can be safely performed in patients with acute respiratory failure (ARF) with NIV support.[430] The procedure for performing NIV-assisted FB is described in Appendix 6.[426]

Evidence statement

- Bronchoscopy with NIV assistance is feasible and safe in patients with mild-to-moderate ARDS.
- NIV is superior to oxygen alone during bronchoscopy of hypoxemic patients in terms of oxygenation although intubation rates do not differ.

Recommendation

- Bronchoscopy in mild-moderate ARDS should be performed with non-invasive ventilation (NIV) assistance (1A)
- NIV-assisted bronchoscopy should be performed by an experienced operator (UPP)
- While performing bronchoscopy with NIV, backup facilities for invasive ventilatory support should be readily available (UPP).

EQUIPMENT DISINFECTION

Bronchoscopes are considered as semi-critical devices and should routinely undergo high-level disinfection. High-level disinfection is defined as the one which removes all the viable microbes except some spores and prions when present in significant load.[431] Currently, no uniform guidelines exist regarding standard protocols for disinfection of flexible bronchoscopes. The main steps in bronchoscope disinfection are depicted in Figure 1.

Where should bronchoscope disinfection be performed?

Bronchoscopes being delicate and complex devices are associated with risk of contamination and infection, and hence, it is important to carry out all the stages of disinfection properly.[431] Although no studies regarding the most suitable site for bronchoscope disinfection are available, expert committees have given consensus-based recommendations as to where bronchoscope disinfection should be carried out.[6,18,432]

For the prevention of bronchoscope-associated infection, it is recommended to maintain designated "clean" and "dirty" (reprocessing) areas in the bronchoscopy suite to segregate the used instruments from clean ones.[18] A dirty area is one where used bronchoscopes are cleaned and disinfected. This area should contain at least one sink large enough to hold the bronchoscope without causing damage and should be made of materials impervious to water (glass/stainless steel, etc.). Facility of both hot and cold water supply should be available. Similarly, the clean area should be sufficiently large for reassembling the bronchoscope after disinfection and also allow adequate ventilation of hazardous substances.[432] A one-way flow of the equipment from dirty to clean areas is desirable to prevent cross-contamination.[6]

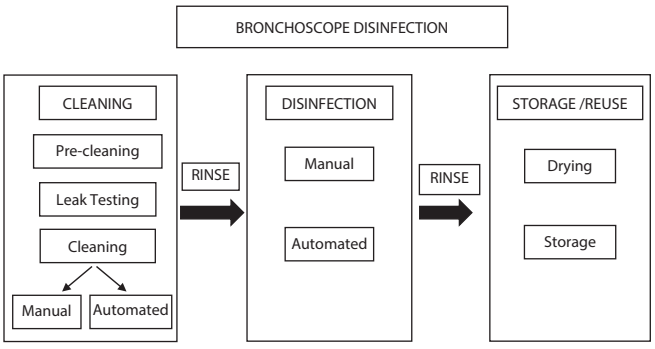

Figure 1: Bronchoscope disinfection: This includes 3 steps - Cleaning, disinfection and storage or reuse. Cleaning consists of *pre-cleaning* to remove inorganic burden and visible soiling followed by *leak testing* to check for leaks in the sheath and *proper cleaning* which can be done either manually or in Automated endoscope reprocessor (AER). After rinsing, *disinfection* is performed either manually or in AER. Rinsing is repeated and is followed by *drying and storage* of the scope

Evidence statement

- No study has addressed the need or description of suitable areas for bronchoscope cleaning. However, experts have emphasized the importance of maintaining a separate designated area for bronchoscope cleaning. This area should have separate dirty and clean areas and to allow one-way direction of the flow of bronchoscope to prevent cross-contamination.

Recommendation

- We recommend that flexible bronchoscopes should be cleaned and disinfected in specific, separate designated areas (3A).

Which agents should be used for precleaning and cleaning of bronchoscopes?

