Upper and Lower Airways Functional Examination in Asthma and Respiratory Allergic Deseases. Considerations in the SARS-CoV-2 Post-Pandemic Situation

Running title: Upper Airway Examination Post COVID-19 Pandemia

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Abstract

Airway examination techniques are procedures that can potentially transmit infectious diseases to both patients and healthcare professionals who perform them, by various mechanisms. The pandemic situation due to the COVID-19 disease has practically halted most of the activity of the clinics and laboratories of pulmonary and nasal function, with clear recommendations in this regard. Being already in the early stages after the peak of the pandemic, we still do not know for sure what its consequences will be in the short or long term, since there are important gaps in the knowledge of aspects as fundamental as the transmission mechanisms of the virus, its pathophysiology and immune response or its diagnosis.

In this review we will examine the different examination techniques available on the assessment of patients suffering from respiratory allergy, asthma and associated diseases, int the postpandemic momentum, highlighting their possible advantages and disadvantages. For this reason, we wanted to focus on exploring the entire upper and lower airways, from the perspective of the safety of both the healthcare professionals and patients and their specific characteristics. And at the same time we will approach the analysis of the intrinsic value that these interventions provide from the point of view of both diagnosis and management of these patients.

The changing situation of this disease may cause some modifications of the assertions presented in this review in the future.While this guidance seeks to ensure a consistent wide approach, some differences in operational details may be applied due to local regulations.

Key words: Asthma. Allergic rhinitis. Bronchaill challenge. Inflammatory biomarkers. Lung function tests. Upper airways examination.

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Resumen

Las técnicas de examen de las vías respiratorias son procedimientos que pueden transmitir enfermedades infecciosas, por diversos mecanismos, tanto a los pacientes, como a los profesionales de la salud que las realizan. La situación de pandemia debido a la enfermedad COVID-19 prácticamente ha detenido la mayor parte de la actividad de los laboratorios de función pulmonar y nasal, con recomendaciones, específicas, de múltiples sociedades y guías nacionales e internacionales. Aunque estemos ya en las primeras etapas después del pico de la pandemia, todavía no sabemos con certeza, cuáles serán sus consecuencias a corto o largo plazo, pues existen lagunas importantes en el conocimiento de aspectos tan fundamentales como los mecanismos de transmisión del virus, su fisiopatología y respuesta immune, o su diagnóstico.

En esta revisión examinaremos las diferentes técnicas de examen disponibles en la evaluación de pacientes que sufren enfermedades alérgicas como la rhinitis o el asma y enfermedades asociadas a ellas, destacando sus posibles ventajas y desventajas, en la situación próxima ya fuera de la pandemia del SARS-CoV 2. Por esta razón, queríamos centrarnos en explorar todas las vías aéreas superiores e inferiores. Lo haremos desde la perspectiva de la seguridad tanto de los profesionales de la salud como de los pacientes y sus características específicas. Paralelamente abordaremos el análisis del valor intrínseco que proporcionan estas intervenciones desde el punto de vista tanto del diagnóstico como del tratamiento de estos pacientes.

La situación cambiante de esta enfermedad puede causar en el future, modificaciones de las afirmaciones presentadas en esta revisión. Si bien esta guía busca garantizar un enfoque amplio y consistente, puede ser necesario aplicar algunas diferencias en los detalles operativos, debido a las distintas regulaciones o situaciones locales.

Palabras clave: Asma. Rinitis alérgica. Provocación bronquial. Biomarcadores inflamatorios. Pruebas de función pulmonar. Examen de las vías aéreas superiores.

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1. Introduction

Airway examination techniques are procedures that can potentially transmit infectious diseases to both patients and healthcare professionals who perform them, by various mechanisms, including environmental transmission by aerosols. The pandemic situation due to the COVID-19 disease has practically halted most of the activity of the clinics and laboratories of pulmonary and nasal function, with clear recommendations in this regard from multiple national and international societies and guidelines [1-3]. Being already in the early stages after the peak of the pandemic, we still do not know for sure what its consequences will be in the short or long term, since there are important gaps in the knowledge of aspects as fundamental as the transmission mechanisms of the virus, its pathophysiology and immune response or its diagnosis. Further more, today we do not have any curative or preventive therapy, which has been reliably proven effective.

Furthermore, this crisis has made us aware of our responsibility in the transmission of infectious respiratory diseases, and undoubtedly, new systems, protocols and assumptions will also emerge within the field of functional exploration, which will completely replace many of those that until now we considered valid. In these uncertain circumstances, it is therefore more honest simply defining possible different scenarios that contemplate the properties that have been nominated as necessary for this new reality to be safe and lasting [4]. Within the field of studying lung function, some of these properties have always been found, such as the value of protocols and the standardization of studies or the culture of protection of healthcare personnel. On the other hand, this so-called new normality will make us question the value of all our

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interventions, without forgetting the importance of an objective diagnosis, in a disease such as asthma and on which we have insisted so much.

In this review we will examine these possible scenarios in the post-pandemic momentum, based on the different examination techniques of the patient with respiratory allergy and asthma and associated diseases, highlighting their possible advantages and disadvantages. For this reason, we wanted to focus on exploring the entire upper and lower airways. We will also review them from the perspective of the safety of both the healthcare professionals and patients and their specific characteristics. And at the same time we will approach the analysis of the intrinsic value that these interventions provide from the point of view of both diagnosis and management of these patients.

2. Mechanisms of transmission of SARS-CoV-2

The four possible routes of exposure to viral respiratory infections, which are represented in the figure and summarized in table I, are 1) the contact of the hands and fingers with surfaces or objects contaminated by the virus, known as "fomites" and subsequent contact of the fingers with the eyes, nostrils, and lips; 2) the spray of droplets, consisting in the direct projection of the virus transported in the first and larger cough or sneeze particles, generally with an aerodynamic diameter (da) greater than 100 µm on membranes of the face, 3) the inhalation of viruses carried in airborne cough or sneeze secondary particles, which have a da between 5 µm and 100 µm, inhalable but non-breathable particles and usually deposited in the upper or conjunctive airways, and finally and perhaps of less important in viruses such as influenza, 4) the

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inhalation of viruses transported in the air in small particles of less than 5 µm da, and therefore breathable, which originate, after an initial evaporation process, both from coughing, sneezing such as by speech, exhalation manoeuvres or breathing itself. Respirable particles are deposited throughout the respiratory tract, including the alveolar region, while inspirable particles are deposited in the upper respiratory tract and major tracheobronchial regions [5]. Unlike routes 1 and 4, routes 2 and 3 require "close contact", generally defined as being less than 1 or 2 meters from the possible transmiter. The importance of each of these pathways is variable for each different infectious agent, and continues to be the subject of much controversy [6]. Current data suggest that transmission of SARS-CoV-2 infection occurs from person to person primarily during close exposure to a person infected with the virus, through respiratory droplets produced when the infected person speaks, coughs, or sneezes. These droplets may fall into the mouth, nose, or eyes of people who are nearby or possibly be inhaled. Transmission can also occur through contact with contaminated surfaces followed by contact with their eyes, nose or mouth. Supported by this envision, the public health councils have focused on four main measures: frequent and thorough hand washing; maintain social distancing and practice good respiratory hygiene. The general hand hygiene is deemed the cornerstone of infection prevention and is essential to minimize the colonization and the transmission of the virus [7]. An update on hand hygiene recommends a modification of the WHO I formulation with 6mL during 60 seconds (80% wt/wt ethanol, 0.125% vol/vol hydrogen peroxide, and 0.50% vol/vol glycerol) or with 3mL during 30 seconds for modification of the WHO II formulation (75% wt/wt isopropanol, 0.125% vol/vol hydrogen peroxide, and

