AAAAI Work Group Report

American Academy of Allergy Asthma & Immunology

Pulmonary Procedures During the COVID-19 Pandemic: A Workgroup Report of the AAAAI Asthma Diagnosis and Treatment (ADT) Interest Section

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The COVID-19 pandemic has placed increased demands on the ability to safely perform pulmonary procedures in keeping with Centers for Disease Control and Prevention (CDC), American Thoracic Society (ATS), and the Occupational Safety and Health Administration (OSHA) recommendations. Accordingly, the American Academy of Allergy, Asthma & Immunology (AAAAI) Asthma Diagnosis and Treatment convened this workgroup to offer guidance. The workgroup is composed of specialist practitioners from academic and both large and small practices. Individuals with special expertise were assigned sections on spirometry, fractional exhaled nitric oxide, nebulized treatments, and methacholine challenge. The workgroup met periodically to achieve consensus. This resulting document has recommendations for the allergy/asthma/immunology health care setting based on available evidence including reference documents from the CDC, ATS, and OSHA. **(J Allergy Clin Immunol Pract 2022;■:■-■)**

Key words: *SARS-CoV-2; COVID-19; Spirometry; FeNO (exhaled nitric oxide); Pulmonary function testing; Pulmonary procedures; Nebulized medication; Methacholine challenge*

SARS-CoV-2 (COVID-19) infections were first reported in December 2019, and the World Health Organization (WHO) declared a pandemic in March 2020. The virus has caused significant morbidity and mortality worldwide.[1] The source of transmission is via respiratory droplets and aerosol particles.[2] The significance of airborne and aerosol-generating procedures (AGPs) in the dissemination of SARS-CoV-2 remains unclear.[3] Common pulmonary procedures and treatments in an outpatient setting include spirometry, fractional concentration of

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Abbreviations used
AAAAI- American Academy of Allergy, Asthma & Immunology
AGP- Aerosol-generating procedure
ATS- American Thoracic Society
CDC- Centers for Disease Control and Prevention
FeNO- Fractional concentration of exhaled nitric oxide
FEV- Forced expiratory volume
FVC- Forced vital capacity
HEPA- High-efficiency particle arrest
MDI- Metered dose inhaler
NAAT- Nucleic acid amplification test
NHLBI- National Heart Lung and Blood Institute
OSHA- Occupational Safety and Health Administration
PFT- Pulmonary function testing
PPE- Personal protective equipment
SVC- Slow vital capacity
TLC- Total lung capacity
WHO- World Health Organization

exhaled nitric oxide (FeNO) testing, nebulized treatments, and airway provocative challenges, for example, methacholine. Many of these procedures and therapies were paused during the early stages of the pandemic due to concern over transmission of COVID-19.[4] At this time, there is no expert consensus nor sufficient data to develop a definitive and comprehensive listing of AGPs and their relative risks in the health care setting. As the pandemic has evolved, some physicians have stopped performing these pulmonary procedures entirely; others have resumed them with various restrictions and risk reduction strategies.

This workgroup report has been requested by the American Academy of Allergy, Asthma & Immunology (AAAAI) to develop suggestions for the practitioner employing pulmonary testing and treatments in the current, evolving setting of the COVID-19 pandemic. The members of this workgroup represent a diverse group of allergy/asthma/immunology and pulmonary specialist physicians from various professional backgrounds including academic practice, large community practice, and smaller (including solo) community practice settings. This document is intended to contain and supplement guidance from the Centers for Disease Control and Prevention (CDC), Occupational Safety and Health Administration (OSHA), American Thoracic Society (ATS), and the available literature to assist patients, practitioners, and institutions in developing an approach to pulmonary procedures. Although guidelines are often institution specific, we hope that they may be impacted by this document and other cited evidence-based guidance from the CDC, OSHA, and ATS. We also hope that these guidelines will be helpful for providers, respiratory care practitioners, and patients. The recommendations set forth by this workgroup apply to the performance of various pulmonary procedures and treatments common in the allergy/asthma/immunology health care setting during the pandemic and postpandemic era (see Figure 1).

METHODS

Members of the workgroup were selected for their expertise and interest. After individual research and writing, the entire draft document was shared with all contributors to allow time for comprehensive refinement. The final recommendations were based on consensus opinion.

Overview of factors affecting all pulmonary procedures

Risk assessment. Risk assessment is a complex multifactorial process. The risk of COVID-19 transmission should be viewed from the perspective of the community, the individual patient, and the specific pulmonary procedure. Each element has factors that lie on a continuum of lower to higher risk. The composite summary risk of the elements is currently not fully defined. We hope to identify the elements of relative risks in each area to assist practitioners in the allergy/asthma health care setting to better assess the composite summary of risk of viral transmission (see Figure 2).