Flexible bronchoscopes can be cleaned using various detergent-based solutions which can be enzymatic (mono- or multi-enzymatic-containing enzymes such as protease, lipase, cellulase, and amylase) or nonenzymatic. Commercially available bronchoscope cleaning detergents contain ethylene glycol, surfactants, methoxymethyl ethoxy propanol, sodium tetraborate decahydrate, C10-16 alkyl derivatives, and glycerine.

Nonenzymatic detergents have been found more efficacious in reducing bacterial load compared to monoenzymatic detergents for precleaning and cleaning of flexible bronchoscopes. An experimental study by Fang *et al*.[433] on 15 hollow Teflon tubes compared the efficacy of nonenzymatic versus multienzymatic detergents in reducing bacterial biofilm load and found that only the nonenzymatic detergent significantly reduced bacterial load. Similarly, Ren *et al*.[434] reported that nonenzymatic detergent significantly reduced biofilm load compared with enzymatic detergent, irrespective of the contact time. In an *in vitro* experimental study on bacteria contaminated well-plates, the sequential addition of enzymes (protease, lipase, amylase, and cellulase) to nonenzymatic detergent base showed that the efficacy of nonenzymatic detergent base improved only after addition of four enzymes.[435]

Evidence statement

- Detergent-based nonenzymatic solutions are more efficacious than enzymatic solutions in reducing biofilm burden when used in precleaning and cleaning of experimental models of flexible bronchoscopes
- Efficacy of nonenzymatic detergent base can be enhanced by the addition of four or more enzymes.

Recommendation

- Precleaning and cleaning of flexible bronchoscopes should be performed using either nonenzymatic or multienzymatic detergent solutions containing a\t least four enzymes (2A).

How frequently should leak testing be done?

Leaks in a bronchoscope can occur as a result of mechanical or procedure-related trauma and may result in contamination and subsequent transmission of infection to other patients, resulting in pseudo-outbreaks. *Mycobacterium tuberculosis* (MTB) pseudo-outbreak has been reported in nine consecutive patients undergoing bronchoscopy due to a damaged bronchoscope with a hole in the outer sheath. This hole remained undetected because leak testing was not routinely performed. Cessation of this pseudo-outbreak was achieved after introducing routine leak testing practice, thereby emphasizing the importance of this maneuver in bronchoscopy practice.[436]

The ACCP and American Association for Bronchology Consensus Statement in 2005 for the prevention of bronchoscopy associated infection recommend that after each bronchoscopy procedure, leak testing should be performed to detect any damage that might have occurred.[18]

Evidence statement

- Leaks in a bronchoscope can cause transmission of infection and result in outbreaks. Routine leak testing practices have been shown to ameliorate pseudo-outbreaks caused by sheath damage and leaks.

Recommendation

- Leak testing should be performed ideally after every bronchoscopy procedure (3A).

What should be the preferred method (manual or automated) for bronchoscope disinfection?

Bronchoscope disinfection can be carried out either manually or using an automated endoscope reprocessor (AER). AERs provide safety from exposure to toxic fumes and vapors of disinfectants; however, these equipments are costly and require reverse osmosis (RO) water supply. Manual bronchoscope disinfection using any of the disinfectants is associated with significant exposure of fumes to the individuals involved in bronchoscope disinfection. Although both techniques are in use, the superiority of one method over the other is not yet established.

Experimental and clinical comparisons between manual and automated techniques have found similar efficacy in disinfection of flexible bronchoscopes. Fraser *et al*.[437] compared the residual contamination rate after manual versus automated disinfection of 60 gastrointestinal endoscopes and found no significant difference between the two methods (37% and 27% contamination rate, respectively). Similar results were reported in experimental studies on bronchoscopes and endoscopes using glutaraldehyde.[438,439] However, Alfa *et al*.[440] demonstrated superior efficacy of AER over manual cleaning of 75 bronchoscopes for removal of organic and inorganic bioburden. Since AERs provide safety to healthcare staff from exposure to toxic fumes and vapors of disinfectants, these are usually preferred over manual techniques if resources permit.