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0.50% vol/vol glycerol) [8]. It is also essential to perform routine cleaning and disinfection of environmental and other frequently touched surfaces, together with a complete cleaning of rooms after every procedure

On the other hand, new research has clearly demonstrated that transmission through aerosols or droplet nuclei is another important mechanism. Van Doremalen et al [9] have described that SARS-Cov2 is stable and remain infectious for several hours or days in aerosols and on surfaces: it is detected in aerosols up to 3 hours, up to 4 hours in copper, up to 24 hours in cardboard and up to 2 to 3 days in plastic and stainless steel. During airway examination, transmission can also occur through routes 3 and 4. It is well demonstrated that these inspirable particles are large enough to carry a variety of respiratory pathogens such as the measles virus, Influenza virus and SARS-CoV and SARS CoV-2 [10]. They are also potentially more infectious, as they persist in the air for longer periods of time before forging by gravity, increasing the likelihood of inhalation by susceptible individuals and have an increased chance of further penetrating the respiratory tract to initiate an infection of the lower respiratory tract. Therefore, the top priority in preventing and mitigating the disease is avoiding breathing of airborne particles and cough-generated droplets. For the protection of patients and healthcare personnel from breathable or inspiring particles, additional measures are necessary, including the use of more complex personal protective equipment with potents face mask respirators, and the close control of ventilation/air conditioning systems [11], as will be detailed later. The emission capacity of breathable and inspirational particles is highly variable potentially depending on various circumstances such as the intensity of speech or the flow of exhalation [12]. Furthermore, the

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existence of super-remitting individuals is also known, which are contagious individuals that infect a disproportionately large number of susceptible contacts. Its existence has been adequately documented in previous coronavirus pandemics, such as the MERS-CoV, SARS-CoV and SARS-CoV-2 outbreaks [13].

3. Environmental Considerations of airborne precaution rooms (VENTILATION)

The association between ventilation, air movements in buildings and the transmission/spread of some infectious diseases, especially for respiratory viruses, has been well demonstrated. In the COVID-19 era, most lung function guidelines recommend proper ventilation of the room and increasing times between patients examinations [1-3]. The general purpose of ventilation in buildings is to provide healthy air by both diluting the pollutants originating in the building and removing the contaminants from it [14,15]. Ventilation refers to introducing and distributing outdoor and or properly treated recycled air into a building or a room. Ventilation reduces the risk of exposure to a pathogen or infected source hazard, together with other methods of isolation. Therefore, it is part of the safety measurements for patients and health care workers.

The clearance of aerosols depends on the ventilation and air change within the room. Increasing ventilation rate can effectively reduce the risk of long-range airborne transmission but may be of little utility in preventing the droplet-borne transmission. Among the different types of ventilation, natural ventilation includes natural forces able to drive outdoor air through purpose-buil and

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building envelope openings. Purpose-built openings include windows, doors, solar chimneys, wind towers and trickle ventilators. This natural ventilation of buildings depends on the climate, building design, and human behavior. In naturally ventilated airborne precaution rooms, the airflow should be directed to areas free of transit or permit the rapid dilution of contaminated air into the surrounding areas and the open air [16]. Natural ventilation has many drawbacks, is variable and depends on external climatic conditions, may be difficult to control in term of flow and its direction and often do not work as expected, and regular operation may be interrupted. Because of these problems, natural ventilation systems may result in the spread of infectious diseases through health-care facilities, instead of being an important tool for infection control.

Mechanical ventilation includes different types of fans. In a positive pressure system, the room air is leaked out through envelope leakages or other openings. In a negative pressure system, “sucking” air from the outside compensates the room air. The room pressure may be maintained at either slightly positive or negative pressure by using unequal supply or exhaust ventilation rates [17]. Filtration systems can be installed in mechanical ventilation to remove harmful microorganisms, particulates, gasses, odors, and vapours. In an airborne precaution room for infection control, a minimum negative pressure of 2.5 Pa is often maintained relative to the corridor [18]. Mechanical ventilation is expensive to install and maintain in isolation rooms. It often does not deliver the recommended ventilation rate and may fail to maintain negative pressure. Hybrid or mixed-mode are used when the natural ventilation flow rate is too low. An airborne precaution room can be naturally or

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mechanically ventilated but require ≥12 air changes per hour (ACH) and controlled direction of airflow (CDC) (WHO recommends the double, 160 l/s/patient -hourly average ventilation rate-). Once an end to dispersion can be defined (such as the patient leaving the room), a single air change of a room is estimated to remove 63% of airborne contaminants and similarly with each subsequent air change. After 5 air changes, less than 1% of the original airborne contamination is thought to remain.

In an isolation room with 10 to 12 air changes per hour (ACH), a minimum of 30 minutes will reduce contamination to less than 1% (equivalent to 80 L/s/patient in a 4×2×3 m^3 room). In a side room with 6 ACH, one hour would be a pragmatic time, allowing aerosols to settle and be removed by ventilation. Natural ventilation, opening windows, and doors may provide a good ACH but rely on correct door and window operation. However, habitually the rooms are not operated with windows and doors open.

It is of great importance considering ventilation systems to properly maintain the airflow direction from clean zones to dirty zones. This can be obtained with air pressure control technologies but at a cost. Different requirements of pressure difference or imbalance of airflow rate range from 2.5 to 15 Pa. The required pressure difference should be used to avoid the bi-directional flow, which occurs due to temperature difference and wind force.

Air conditioning systems potentially may cause droplet transmission. A recent publication of a COVID-19 outbreak in China suggests that air conditioning contributed to the outbreak and close contact among subjects. Interestingly, smear samples from the air conditioner were negative for SARS- CoV-2 by reverse transcription PCR analysis[19].

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To summarize, there is sufficient and robust evidence to demonstrate the association between ventilation, air movements in buildings and the transmission/spread of some infectious diseases but there are insufficient data to specify and quantify the minimum ventilation requirements in hospitals and isolation rooms concerning the spread of infectious diseases via the airborne route [20-22].

4. Health care workers protection (HCW)

A detailed description of al issues related to HCW protective measures goes beyond this review and extensive and specific guidelines had been published elsewere[1-3]. As previously presented, the spread of respiratory viral infections occurs primarily through contact and droplet routes but new research suggests severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can remain viable and infectious in aerosols for hours [9]. Therefore, the use of masks as appropriate personal protective equipment (PPE) is often considered when preventing the spread of respiratory infections. A recent meta-analysis of 21 studies provided the latest evidence on the efficacy of masks in preventing the transmission of the infection [23]. They concluded that the protective effects of masks were not only significant for both healthcare workers and patients but also consistent between Asian and Western populations. Because the disease is highly contagious, the use of an FFP2/FFP3 (Face Filtering Piece) respirator mask is recommended for all aerosol-generating procedures performed when caring for patients. The FFP2 mask filters approximately 92% of air particles, protecting against nontoxic residues and fibrogenic elements, preventing the inhalation of toxic fluids of dust, aerosols and fumes. FFP3 mask filters 98% of

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air particles, protecting against poisons and toxins of dust, smoke and aerosols, as well as bacteria, viruses and fungal spores. For isolation procedures and where infectious aerosols might be generated, the WHO recommends using a respirator with a filtration efficiency of at least 95% for 0.3m diameter particles, which is equivalent to an N95 facemask, according to the US National Institute for Occupational Safety and Health (NIOSH) regulations. Given that the US regulations differ from the European, this level of protection is between FFP2 and FFP3. Staff must additionally wear protective goggles and a waterproof apron or gown [16]. A Cochrane review concluded that for donning and doffing procedures, a one-step glove and gown removal, double-gloving, spoken instructions during doffing, and using glove disinfection may reduce contamination and increase compliance [24]. Another systematic review and meta-analysis support physical distancing of one meter or more and provide quantitative estimates for models and contact tracing [25]. Adequate preventive measures and the correct use of personal protective equipment (PPE) are essential to prevent the transmission of the disease and minimize the risks of personnel exposed to the aerosols generated during the different explorations that are carried out. All pulmonary function laboratories must follow the guidelines for prevention and control of Covid-19 infection. Specific issues of each procedure are addressed on the sections below.