Community considerations. Risk assessment should begin with understanding the transmission risk in the local population. The CDC divides the risk of transmission into 4 categories: high, substantial, moderate, and low. The categories are based on a 1-week running composite of new cases per 100,000 and percentage of positive nucleic acid amplification tests (NAATs). The CDC provides updated community transmission levels by county at https://covid.cdc.gov/covid-data-tracker/index.html#datatracker-home.[5] Transmission risks should be used as a part of a composite with other considerations to assist in selecting appropriate levels of risk reduction strategies. For example, when there is substantial or high risk of transmission in the community, the risk of asymptomatic spread is also elevated. As a result, it would be less effective to rely on symptom-based and exposure screening, even in vaccinated patients if the community transmission levels were high. However, if the community transmission levels are low, symptom-based and exposure screening in vaccinated patients might be acceptable for selected encounters. Higher community transmission rates suggest emphasis on postponement of procedures and/or stricter risk reduction strategies.

Patient considerations. The risk of transmission for individual patients should be assessed before and at every visit. Vaccinated patients are at significantly lower risk for transmission, whereas unvaccinated patients are at higher risk. Similarly, patients with symptoms of possible COVID-19 infection and/or known exposures to COVID-19 in the prior 2 weeks are at higher risk and should have their office visit postponed and recommended to quarantine. However, in practices focused on treating patients with chronic respiratory symptoms, the symptom-based screening may require a nuanced approach. The list of COVID-19-associated symptoms from the CDC include fever, chills, cough, shortness of breath, difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congested or runny nose, nausea, vomiting, and diarrhea.[6] Patients selected to undergo pulmonary procedures or treatment in an allergy/asthma/immunology health care setting or other providers' office may not be symptom free. They may have symptoms such as cough and dyspnea that, by questionnaire alone, raise concern for COVID-19 infection. Distinguishing factors would be the number, type, and chronicity of symptoms. In select circumstances, if the patient were afebrile, had a negative COVID-19 NAAT, had only chronic respiratory symptoms, and otherwise fit the criteria to leave quarantine (onset of symptoms >10 days prior, afebrile for >24 hours, and symptoms improving), then pursuing an office visit and possible pulmonary testing would likely be lower risk. Additional factors such as community transmission levels, patient vaccination status, preprocedure testing, and other risk reduction measures may allow

Relative Risk	Low → Intermediate → High			
	FeNO	**Spirometry**	**Nebulized Meds**	**Methacholine**
Pre-procedure testing • SARS-CoV-2 NAAT within 3 days of pulmonary procedure testing*	✓*	✓*	✓	✓
Location • Dedicated room with 6-12 air exchanges/hour	✓	✓	✓	✓
Scheduling • Pre-schedule patients • Timing between appointments will depend on room characteristics** • Conduct prior to tests that require forced exhalation maneuvers	✓ ✓ ✓	✓ ✓	✓ ✓	✓ ✓
Screening • Conduct symptomatic screening • Reschedule procedure with any positive responses	✓ ✓	✓ ✓	✓ ✓	✓ ✓
Equipment • Gown, gloves, eye protection, N95 or Powered air purifying respirator for healthcare worker • Single-use equipment if possible (e.g., nose clips, single filters) • In-line bacterial & viral filters	 ✓ ✓	✓ ✓ ✓	✓ ✓ Exhalation port filter	✓ ✓ ✓
Bronchodilator treatment/testing • **Preferred:** Use albuterol MDI with valved holding chamber • **Alternative:** Mesh nebulizer vs. jet nebulizer		✓ ✓	✓ ✓	✓ ✓
Cleaning • Hand hygiene • Disinfection of surfaces and equipment with 70% isopropyl alcohol or per manufacturers recommendation for equipment	✓ ✓	✓ ✓	✓ ✓	✓ ✓
Additional considerations • Room, in-system HEPA filtration • Outdoor performance • Negative pressure room • Blood eosinophils • Home spirometer, PEF meter	✓ ✓ 	✓ ✓ ✓ ✓	✓ ✓ ✓ 	✓ ✓

FIGURE 1. Preprocedural testing such as NAAT, location, scheduling, cleaning procedure, and additional considerations are listed in the left-hand column with checks for these listed items under the procedure where they are indicated. *Consider waiving the COVID-19 NAAT preprocedure test if the patient and staff are fully vaccinated and boosted. Any risk is further mitigated if the local prevalence of the virus is low, and the patient is not demonstrating significant acute airway symptoms. **For example, 12 air exchanges/h will remove 99% of room air in 46 minutes; 6 air exchanges/h will remove 99.9% of room air in 69 minutes. *FeNO*, Fractional concentration of exhaled nitric oxide; *HEPA*, high-efficiency particle arrest; *MDI*, metered dose inhaler; *NAAT*, nucleic acid amplification test; *PEF*, peak expiratory flow.

testing of select chronically symptomatic patients who lack other symptoms of COVID-19 infection.