Evidence statement

- Manual disinfection and AERs are equally efficacious in disinfection of flexible bronchoscopes.

Recommendation

- Disinfection of flexible bronchoscopes may be performed either manually or using AER (2A)
- If resources permit, AER is preferred over manual disinfection in view of better safety profile to healthcare staff (UPP).

Which is the preferred agent for bronchoscope disinfection?

Several agents are used for bronchoscope disinfection, including alkylating agents such as glutaraldehyde; orthophthaldehyde (OPA), glutaraldehyde with isopropyl alcohol and oxidizing agents such as hydrogen peroxide; peracetic acid (PAA); other chlorine-based agents. Alkylating agents are compatible with AERs but are more toxic compared to oxidizing agents. However, oxidizing agents have superior sporicidal effects.[431]

Glutaraldehyde has a wide spectrum of activity against organisms, including bacteria, fungi, viruses, and mycobacterium tuberculosis (MTB). It is cheap, noncorrosive, noncarcinogenic and can be used for manual or AER systems. However, it has a pungent odor and it promotes biofilm formation. Exposure to glutaraldehyde may also cause skin and mucosal irritation as well as occupational asthma.[19,441]

The efficacy of glutaraldehyde was tested by Scheidt,[442] who found that complete disinfection of a single bronchoscope was achieved in 65 min using 2% solution; however; disinfection for 20 min was only partially effective. Using 2% glutaraldehyde achieves 99% disinfection for MTB in 10 min and for atypical mycobacteria in 30–40 min. Comparison of different glutaraldehyde concentrations have shown that 2% solution was equally effective as higher concentrations.[441]

Orthopthaldehyde (OPA) is another commonly used alkylating agent for bronchoscope disinfection. It is more effective than glutaraldehyde at lesser concentration (0.5%) and less irritant to skin and mucus membranes.[443] Furthermore, it has superior mycobactericidal activity at a contact time of 5 min.[444] However, this agent causes staining of endoscopes and remains adherent to the scope despite rinsing and may lead to allergy and anaphylaxis in patients as well as increased risk of occupational asthma.[445]

Peracetic acid (PAA) is a relatively safe disinfectant and is effective against viruses, bacteria, bacterial spores, mycobacteria, and fungi. However, it is expensive and has corrosive action on metals. The use of 0.25% PAA is effective against mycobacteria, including atypical mycobacteria at a contact time of 5 min.[446] The contact time required for effective disinfection of mycobacteria can be significantly reduced with the use of PAA compared to glutaraldehyde (20 vs. 30 min).

Evidence statement

- Glutaraldehyde, OPA, and PAA are effective disinfectants for flexible bronchoscopes
- Glutaraldehyde requires longer time (20 min) for eradication of MTB from bronchoscope as compared to OPA and PAA (5 min)
- Exposure to glutaraldehyde and OPA can cause irritation to skin and mucosal surfaces with increased risk of occupational asthma
- PAA is a nonirritant and relatively safer disinfectant.

Recommendation

- The use of peracetic acid (PAA) is recommended for disinfection of flexible bronchoscopes with a contact time of 5 min (3A)
- Glutaraldehyde (2%) and OPA (0.5%) can be used as alternative disinfectant agents with contact time of 20 and 5 min, respectively (UPP).

What is the role of alcohol purge as the final step after disinfection?

Alcohol purge has been used to decontaminate and facilitate the drying of bronchoscopes in the final step after disinfection. An observational study showed a three-fold decline in *Pseudomonas* contamination rates with the use of 70% alcohol rinse followed by forced air-drying in machine-disinfected scopes.[447] Furthermore, alcohol purging after machine disinfection of flexible bronchoscopes has shown to eliminate bacterial pseudo-outbreaks and reduced contamination rates from 4.7% to 0.6%.[448-450] However, it must be kept in mind that alcohol acts as a fixative and may promote biofilm formation.