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5. Patient protection and screening. Itinerary and conditions of access to pulmonary function laboratory.

5.1 Organization

As a general rule, pulmonary function tests should not be performed on patients with suspected or diagnosed COVID-19. In the pandemic phase, according to the recommendations of the European Resoiratory Society (ERS) [1] and the Spanish Society of Respiratory Pathology (SEPAR) [2], spirometry will only be performed for the preoperative evaluation of surgery for lung cancer. Nevertheless, some exceptions must be considered on a case by case basis. Once this phase has been overcome, the performance of spirometry will be prioritized when it is considered essential for clinical decision-making.

In the post-peak phase (phase 1 onwards), spirometry and bronchodilator testing can be performed following guidelines and the recommendations of the scientific societies ERS [1], SEPAR [2] and SEAIC [3], which are summarized below.

During the appointment of the patient, a preliminary screening questionnaire will be carried out and, if there is no suspicion of COVID-19 infection, the patients will be provided with the indications for interruption of the usual asthma treatment prior to the test, as well as the location (wing, room) and the exploration time, requesting that they come 5 minutes in advance, but no more.

Patients will be instructed to go alone to the facilities, accepting a companion or caregiver only when necessary.

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5.2 Waiting room.

Blocking chairs will ensure the distance of two meters between patients, the room will lack objects that could suppose the transmission of fómites, and its periodic cleaning will be intensified.

When the patient arrives in the waiting room:

- The patient (and companion, if any) will be provided with a surgical mask, asked to only occupy one chair, and rest seated until called to the diagnostic laboratory
- The COVID-19 situation will be examined again by means of a screening questionnaire.
- If possible, a temperature measurement on the forehead through remote monitoring should be taken. Only patients without suspected COVID infection will undergo spirometry. In other cases, the patient will be referred to the corresponding healthcare circuit.

5.3 Pulmonary function test (spirometry) room:

It must be a specific isolated room for carrying out this test, with a minimum space of 2.5*3 m and natural ventilation or individual air conditioning, which must have a sink. One patient can only occupy it at any time and the companion will not be allowed to enter.

The patients' appointments will be arranged so that there is twice the time to carry out the test. Vulnerability should be kept in mind in order to prevent infection in at risk populations. It is advisable to reserve some appointments in the agenda for elderly patients, severe asthmatics or people suffering from

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other chronic or debilitating diseases. Children and adults should be kept separated, using different rooms or time slots.

Once the test is done, the room will remain empty for at least 15 minutes to guarantee its ventilation and cleanliness. Ventilation must be performed taking into accounts the proposals presented in section 2.

When the patient enters the spirometry room:

- Gloves, if any, will be removed, and will perform hand hygiene with hydroalcoholic solution.
- Patient will be instructed not to touch any surface in the room.
- The facemask will be removed, from back to front, only during the test.

When leaving the spirometry room:

- The patient will again perform hand hygiene with hydroalcoholic solution and will put on the mask.
- Patient will be instructed that when getting home, he/she should wash his/her clothes in hot water, and air out clothes that cannot be washed.

After completing the test for each patient, the room will remain empty for at least 15 minutes for adequate ventilation and cleaning. Ventilation must be performed taking into account the proposals presented in section 2.

6. Spirometry

As spirometry measures the maximal volume of air that an individual can inspire and expire with maximal effort, it constitutes a fundamental procedure in the assessment of general respiratory health. In asthma, spirometry plays a key role in achieving the proper diagnosis of the disease and in the evaluation of patients at risk of having an asthma exacerbation [26].

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The major goal of infection control should always be the prevention of the transmission of infection to patients and staff during the manoeuvres, whenever the procedure is performed. However, in the context of a post-pandemic scenario, some additional safety precautions during spirometry must be kept in mind as, in less proportion to other lung function tests, it also could generate aerosols through its potency for coughing and droplet formation.

Performing the procedure, direct contact with surfaces could transmit the infection. The professional ought to maintain a minimum of 1 meter distance to the patient. Physical barriers might be useful to avoid direct contact with the staff and/or the equipment, and a proper regular room ventilation is mandatory wherever negative pressure in testing areas is not available. To diminish the infection risk, it is recommended to use single-used mouthpieces and nose-clips, and to clean the testing space between patients with appropriate cleaners, wiping-down contact surfaces such as handheld spirometers, chair arms, tables, and immediate proximal surfaces of tubing and valves, with appropriate wipes with alcohol or other approved disinfectants. In-line bacterial and viral filters are needed with minimum proven efficiency for high expiratory flow of 600-700 L/min [1]. Each lab should continue using their usual pneumotachographs as long as they meet the ATS / ERS quality standards[28] and cleaning them according to the protocols of each manufacturer. The cleaning protocol for pneumotachographs and all their removable parts requires a high-level cleaning and disinfection process, which includes cleaning with enzymatic soap or non-enzymatic detergent, disinfection by prolonged immersion in a disinfecting solution, rinsed with sterile water and dried with sterile compresses. The pre-screening of patients and the use of antibacterial /

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antiviral filters are sufficient for this process to be carried out only at the end of each work day (morning or afternoon), although it is also exceptionally recommended after examining patients with a very intense cough or bronchorrhea.If there is suspicion of any type of infectious pathology, they should be changed after the patient has been explored or single-use pneumotachographs must be used. Also in the alleged case of outbreaks of the pandemic by COVID 19. Whenever the pneumotachograph is changed and in the case of single-use pneumotachographs, a volume calibration should always be done. In the case of facing the acquisition of new lung function equipment, current circumstances may reinforce the choice of disposable combined nozzle/ pneumotachograph equipment, in general, by using Lilly-type pneumotachographs.

Regarding personal protective equipment, it is necessary in all circumstances and the professional well trained in how to put on, remove and dispose of it [27]. The use of either FPP2 or FPP3, eye protection (face shield or googles), nitrile gloves should be discarded after each patient, and standardized gown and apron would be adapted to the different phases of pandemic standards would require. Hand hygiene with an alcohol-based hand rub should be performed between patients.

In a very low pre-test probability of infection settings, spirometry will be implemented according to conventional standards [28] but these recommendations may supersede to return to strict safety measures if the risk/benefit ratio would also continue to change over time. Bronchodilator responsiveness testing must be perform with a bronchodilator MDI inhalator attached to valve spacing chamber [1].

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7. Oscilometry

Oscillometry is performed at tidal volume, being easily carried out by both children and adults who are incapable or in whom it is not advisable to perform forced expiratory manoeuvres. Potentially, it involves a lower ability to generate aerosols or induce coughs. The technique is now well standardized and ready to be used in daily clinical practice, and it has also been defined that it is considered a positive bronchodilator response (an absolute increase in R5 equal to or greater than 40% of the baseline situation), which facilitates its implementation as a diagnostic test [29]. Furthermore, various studies, and computational lung models, have suggested that 5Hz (R5) -resistance to 20Hz (R20) is an anatomically sensitive measure of small airway disease [30, 31]. This parameter seems to have a close relationship in both asthma control and quality of life, and can be used to predict responses to therapeutic intervention, which gives it qualities for clinical use that are superior to the classic spirometric parameters.

8. Bronchial challenge tests

Bronchial hyperresponsiveness (BHR) is an abnormal increase in airflow limitation following exposure to a non-allergic or allergic stimuli. BHR to different stimuli like allergens, methacholine o hypertonic saline is a characteristic feature of asthma; nearly all patients with asthma exhibit increased responsiveness, but is not specific and also is present in chronic obstructive

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pulmonary disease (COPD) [32]. In general, bronchial hyperresponsiveness is frequently used to help diagnose and characterize individuals with airway diseases. Methacholine bronchial challenge is especially relevant in ruling out asthma [32].