Pulmonary procedure considerations. Although each of the outlined procedures will be considered separately, there are general considerations that apply to all pulmonary procedures. An important risk for COVID-19 transmission in pulmonary procedures is via airborne transmissible aerosol particles. Although known to represent a somewhat arbitrary delineation across a continuum, the WHO defines 5 μm as the differentiation between a droplet and an airborne transmissible particle.[7] The size of respiratory particles generated by humans during normal

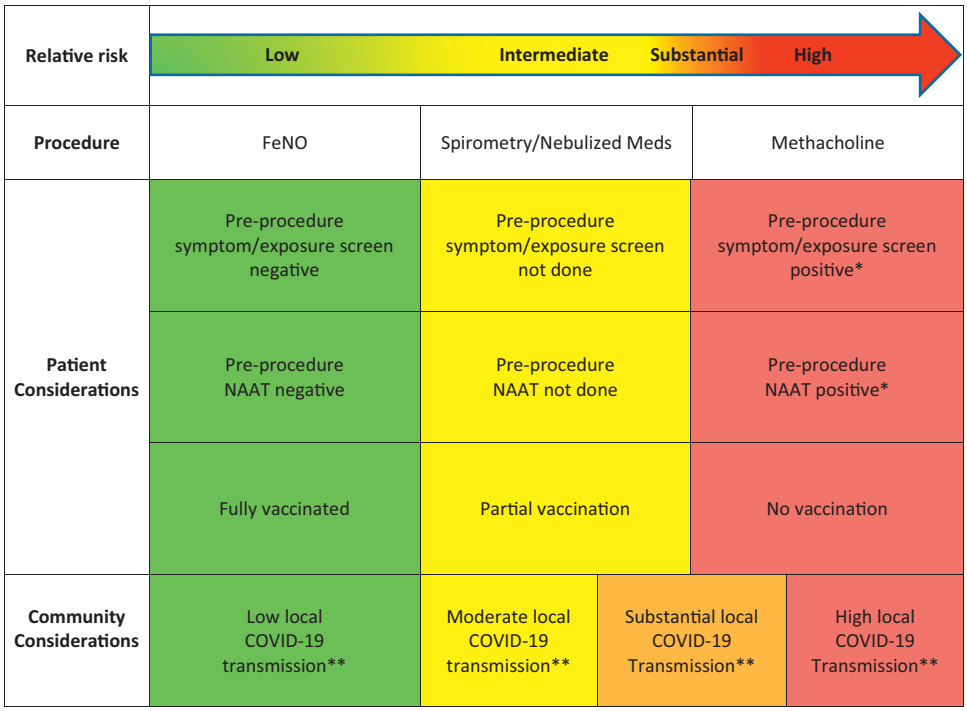

FIGURE 2. The risk continuum for each factor (patient or community consideration) denoted is meant to be a relative assessment. Each column denotes patient or community factors that a clinician can consider when determining the relative risk for viral transmission before performing a pulmonary procedure. *Pulmonary procedure should be deferred if preprocedure symptoms/exposure screen is highly suggestive of COVID-19 or if NAAT is positive. **CDC-defined local transmission rates (new cases/100,000 persons in the last week): low 0 to 9.99, medium 10 to 49.99, substantial 50 to 99.99, and high ≥100. *FeNO*, Fractional concentration of exhaled nitric oxide; *NAAT*, nucleic acid amplification test.

physiology (breathing, talking, coughing, etc) range from 0.01 to 1000 μm. The risk of coronavirus transmission occurs across the continuum of particle sizes where larger particles and droplets (>5 μm) settle rapidly on surfaces and people nearby. Smaller airborne transmissible particles (≤5 μm) remain airborne for longer periods and larger distances. Particles ≤5 μm are also optimized for deposition in the airways when inhaled by bystanders.[8] Evidence has supported the greater risk of COVID-19 spread with aerosolized particles especially indoors and with greater expiratory activity. Bazant and Bush[8] calculated the relative infectious quanta of COVID-19/m^3 across a range of physiologic activities from nasal tidal breathing (1.1) to quiet speech (29) to loud speech (104) to singing (970). These relative quanta corresponded in trend and magnitude to a greater fraction of aerosolized particles from 0.2 to 5 μm. In addition, the increasing levels of infectious quanta were modeled and corresponded closely to known outbreaks and superspreader events. Similarly, coughing, exercise, and high-minute ventilation increase the risk of aerosol production.[9]