Evidence statement

- The use of 70% alcohol purge after disinfection results in a significant reduction in contamination rates of bronchoscopes as well as pseudo-outbreaks.

Recommendation

- It is recommended that 70% of alcohol purge be performed as the final step of bronchoscope disinfection (3A).

What type of water should be used for final rinse following bronchoscope disinfection?

Water is used for rinsing bronchoscopes following disinfection to remove residual chemicals. The source of water used for rinsing may be tap water, reverse-osmosis (RO) water, or sterile water. The use of contaminated tap water for bronchoscope rinsing has been associated with a pseudo-epidemic of *Legionella*.[451] However, the superiority of one water source over the other for rinsing is yet unclear.

An observational study evaluated the contamination rates of rinse water over a 5-year period in a bronchoscopy facility where RO units supplied water to three AERs. No organisms were isolated from the rinse water during this period, thereby highlighting the efficacy of RO water in preventing bronchoscope contamination.[452] Currently

available international guidelines recommend sterile or filtered tap water for final rinsing of bronchoscopes and discourage use of raw tap water.[6,18]

Evidence statement

- No direct comparisons have been made between various sources of water to be used for final rinsing of a bronchoscope. Use of tap water for this purpose may lead to scope contamination.

Recommendation

- It is recommended that RO water/sterile water be used for final rinse of the flexible bronchoscope after disinfection (3A).

How should reusable bronchoscope accessories be disinfected?

There are no uniform standard protocols for disinfection of reusable bronchoscopic accessories such as forceps and brushes. These accessories can be disinfected and sterilized either manually or using AERs using the same disinfecting agents as for the bronchoscope. Although AERs provide safety against toxic fumes and vapors to healthcare staff, this equipment is more costly compared to manual disinfection and required RO water supply. Since there are no direct studies available that have compared different methods for disinfection of bronchoscope accessories, the committee reviewed previously available recommendations.[6]

All nondisposable bronchoscope accessories (such as forceps) that breach the bronchial mucosa should be sterilized after a thorough mechanical cleaning and disinfection. Used needles should be discarded after a single patient use since they cannot be properly sterilized. It is preferable to use single-use accessories over reusable accessories wherever possible. Bronchoscope cleaning brushes should also be disposable or thoroughly cleaned and disinfected or sterilized after each use.[6]

Evidence statement

- There are no uniform standard protocols for disinfection of reusable bronchoscope accessories. These accessories can be disinfected and sterilized either manually or using AER after each procedure. AERs provide safety to health - care staff from exposure to toxic fumes and vapors of disinfectants.

Recommendation

- Either manual methods or AER may be used for disinfection of bronchoscope accessories (3A)
- Reusable accessories such as forceps should be thoroughly cleaned, disinfected, and sterilized after each use (3A)
- Cytological needles and cytology brushes should preferably be single use since they cannot be sterilized (3A)
- Bronchoscope cleaning brushes should preferably be used only for a single patient; in case reused, they should be sterilized after each procedure (3A).

Where should bronchoscopes be stored when not in use?

Bronchoscopes are delicate devices and need proper storage. It is a common practice to store bronchoscopes in carrying cases or in ventilated/nonventilated storage cabinets. However, this practice is associated with a likelihood of moisture accumulation which may become a source of bacterial and fungal growth.

The routine practice of storing bronchoscopes in carrying cases has led to pseudo-outbreaks of *Serratia marcescens*.[453] On the other hand, drying storage cabinet is associated with decreased microbial contamination rates as compared to open ventilated cabinets.[454] However, an observational study found no difference in bacterial contamination between ventilated and unventilated cupboard.[455]

Flexible bronchoscopes should be hung vertically without valves attached, in a roomy cabinet with adequate ventilation to prevent moisture accumulation. Moisture may be further decreased by placing the bronchoscope in a drying cabinet that utilizes a desiccant to reduce relative humidity. Drying and storage cabinets are available in various sizes capable of holding 6–20 bronchoscopes, hanging vertically on racks which prevent contact between scopes. High Efficiency Particulate Air (HEPA) filters with an average air exchange of every 20 seconds are also usually employed. A carrying case should be used only for long-distance transportation of bronchoscopes.[6,18]

Evidence statement

- The use of carrying cases for bronchoscope storage is associated with risk of contamination. The storage of bronchoscopes in ventilated drying cabinets may reduce contamination rates.