These tests include the use of direct agents (direct effect on airway smooth muscle) as methacholine or histamine and indirect agents (act by causing the release of endogenous mediators) as adenosine, mannitol, eucapnic voluntary hyperpnoea of dry air (EVH), non-isotonic aerosols, different types of exercise tests, aspirin/NSAID and occupational and non-occupational allergens.

Direct airway challenges have been used widely and are well standardized [33,34]. They are highly sensitive in comparison with indirect tests but are not interchangeable [35]. Indirect bronchial stimuli may reflect more directly the ongoing airway inflammation and are therefore more specific to identify active asthma or subtypes of asthma as exercise-induced bronchoconstriction (exercise test or EVH) [36].

Inhalation protocols of some agents (methacholine, histamine, adenosine, aspirin, allergens) include a dosimeter (five breath method) or the 2-min tidal breathing method with a breath-actuated or continuous nebulizer. In both types of inhalation protocols is mandatory to use a validated expiratory filter to avoid air room contamination with the substance and exhaled particles from the patients. The risk of expiratory flow leakage is lesser in the dosimeter technique. Thus, it is recommended in our current situation. Inhalation of non-isotonic aerosol requires high airflow nebulizers, and therefore its use is not recommended. Mannitol inhaled as a dry powder could be another safe alternative [12], but frequently induces cough. Bronchial challenge tests with

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allergens are seldom indicated. Still, they may allow for the demonstration of a direct relationship between the allergen and the bronchial response, and also for studying mechanisms of disease and efficacy of a therapeutic intervention [37]. In the case of bronchial challenges with occupational agents, its use is more frequent since it is considered a “gold standard” method to demonstrate occupational asthma/hypersensitivity pneumonitis, and therefore necessary in some cases [38]. These challenges should be performed in enclosed challenge rooms equipped with an adequate exhaust ventilation system or using closed-circuit devices.

A summary of the recommendations suggested to perform bronchial challenge tests, faced to prevent exposure to potentially harmful aerosols to technicians and the tested patient, are presented in table II. Performing RT-PCR immediately before the procedure should be considered .

9. Lung volumes

Lung volumes testing provides indices such as total lung capacity (TLC), residual volume (RV) or functional residual capacity (FRC), which are useful to assess lung mechanic. Measure procedures by either plethysmography or dilutional gas methods are widely standardized [41]. Although it may slightly overestimate the lung volumes [42], plethysmography is the preferred method in patients with asthma because dilutional methods lead to a greater underestimation of lung volumes [43]. Moreover, plethysmographic lung volumes discriminate asthma severity [44].

The main indications for plethysmography in asthma are air trapping identification, evaluation of lung hyperinflation, assessment of obese patients

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with asthma, and confirmation of a restrictive disorder. Air trapping, usually defined by an increase of RV or RV/TLC ratio, is frequent in patients with severe asthma [45] and correlates with inflammation [46] and airway responsiveness [47]. Some studies have reported normalization of RV in patients with non-severe asthma receiving inhaled corticosteroids [45] or after montelukast treatment [47]. Other times, air trapping may be the first functional manifestation of mild asthma, prior the development of spirometric abnormalities [48].

Plethysmography is necessary to detect lung hyperinflation, which may be caused by airway narrowing or by loss of elastic recoil, increasing FRC [45]. Evaluation of this disorder is particularly important in asthmatic patients with fixed obstruction because it has been attributed to an increase in lung parenchyma distensibility [49].

In obese patients with asthma, the determination of lung volumes allows to discriminate the impact of both entities on lung function and, eventually, on respiratory symptoms. Unlike asthmatics, obesity causes a decrease in the FRC and RV, with an even greater reduction in expiratory reserve volume [50]. On other occasions, it is necessary to know the value of the lung volumes to confirm or rule out a possible restrictive alteration, a circumstance reported in up to 8% of asthmatic patients [51]. This is particularly relevant in patients with air trapping, in whom a reduction in FVC can cause a falsely normalized FEV_1/FVC ratio [52].

The need to remain inside a closed cabin during the plethysmography can favor the storage of droplet aerosols, mainly if the patient coughs during the test. Therefore, this exploration should be delayed until the local epidemiological

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scenario corresponds to a low COVID transmission rate. An adequate ventilation of the cabin must be guaranteed for at least 15 minutes after each test. Moreover of high-level cleaning and disinfection of the pneumotachograph, cabin seat and walls as well as all contact surfaces must be cleaned with non-enzymatic soap or alcoholic solution. Ventilation should be done judiciously and always taking into account the recommendations given in section 2.

10. Diffusing capacity

Lung diffusing capacity of carbon monoxide (DLCO) represents the gas transfer from alveoli to pulmonary capillaries. According to current guidelines [53], the single-breath technique is the method of choice and GLI reference values are available for evaluation [54].

Low DLCO has been generally described in anemia, emphysema, interstitial lung diseases or pulmonary vascular diseases [48]. Whereas alveolar destruction decreases DLCO, in asthma, DLCO is typically preserved or may even be elevated [55], due to either increased pulmonary blood flow or reduced apparent alveolar volume (VA) [56]. Therefore, diffusing capacity can help discriminate between asthma-COPD overlap (ACO) and adult-onset asthma, with lower values of DLCO and DLCO/VA among ACO patients compared to those with asthma and fixed airflow limitation [57-59].

In another area, DLCO measurement is useful to evaluate occupational exposure, mainly the identification of longitudinal decrease in at risk workers [60]. In hypersensitivity pneumonitis (HP), the DLCO reduction is also frequent [61], reaching prognostic significance. In a large cohort of HP patients, DLCO decrease was associated with reduced survival, along with older age, a low

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percentage of lymphocytes in bronchoalveolar lavage, the presence of honeycomb on chest examination and the usual interstitial pneumonia histologic pattern [62]. Moreover, DLCO is sensitive to some therapeutic interventions, such as exposure avoidance or corticosteroid treatment [63].

Under normal circumstances and with an adequate technique, the infectious transmission risk of DLCO measurement is similar to spirometry. Therefore, both procedures can be considered from the post peak phase of COVID pandemic, with a low community prevalence, as long as the required protection and disinfection measures are guaranteed.

11. Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) provides a integrative assessment of exercise physiology, involving the cardiopulmonary, neuromuscular and metabolic responses [64]. In patients with asthma, CPET is useful to diagnosis of exercise-induced bronchoconstriction (EIB), evaluate the exercise capacity and determine the limiting factors, identify dynamic hyperinflation [65] and assess the response to several therapeutic interventions (Table 1) [66].

Exercise challenge is commonly used to assess the presence of airway hyperresponsiveness [67]. According to ATS guidelines [68], exercise protocol must induce for at least 4 minutes a ventilation of 40% to 60% of the maximal voluntary ventilation, followed by sequential measurements of FEV_1. This supposes a considerable level of hyperventilation and a large duration of the test. EIB allows establish the diagnosis of asthma, especially in subjects with normal spirometry, minimal reversibility and high probability of asthma [43]. Moreover, it can serve to stratify the severity of asthma [69]. Exercise challenge

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has a high specificity for the diagnosis of asthma, mainly in children [70], but its sensitivity is low [67,71].

CPET utilization can precisely define the mechanism of persisting symptoms in patients with difficult asthma and guide the steroid reduction in those without ventilatory limitation [72]. CPET is also valuable tool for differentiating the physiological changes induced both by asthma or obesity [73,74] and, therefore, might be applied to assess the cause of breathlessness among obese subjects with or without asthma [75].

Duration of CPET and the hyperventilation level achieved increase the risk of aerosols emission and the transmission of infections. High respiratory flows does not allow coupling bacterial and viral filters in the expiratory ports of many equipments and, more importantly, there is not data about the retention efficiency of avilable filters at such high expiratory flows and for prolonged periods. Therefore, CPET should be considered a high-risk procedure and it is recommended delay its implementation until all COVID post-pandemic phases have been overcome, when the local authorities declare the situation controlled. If neccesary, consider performing PCR just before the procedure to rule out active SARS-CoV-2 infection. Even in these circumstances, maximal protection for technicians and high-level disinfection of all removable components after each test are recommended.

12. NO measurement in exhaled air (FeNO)

FeNO has proven to be an adequate tool, especially in the diagnosis of asthma, being recommended by high-quality guidelines such as GEMA 5.0 [24] or NICE [76]. Also has a well-documented role in predicting response to

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corticosteroid treatment [77], risk analysis for exacerbations [78], adherence to treatment [79], or assessing the relevance of exposure to inhalant allergens [80] The exhalation maneuver is performed at a low flow to a sealed equipment, and its ability to induce cought, is also much less than that of the forced spirometry maneuver or provocation tests. It is potentially a procedure that also it involves less risk of aerosol generation. Various techniques are currently used to analyze exhaled NO concentrations including chemiluminescence, electrochemical sensor devices, and laser-based technology [81]. The simplicity, portability, simple operation, without daily calibration processes, and its low price, have placed equipments that use electrochemical sensors such as those preferably for clinical uses, leaving chemiluminescence systems in the field of research. For FENO analyzers, is mandatory the use of antibacterial / antiviral filters , it is recommended to perform the same cleaning procedure presented for the spitometers pneumotachs presented previously, with the detachable part of the flow transducer, in case it is recommended bay the manufacturer. . Since most use ultrasound transducers, the need for cleaning only affects the nozzle and socket.

Table IV summarizes the main performance and safety characteristics of the equipment availables on the market. Currently there are systems that make the measurement without needing to carry out a previous inhalation through the equipment, but directly from the environment. These systems have been shown to make accurate and reproducible measurements. On the other hand, some of these eNO measurement equipment can be operated remotely by remote connection to laptops or tablets, which allows the operator to be at an adequate distance from the patient, while monitoring the test and guiding the patient in

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the performing a correct maneuver. Finally, some of these devices, such as evernoa or Vivatmo, offer equipment for home monitoring of the patient [84,87]. FeNO could potentially be considered as a crucial help in diagnosing and monitoring asthma patients in this post.pandemic phase [92]

13. Cytologial analysis of induced sputum samples

Currently, sputum induced inflammatory cell counts represent the most effective non-invasive screening for bronchial inflammation and a valuable tool for predicting therapeutic responses in patients with asthma [93,94]. However, to obtain the induced sputum sample, induction through an ultrasonic nebulizer is required, usually with hypertonic saline (at incremental doses) with the next expectoration of the patient's mucus, for this reason this procedure is considered to be of high risk of contagion in patients with SARS-CoV-2 infection.

Another potencial scenario could be ussing mannitol to induce sputum samples. Hypertonic saline and mannitol showed similar capacity to produce valuable sputum samples and eosinophilic phenotype remained stable in most patients with both stimuli [95, 96]. Dry powder mannitol challenge is a procedure that has less capacity of aerosol generation [12].

One aspect to consider of this technique is that despite all the utilities that sputum induced may have in normal clinical practice, this test is complementary and its results help the professional to make clinical-therapeutic decisions in an appropriate context, but they are not essential. For this reason, this test should not be performed in patients with suspected or diagnosed

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coronavirus, nor should it be performed during the peak period of a coronavirus pandemic.

Due to the current situation of uncertainty about the evolution of the COVID-19 pandemic, it must be selective when choosing patients and be rigorous in the indication, limiting it to those in selected cases in which the sputum result helps direct a treatment that can change the evolutionary course of the disease. This situation would occur, for example, in the case of a severe asthmatic in whom the initiation of a biological treatment depends on his inflammatory pattern in sputum or one already treated in whom we consider suspending treatment or performing a switch due to inadequate response [97, 98]. So, once professionals begin their activities and routine post-COVID-19 testing, a series of recommendations should be followed for testing and personal protection, as well as disinfection measures should be carried out as if all patients were suspected of having the disease.

13.1 Preparing the patient

Before going to the test planning, the patient must have an informative material that explains the measures that must be complied with, such as: not going to the visit if there are symptoms of fever or respiratory infection, going to the visit with a surgical mask, performing adequate hand hygiene, as well as explanation on the procedure to be performed.

In a pandemic period and prior to performing the test, it is advisable to assess the patient 24-72 hours before, for the search for COVID-19 symptoms, we will question him about contacts with diagnosed or symptomatic people and we will perform a polymerase chain reaction (PCR) to detect SARS- CoV-2.

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13.2 Physical space

The ideal physical space to perform sputum induction is in negative pressure booths. If these booths are not available at the test center, a future alternative would be to create booths or areas that have portable fans with high efficiency particulate air (HEPA) filtration [99]. These devices can increase the effective air changes per hour of clean air to the patient room, reducing the risk of people entering the room without respiratory protection. NIOSH (National Institute for Occupational Safety and Health) has developed a guide for using portable HEPA filtration systems to create convenient patient isolation rooms. The minimum recommended space is 2,5x3 m because transmission through secretions from infected persons by contact with droplets larger than 5 microns is up to two meters. The room should also have patient-accessible tissues (for single use only), waste containers with a lid opening with a foot pedal. The working surfaces of the room should be free of any materials to facilitate cleaning later.

If this physical space is not available, another option would be to have two rooms, one where the nebulization is performed and the stimulation of the productive cough together with another adjoining room separated through a glass where the spirometry could be performed of control.

The estimated time to achieve correct ventilation in the room where the test is carried out is 15 minutes and the estimated time for cleaning surfaces and components in a 2.5x3m room is 5 minutes [11]. Ventilation should be done

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judiciously and always taking into account the recommendations given in section 2.

13.3 Personal protective equipment

Personnel should be provided with long-sleeved waterproof gown, mask FPP2 or preferably FPP3 (if available), integral frame eye protection or full face shield, double gloves, hydroalcoholic solution (UNE 14476), for patient and staff to wear before, during and after the procedure, closed hospital footwear [99].

13.4 Induction and sample collection

To perform the induced sputum technique, the personnel performing the test should explain to the patient what induction and sample collection consists and this should ideally maintain a distance of 2 meters. The procedure for the extraction of the mucus and the placement of the sample in a waterproof, sterilized, disposable container with a screw cap, identified and then transferred with a double bag to the place of processing, should also be explained.

For the safety of the test and prior to induction with hypertonic saline, the administration of bronchodilator should always be done with a pressurized MDI canister and a double valve spacer chamber, which can be dismantled for correct disinfection.

13.5 Sample processing

Once the sputum sample has been collected, it must be processed in Class II certified biological safety cabinet (BSC) with additional precautions to provide a

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barrier between the sample and the personnel. Examples of these additional precautions include personal protective equipment (PPE), such as a surgical mask or face shield, or other physical barriers, such as a splash guard; centrifuge safety cups; and sealed centrifuge rotors to reduce the risk of exposure to laboratory personnel. Before and after working in this type of cabin, the ultraviolet light should be applied for 30 minutes. Each time a tube or other material is introduced or removed from the biosafety cabinet, it should be pre-sprayed with 70% (v/v) alcohol or 10% (v/v) bleach. Make sure that all tubes are properly capped and closed before removing them from the biosafety cabinet. If possible, use pipette tips with filters to prevent the generation of aerosols [100, 101,102]*.*

13.6 Cleaning of material and physical space

For cleaning nebulizers and other materials to be used for sputum induction, we recommend Peracetic Acid, STERIS® 20 or Glutaldehyde-Phenolate, at a dilution of 1/16 for 10 min* (3min). For cleaning other surfaces, we recommend a virucidal antiseptic (UNE 14476).