Recommendation

- During storage, flexible bronchoscopes should be hung vertically without any valves attached (3A)
- Ventilated drying cabinets are preferred for storing bronchoscopes when not in use (3A)
- Alternatively, roomy, well-ventilated cabinets can be used to store bronchoscopes (3B).

How should bronchoscope infection surveillance be performed?

Several studies have shown that bronchoscopes can be a source of contamination and pseudo-outbreaks.[436,448-452,456] Active infection surveillance may identify the source of contamination, thereby allowing measures to curtail outbreaks. This involves periodic sampling and testing of bronchoscopes as well as the rinse water and AER for any possible evidence of contamination. However, no studies have directly assessed the effectiveness of active surveillance for preventing bronchoscopy-related infections and pseudo-outbreaks. Various international societies have formulated different recommendations regarding surveillance. Routine active bronchoscope infection surveillance is not recommended by American,

British, and Canadian societies; however, the Australian and New Zealand endoscopy guidelines recommend periodic active surveillance, including simultaneous testing of bronchoscope, AER, rinse water, and accessories.[6,18]

Evidence statement

- There is no definite evidence regarding the role of active bronchoscope infection surveillance. However, some international guidelines suggest to carry out periodic active bronchoscope surveillance.

Recommendation

- It is recommended to carry out periodic active bronchoscope infection surveillance, preferably at 1–3-month intervals (3B).

CONCLUSIONS

The flexible bronchoscope is an essential tool in the armamentarium of a pulmonologist. However, significant variability exists in its practice and performance. This document is an evidence-based synopsis of available scientific literature on basic diagnostic flexible bronchoscopy that covers various important aspects, including bronchoscopy suite setup, patient selection and preparation, diagnostic bronchoscopic procedures, equipment disinfection, and bronchoscopy in critical care setting. This guideline aims to provide standard technical and procedural recommendations of bronchoscopy practices to respiratory physicians in India and worldwide.

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Conflicts of interest

There are no conflicts of interest.

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Appendix 1: Modification of antiplatelet therapy in patients undergoing bronchoscopy according to pre-existing medical condition (Adapted from refs [6,52])

Conditions	Type of bronchoscopic procedure planned	
	Low-risk procedure (airway inspection, bronchial washing, BAL, or brushing)	High-risk procedure (transbronchial needle aspiration, endobronchial biopsy, or TBLB)
Low-risk condition*	Continue clopidogrel, prasugrel or ticagrelor	Stop clopidogrel, prasugrel, or ticagrelor 5 days before procedure
High-risk condition#	Recommendations for low-risk procedure are the same in low-risk condition as well as in high-risk condition.	May stop clopidogrel, prasugrel or ticagrelor 5 days before procedure after liaison with concerned specialist if: ->1 year after placement of drug-eluting stent ->1 month after placement of bare metal stent

Aspirin can be continued in all cases if already prescribed. Antiplatelet agents can be restarted on the evening of procedure at usual doses. *Low-risk conditions: Ischemic heart disease without stent, peripheral vascular disease, cerebrovascular disease. #High-risk conditions: Coronary artery disease with stent *in situ*. TBLB: Transbronchial lung biopsy, BAL: Bronchoalveolar lavage

Appendix 2: Modification of anticoagulation before various bronchoscopic procedures (Adapted from refs [6,52])