The residues generated are considered to be class III or as special bio-sanitary waste of group 3 (similar to tuberculosis). Currently, there is no evidence to suggest that these laboratory residues require additional packaging or disinfection procedures.

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14. Risks and safety in upper airway diagnostic tools

14.1. Anterior rhinoscopy and nasal endoscopy

Anterior rhinoscopy makes a quick but limited internal inspection of the anterior parts of the nasal cavities, evaluating the presence of nasal discharge or mucosal swelling, crusting, septal desviations and perforations, and/or large nasal polyps. Compared with the anterior and posterior rhinoscopy, nasal endoscopy offers the advantage of a global evaluation of the endonasal cavity, from the vestibulum to the cavum [103]. Endoscopic examinations such as nasal endoscopy are associated with airborne aerosol production irrespective of whether a rigid or flexible scope is utilized, require prolonged close proximity to the patient, and carry a distinct yet unpredictable risk of triggering sneeze events [104]. Extremely care should be taken when performing nasal examination with these tools during COVID-19, and performing RT-PCR immediately before the procedure should be considered.

The objectives of diagnostic nasal endoscopy are: 1) the physical examination of the nasal cavities and paranasal sinuses, 2) to assess nasal abnormalities, severity, and to follow-up of sinonasal diseases, and 3) to obtain a biopsy for differential diagnosis [105].

a) Site conditions:

The patient sits in an upright position and the scope is gently passed through the nasal cavity to the back of the nose.

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b) Safety for personnel and patients:

Protection protocols have been developed during endoscopic procedures including protective clothing, N95 masks, goggles, face shields, and hand and feet covers [106].

c) Equipment:

Nasal endoscopy is performed by a flexible or rigid scope attached to a light source by glass fiber. For diagnostic examination, an endoscope with an optic angle from 0–45° is used with a caliber of 2.8–4 mm. When used, a liquid sterilization of endoscopes during 5 minutes should be done.

The Slide-On EndoSheath System is a sterile, disposable cover for flexible endoscopes that provides a latex-free barrier between the scope and the patient. The system is designed to reduce patient contact with organic debris and staff exposure to hazardous chemicals. When an endoscopic procedure is completed, the sheath is discarded, and the endoscope is wiped with alcohol and reused [107].

d) Pre-treatments:

In general, no pretreatment is mandatory. If an examination is difficult to perform, bothersome, and/or painful, local anesthesia (lidocaine, cocaine) may be used. A nasal decongestant may useful mainly in the presence of nasal deviation, turbinate hypertrophy or swollen mucosa [105]. An individual set application is recommended to avoid viral transmission among physicians and patients in the COVID-19 outbreak.

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14. 2. Assessment of nasal obstruction and patency

14.2.1. Acoustic rhinometry:

Acoustic rhinometry (AcR) is a non-invasive technique for assessing nasal airway obstruction [108], mainly nasal cavity geometry (volumes and areas). It can be indicated to evaluate nasal airway obstruction in both adults and children [109],in allergic and non-allergic rhinitis, before and after surgery (septoplasty, turbinoplasty, sinus surgery, facial/cosmetic, maxillofacial expansion procedures, adenoidectomy), cleft lip, palate, or nose, antrochoanal atresia, sleep disorders, mechanical nasal dilation. It also can also be used for allergen [110] and aspirin [111] nasal provocation.

a) Site conditions:

AcR is a quick (10 seconds per reading), painless, non-invasive, and reliable technique to be used in both children and adults which provides a topographic map of nasal blockage with details of type (reversible or non-reversible) and location (anterior and mid, less in posterior) with numerical quantifications of nasal volumes and areas [112]. When needed and with appropriate prevention and nasal cannula sterilization is the recommended technique to be used to assess nasal obstruction in the COVID-19 outbreak.

b) Safety for personnel and patients:

1. Site: in both hospital and ambulatory settings.

2. Personnel: a well-trained physician or nurse should perform AcR.

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3. Emergency equipment availability: not required.

4. PPE: AcR has a low risk of aerosolization. During the COVID-19 outbreak, the use of a FFP2 or FFP3 face masks, goggles, or disposable face shield is recommended for the health professional.

c) Equipment:

AcR uses an audible reflected sound wave that is converted to produce an area-distance graph. The measurement provides information on the nasal structures, either as a measure of nasal volume over a standard distance into the nostril or as the minimal cross-sectional area within the nasal cavity.

d) Other considerations: Consider single-use equipment or sterilization if they are in direct contact with patients. The exam should be avoided in case of suggestive respiratory or systemic symptoms of COVID-19.

14.2.2. Anterior rhinomanometry:

Anterior rhinomanometry (RMN) is a non-invasive technique for assessing nasal airway obstruction, mainly for nasal patency (flows and resistances). Having similar indications than AcR. Due to problems in effective material sterilization, this technique is not recommended during the COVID-19 outbreak.

a) Site conditions:

Active anterior RMN is a functional test of nasal aerodynamics that measures transnasal airflow (flow rate) and the pressure gradient allowing calculating nasal resistance to evaluate nasal airway obstruction [113].

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b) Safety for personnel and patients:

1. Site: in both hospital and ambulatory settings.

2. Personnel: a well-trained physician or nurse should perform Anterior RMN.

3. Emergency equipment availability: Not required.

4. PPE: RMN has a high risk of aerosolization. If AcR is not available, it should be performed with the highest standard of PPE during the COVID-19 outbreak.

c) Equipment:

Depending on the position of the probes for registration, anterior or posterior rhinomanometry can be performed, both being valid techniques. When the probe is placed in the mouth, posterior rhinomanometry values can be obtained for both nasal cavities together or for one nasal cavity when sealing of one nostril. In anterior rhinomanometry, the pressure-sensing tube is placed in one nostril and data represent unilateral pressure and flow measures [114].

d) other considerations:

In men, facial shaving is ideal for a good seal of the facemask. We recommend avoiding the test during COVID-19 outbreak. If the examination cannot be delayed. AcR should be preferred.

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14. 2.3. Peak Nasal Inspiratory Flow (PNIF)

PNIF attached to anesthesia mask measures nasal volume and flow for assessing nasal airway patency. Indications for use are similar to AcR and RMN. Due to problems in effective material sterilization, this technique is not recommended during the COVID-19 outbreak.

a) Site conditions:

PNIF is an easy, portable and cheap method for assessing nasal patency. During COVID-19, we recommend performing the test with a single-use mask, and siting an antiviral filter between the mask and the PNIF device.

b) Safety for personnel and patients:

1. Site: in both hospital and ambulatory settings
2. Personnel: a well-trained physician or nurse should perform PNIF.
3. Emergency equipment availability: not required
4. PPE: PNIF has a high risk of aerosolization [115].

c) Equipment:

It requires a single-use nose and mouth mask and measures the maximum volume (liters per minute) inspired during a single maximal forced nasal inspiration, it could be performed using both nostrils simultaneously or by using each nostril by turn. It is recommended to record the average reading of the best of 3 maneuvers.

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d) Other considerations:

In case of suggestive respiratory or systemic symptoms of COVID-19 the exam should be avoided . If available, AcR should be preferred over PNIF. In men, facial shaving is ideal for a good seal of the face mask.