Conditions	Type of bronchoscopic procedure planned	
	Low-risk procedure (airway inspection, bronchial washing, BAL, or brushing)	High-risk procedure (transbronchial needle aspiration, endobronchial biopsy, or TBLB)
Low-risk condition*	May continue warfarin Ensure therapeutic INR range (2-3); optimize dosing if INR >3	Stop warfarin 5 days before procedure; check and ensure INR <1.5 NOACs should be discontinued at least 48 h before procedure; dabigatran should be discontinued 72 h before procedure in case of renal failure
High-risk condition#	NOACs may be continued	Stop warfarin at least 5 days before procedure; LMWH to be started 2 days after stopping warfarin; last dose of LMWH to be given >24 h before procedure[$] Recommendation for NOACs same as above

Aspirin can be continued in all cases if already prescribed. NOACs include dabigatran, rivaroxaban, apixaban, and edoxaban. [$]Warfarin should be restarted along with LMWH on the evening of procedure; LMWH should be continued till therapeutic INR achieved. *Low-risk conditions: Aortic prosthetic heart valve, xenograft heart valve, AF without valvular disease, >3 months after venous thromboembolism, thrombophilia syndromes, #High-risk conditions: Mitral prosthetic heart valve, AF with prosthetic heart valve or mitral stenosis, recent venous thromboembolism (<3 months). AF: Atrial fibrillation, NOACs: Newer oral anticoagulants, TBLB: Transbronchial lung biopsy, BAL: Bronchoalveolar lavage, INR: International normalized ratio, LMWH: Low-molecular-weight heparin

Appendix 3: Various tools for the assessment of depth of sedation[131-133]

MOAA/S	MRSS
5-Responds readily to name spoken in normal tone	1-Awake and alert, minimal or no cognitive impairment
4-Lethargic response to name spoken in normal tone	2-Awake but tranquil, purposeful responses to verbal commands at a conversational level
3-Responds after name called loudly or repeatedly or both	3-Appears asleep, purposeful response to verbal commands at conversational level
2-Responds only after mild prodding or mild shaking	4-Appears asleep, purposeful response to commands but at a louder than conversational level, requiring light glabellar tap or both
1-Responds only to painful stimulation	5-Asleep, sluggish purposeful responses only to loud verbal commands, strong glabellar tap, or both
	6-Asleep, sluggish purposeful responses only to painful stimuli
0-No response to painful stimulation	7-Asleep, reflex withdrawal to painful stimuli only
	8-Unresponsive to external stimuli, including pain

MRSS: Modified Ramsay Sedation Scale, MOAA/S: Modified Observer's Assessment of Alertness/Sedation score

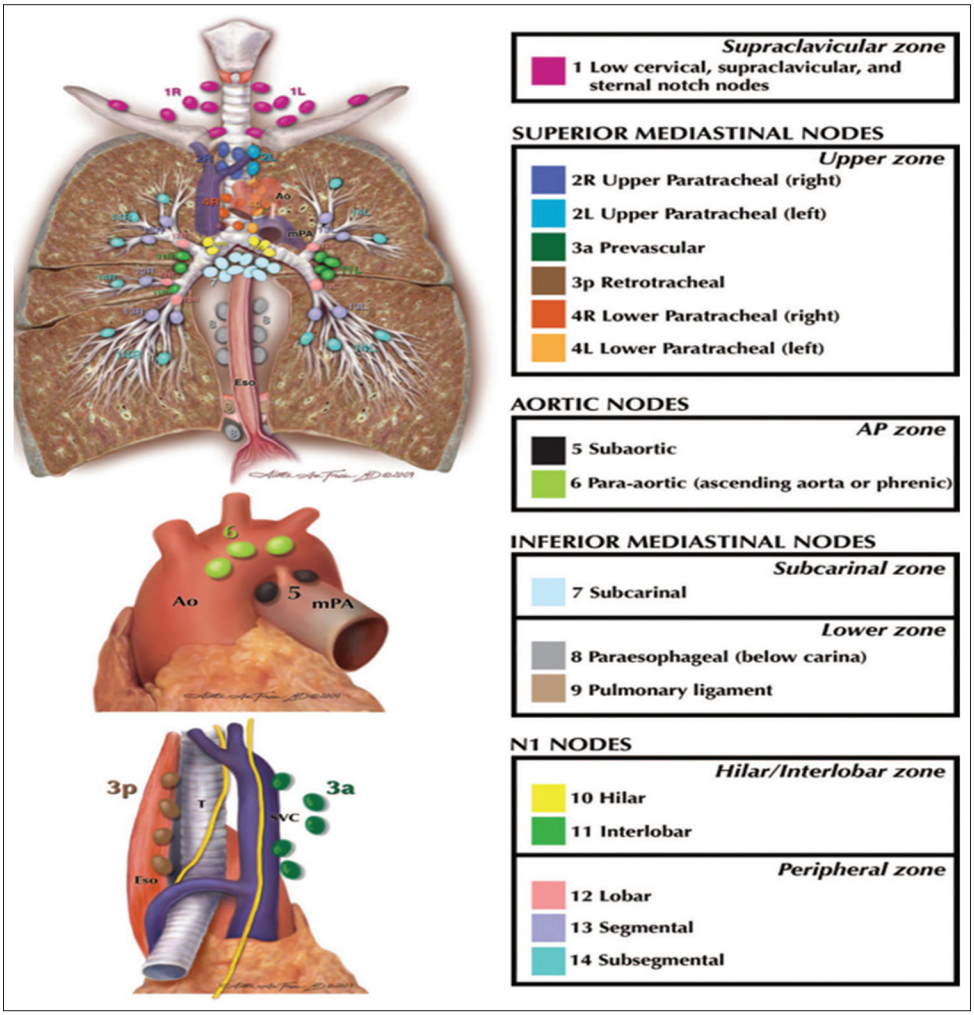
ASASS

	Minimal sedation/anxiolysis	Moderate sedation/analgesia	Deep sedation	General anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal commands and light touch	Purposeful response to repeated or painful tactile stimulation	Unarousable even to repeated or painful stimulation
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be adequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

ASASS: American Society of Anesthesiologist Sedation Scale

Appendix 4: The suggested lignocaine doses according to route administered during flexible bronchoscopy (Adapted from refs [6,52])

Site of administration	Dosage (lignocaine in milligram)
Nose	5 ml of 2% gel (100 mg)
Oropharynx	3-5 sprays of 10% (30-50 mg)
"Spray-as-you-go" method	6 aliquots (1.5 ml each) of 1% lignocaine solution (90 mg), administered as follows: 2 at the vocal cords, 1 each at the trachea and carina and 1 each in the right and left main bronchus
Transcricoid lignocaine	5 ml of transcricoid lignocaine and two alliquots of 1.5 ml in each main bronchus



Appendix 5: The International Association for the Study of Lung Cancer Lymph Node map (ref [259])

Appendix 6: Procedure for noninvasive ventilation-assisted bronchoscopy (adapted from ref [426])

NIV is delivered through oro-nasal or full face mask coupled with T-piece connector or dedicated FB-NIV mask that can allow introduction of bronchoscope without causing air-leak
NIV is started 5-30 min before procedure and continued for a variable time postprocedure (usually for 30-60 min) till patient is able to maintain his SpO_2 on conventional oxygen supplementation
FiO_2 should be kept at 1.0 throughout the procedure
Ventilatory parameters are set at a CPAP of 5 cmH_2O and pressure support of 12-15 cmH2O, adjusted to maintain SpO_2 ≥92%, expiratory tidal volume between 8 and 10 ml/kg, and RR below 25/min
At the start of procedure, mask is removed from the face, FB inserted through the mask and then through the nasal passage to ensure quick access
Once the vocal cords are visible, the mask is again applied over the subject's face and connected to the ventilator
While performing lung biopsy, it is preferable to keep the CPAP at 0 and pressure support not more than 10 cm of H_2O

NIV: Noninvasive ventilation, CPAP: Continuous positive airway pressure, RR: Respiratory rate, FB: Flexible bronchoscopy