14. 3. Nasal Nitric Oxide (nNO)

nNO is a colourless and odourless gas present in exhaled air through the mouth or nose and a marker of sinonasal inflammation [116].

a) Site conditions: Much higher levels (up to 20 times) of nNO are produced in the upper (mainly from maxillary sinuses) than in the lower respiratory tract [117]. nNO can also be measured by chemiluminescence, using non-invasive techniques. It is a reliable measure of upper airway inflammation in allergic rhinitis but not in CRS with nasal polyps. An important decrease of nNO may alert the clinician for a potential defect in mucociliary clearance related to ciliary dyskinesia [114].

b) Safety for personnel and patients:

1. Site: in both hospital and ambulatory settings.
2. Personnel: a well-trained physician or nurse should perform nNO.
3. Emergency equipment availability: Not required.
4. PPE: nNO has a high risk of aerosolization [115]. nNO should be suspended during the current COVID-19 pandemic [118]. In cases of extreme need, health professionals should use an appropriate PPE.

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c) Equipment: . Similar care than for exhaled NO should be taken.

d) Other considerations: Inhalation of nitric oxide (NO) gas is currently being investigated as a preventive measure and treatment against COVID-19 (e.g., clinical trials) [119].

14.4. Sensory assessment

14.4.1. Smell test / subjective olfactometry

Subjective olfactometry is a complementary exploration used in specific centers with trained personnel qualified to perform quantitative assessment of olfactory dysfunction. These tests help to study smell identification, discrimination and threshold.

a) Site conditions: Several techniques, culturally adapted, are currently available for the objective evaluation of the olfactory capacity of both children and adults [120]. In the COVID-19 outbreak, individual validated smell tests should be preferred.

b) Safety for personnel and patients:

1. Site: in both hospital and ambulatory settings.

2. Personnel: smell tests should be self-administered or performed by a well-trained physician or nurse.

3. Emergency equipment availability: Not required

4. PPE: smell tests have a low to high risk of aerosolization depending on the test applied test.

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c) Equipment: The smell test should be validated for the study population, since the different odorants are related to cultural influence for each population. A universal smell test is available for children (U-sniff) but not for adults.

d) Other considerations: Both patients and health professionals should avoid perfumes or body creams on the day of the test. Concerning the COVID-19 pandemic situation, remote use of validated tools (e.g. visual analogue scales, ordinal scales, patient-reported outcome measures, telemedicine) should be considered in those patients whose psychophysical tests are not possible due to high risk of disease transmission [121, 122]. Although these findings should be interpreted with caution [120, 123]. Concerning instrumental smell assessment, a reusable smell test should be avoided. We encourage single-use smell tests such as the University of Pennsylvania Smell Identification Test (UPSIT), that can be self-performed, each one containing scratch and sniff microencapsulated odors [124]. If used in other countries tna US the test should be properly validated [125].

14. 4.2. Chemical gustometry

In COVID-19 outbreak where both smell and taste dysfunctions have been reported the clear discrimination of flavor (smell + taste) from real taste is mandatory [122].

a) Site conditions: Psychophysical chemical gustatory test is performed by applying chemical substances to the patient's tongue for the identification of

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sweet, salty, sour/acidic or bitter taste perceptions. Gustatory assessment can be achieved by threshold, recognition, and/or supra-threshold measures [120].

b) Safety for personnel and patients:

1. Site: in both hospital and ambulatory setting

2. Personnel: gustatory tests are self-administered or by a well-trained physician or nurse.

3. Emergency equipment availability: not required.

4. PPE: gustatory tests have low risk of aerosolization if individualized test kits are used.

c) Equipment: Taste substances (sweet, salty, sour/acidic, bitter) using individualized kits should be preferred during the COVID-19 outbreak.

f) Other considerations: Meals should be avoided one hour before the test. Considering the pandemic situation, reusable gustometry tests should be avoided. We encourage single-use chemical gustometry tests (individual kits) that can be self-performed such as “Taste Strips” [126].

14.5. Nasal sampling (washing, smear, biopsies)

A variety of methods have been used to evaluate the inflammation of the nose and sinuses within the nasal mucosa and secretions [127][Serrano 2012].

a) Site conditions: These approaches include nasal lavage (nasal cavity is washed to flush out mucus ad debris), cytology (swab with nasal secretions), and nasal biopsy (extraction of sample cells or tissues for its histological study)

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b) Safety for personnel and patients:

1. Site: in both hospital and ambulatory settings.

2. Personnel: should be performed by a well-trained physician (in case of biopsies or smears) or nurse (in case of smears).

3. Emergency equipment availability: for potential vasovagal adverse reactions, a reclining chair or a litter should be available.

4. PPE: high risk of aerosolization, non-urgent procedures should be avoided mainly during COVID-19 outbreak. If necessary, we recommend performing biopsies and smears with the highest standard of PPE described above.

c) Equipment: Local anaesthesia and small forceps for biopsy, saline and syringe for nasal lavage and swab for nasal smear.

d) Other considerations: It is recommended avoid this procedure in patients under anticoagulant therapy. If a procedure is required to be performed in a COVID-19 patient, consider performing it in an operating room adapted for this pathology with proper PPE.

Concluding remarks

The purpose of this document has been to summarize the available information, evidence, and guidance for infection control relevant to lung, nasal function testing, and other respiratory techniques in patients during the era after the pandemic caused by the COVID-19. We are hoping to facilitate the daily practice to researchers and clinicians that tackle allergic respiratory diseases like asthma or allergic rhinitis. Our greatest wish is also we all get a lesson from this bitter experience we are living. This lesson should help us to carry out an evaluation of our patients with the best quality and safety standards, and at the

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same time to adding real value to the diagnosis and treatment of their diseases. The changing situation of this disease may cause some modifications of the assertions presented in this review in the future. While this guidance seeks to ensure a consistent wide approach, some differences in operational details may be applied due to local regulations.

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FIGURE LEGEND

Figure. Possibles mechanisms of SARS-CoV-2 transmission during airways assessment.

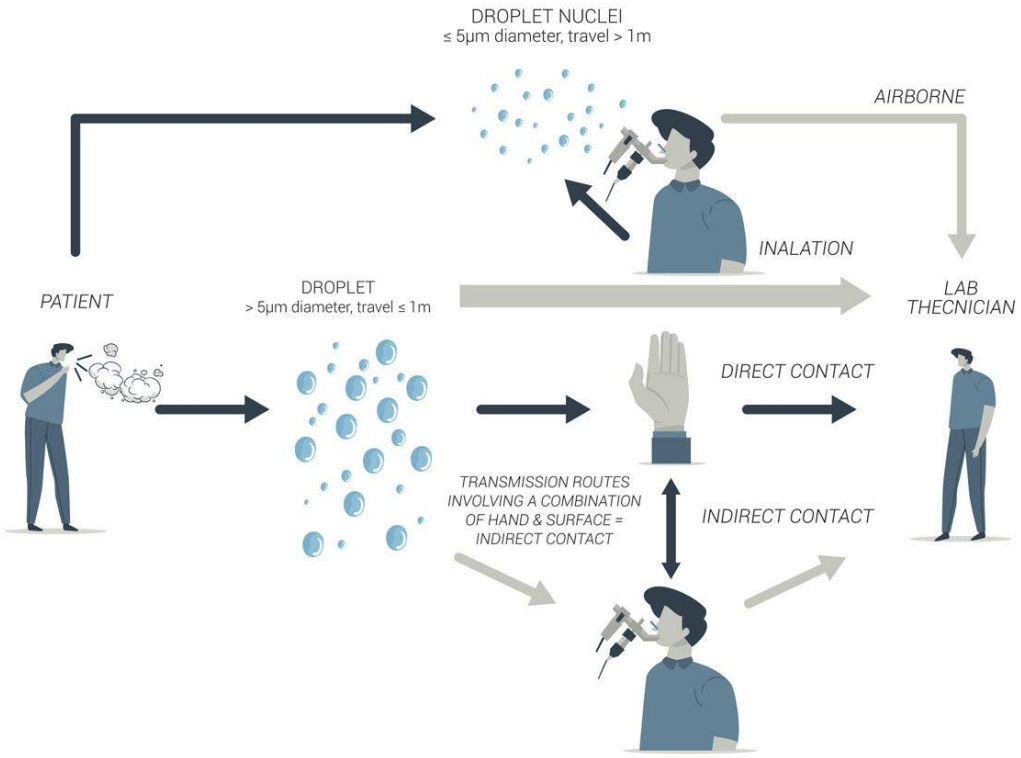

Table 1. Commonly accepted respiratory routes of viral transmission.

Transmission route	Particles involved and characteristics	Characteristics/definition of transmission
Contact		Self-inoculation of mucous membranes by contaminated hands. Virus transfer from one infected person to another. Virus transfer through contaminated intermediate objects (fomites).
Direct	Deposited on persons	
Indirect	Deposited on objects	
Airborne		
Droplet	Droplets (>5µm) Remain only shortly in air (<2 min) Dispersed over short distances (1-2m)	Short range transmission. Direct inoculation on naïve person through coughing/sneezing/breathing of infected person. Deposition mainly on mucous membranes and upper respiratory tract
Aerosol	Aerosols, droplet nuclei (<5µm) Remain in air for several hours Dispersed over long distances (1-10m)	Long range transmission. Inhalation of aerosols in respirable size range. Deposition along the respiratory tract, including the lower airways.

Modified from reference [5].

Table 2. Recommendations to be followed in different bronchial challenge tests.

Procedure	Phase recommended (SEPAR)	Aerosol generating procedure (AGP)	Assume AGP if patient Coughing **,: add Disposable fluid-resistant coverall/gown-FFP3 mask or equivalent)	Appropriate protection for the operator: surgical mask, plastic apron, gloves and visor	Precautions for Patients use hand gel prior to entering and on leaving . Face mask	General infection control measurements: filters, wiping down contact parts with appropriate wipes between patients, etc.) or following instructions of manufacturers	Negative pressure room
Methacholine/Adenosine Tidal volume or dosimeter	4	NO	+	+	+	+	if available
Mannitol	4	NO	++	+	+	+	if available
Exercise Treadmill or cycle ergometer	4	NO	+	+	+	+	NO
Eucapnic hyperventilation	4		+	+	+	+	If available
Non-isotonic aerosols	4	YES	+	+	+	+	Recommended
Allergens/aspirin Tidal volume or dosimeter	4	NO	+	+	+	+	If available
Occupational agents	4	YES***	+	+	+	+	Mandatory *** in close circuit chamber

*In all patients with or suspected COVID-19 infections these test should not be done.
** Coughing are not classified as AGP in some guidelines (Ontario, Canada)
*** for chemical or use tests
SEPAR: Phase 3: Post-peak phase, Phase 4: post pandemic, ERS: Phase 2: Post-peak phase, Phase 3: post pandemic [12]
Modified from References: [11, 12, 37,38]

Table 3. Summary of the main alterations identified with cardiopulmonary exercise testing in asthmatic subjects*

Functional disorder		Main parameters	Characteristic findings
Exercise-induced bronchospasm		FEV_1 post-exercise	>10% fall from baseline value
Dynamic hyperinflation		IC during exercise	Any decrease from baseline
Exercise intolerance		VO_2 peak, Wpeak AT	Decreased (< LLN or <75% pred.) Decreased (< 40% VO_2max)
Exercise limiting factors	Ventilatory mechanical limitation/respiratory muscles dysfunction	BR VT/VE relation Peak *f*	Decreased (< 15%) Early plateau of VT Increased (>55 min^{-1})
	Gas exchange limitation	VE/VCO_2 Peak VD/VT SpO_2 during exercise	Increased (>35 at AT) Increased (>0.25) Desaturation (ΔSpO2 >4%)
	Pulmonary vascular disease	AT VE/VCO_2	Decreased (<30-40% VO2 max) Increased (>35 at AT)
	Cardiac dysfunction	Peak VO2/HR HR slope ECG record Blood pressure	Decreased (<60% pred.) Increased (>12.5 1/ml/Kg) Arrhythmia ∆ DBP >15 mmHg
	Ischemic cardiac disease	ECG record AT HRR	Alterations of ST segment, Q wave… Normal or low (<40%) Abnormal (>50 min^{-1})
	Deconditioning	Peak VO_2/HR HR slope Borg dyspnoea scale	Normal Increased (>12.5 1/ml/Kg) High scores
	Peripheral myopathy	Serum lactate level AT	High (> reference values of local lab.)

		$\Delta VO_2/\Delta WR$ Borg limb fatigue scale	Low (<40% VO2max) Energetic inefficacy (>15 ml/min/w) High Borg fatigue scores
	Anxiety	Breathing pattern HR VE response to VCO_2	Rapid shallow breathing Resting tachycardia and higher HR during exercise Higher than reference values
	Motivation	HR HRR AT RER	Small increase form baseline High (> 50 min^{-1}) Not reached < 1.0
Vocal cord dysfunction		Flow-volume curve during exercise	Inspiratory flow plateau
Changes after treatment		Wpeak VO_2 peak, AT Isotime VE, BR, VE/VCO_2, VO_2/HR or Borg dyspnoea	> MCID (5-10 w) Significant increase (MCID?) Any significant increase

*Abbreviations: FEV_1, forced expiratory volume at 1 second; IC, inspiratory capacity; VO_2, oxygen uptake; W, work rate; LLN, lower limit of normal; AT, anaerobic threshold; BR, breathing reserve; VT, tidal volume; VE, ventilation; *f*, breathing frequency; VE/VCO_2, carbon dioxide ventilatory equivalent; VD/VT, dead space volume/tidal volume ratio; SpO_2, oxyhemoglobin saturation; VO_2/HR, oxygen pulse; HR, heart rate; ECG, electrocardiogram; BDP, diastolic blood pressure; HRR, heart rate reserve; $\Delta VO_2/\Delta WR$, energetic efficacy; VCO_2, carbon dioxide production; RER, respiratory exchange ratio; MCID, minimal clinically important difference.

Table 4. Comparative performance and safety characteristics of the FeNO electrochemical sensors.

	Performance				Safety			
	Range (ppb)	Precision	Accuracy	Cross reactivity of the sensor	Inhalation manoeuvre	Remote operation, with option for patient remote guiding	Connector > 2m	[Ref]
Niox Vero (Circassia)	5-300	FeNO<3: <30 ppb FeNO≥3: <10%	FeNO<50:5ppb FeNO >50: 10%	Not present	Through the device	Yes	No	[82,83]
Evernoa (EVERSENS)	5-300	FeNO< 50 : ±2ppb FeNO >50 ppb:≤ 3%	FeNO<50: 4 ppb FeNO>50:8%	Not present	Ambient air	Yes	Yes	[84,85]
FenomPro (SPIROSURE)	5-300 o 10-200	FeNO <5 ppb: 10%	FeNO<50: 5 ppb FeNO>50: 10%	High for acetonitrile. Measurement with less clinical significance for smokers	Ambient air	No	No	[86,87]
NOBreath (BEDFONT)	0-500	FeNO<50 :5 ppb FeNO >50 10%	FeNO<50:5ppb FeNO >50: 10%	Hight for CO Measurement with less clinical significance for smokers	Ambient air	Yes	No	[88,89]
Vivatmo(BOSCH)	5-300	FeNO <50: 5 ppb FeNO > 50: 10% FeNO >160: 15%	FeNO<50: 5 ppb FeNO > 50: 10% FeNO>160: 15%	Not specified	Ambient air	No	No	[90,91]

Abbreviations: FeNO: fractional exhaled nitric oxide, ppb: parts per billion, Ref: references