Greening et al[10] quantified particle formation during different breathing maneuvers performed by inhaling air through particle-free high-efficiency particle arrest (HEPA) filters and exhaling unfiltered air for sampling. Data for the different breathing maneuvers were obtained from 33 healthy volunteers. The breathing maneuvers included tidal breathing, forced expiratory volume (FEV), slow vital capacity (SVC), and cough at total lung capacity (TLC). FEV resulted in higher particle mass production (+150%) than tidal breathing or SVC. Coughing resulted in the highest mass of exhaled particles compared with all other breathing maneuvers, nearly 500% greater than the particle mass production from FEV. Thereby, coughing is likely to confer significant infectious risk during procedures such as methacholine challenge.[10]

As a result, aerosolized particles present an increased risk for those in the room (health care providers, patients, and attendants) and possibly to individuals in the next room if ventilation is shared between rooms. Because aerosolized particles can remain airborne for hours, aerosolized particles may also present risk to anyone entering the room hours after the aerosol generating event depending on the air exchange of the room.

Risk reduction

Community considerations. National, state, and county COVID-19 transmission rates continue to show generally high or substantial community transmission with few exceptions.[5] Increased vaccination rates, third doses and boosters, vaccine eligibility for broader age groups, and continued public health measures can result in lower transmission rates for the future. For the most part, risk reduction at the community level is undertaken by federal, state, and local authorities and is beyond the scope of this paper.

Patient considerations. During elevated community transmission rates, practices should follow the CDC's COVID-19 infection prevention and control recommendations.[11] Before scheduling a pulmonary procedure, clinic personnel should ensure

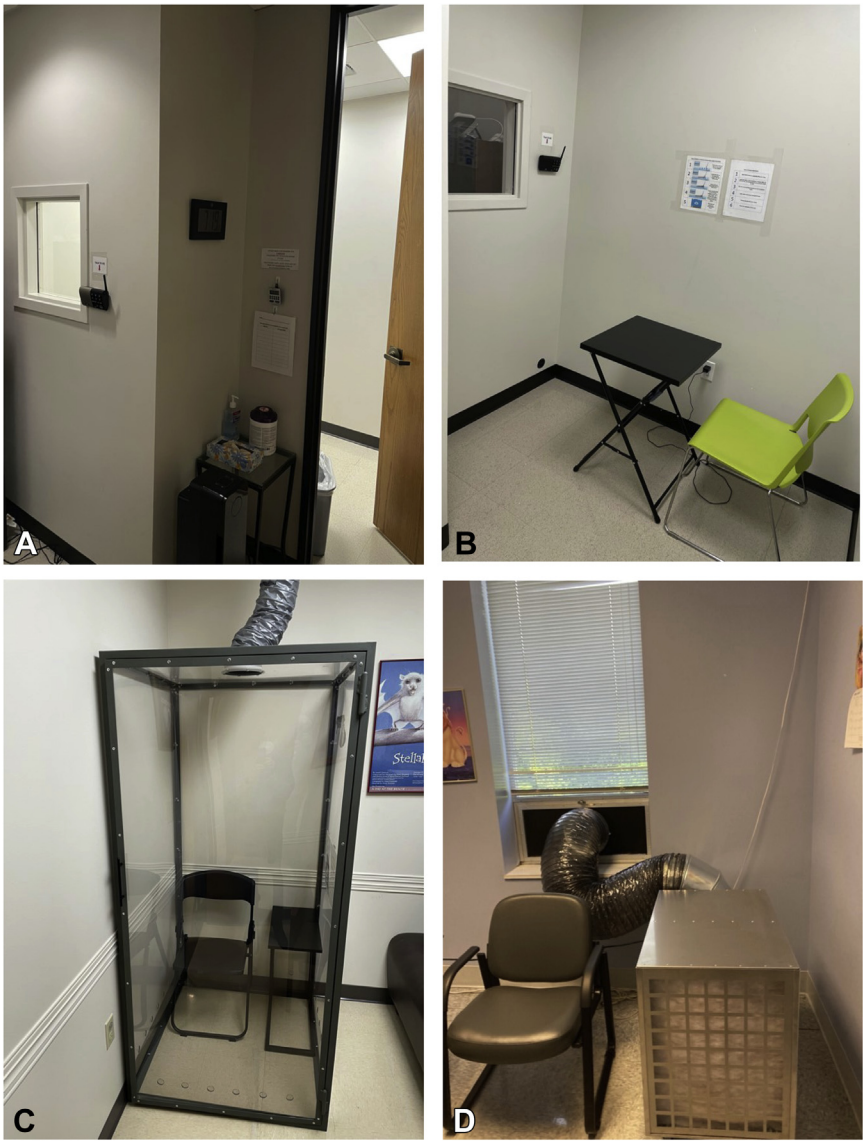

FIGURE 3. Pulmonary procedure room modifications. (**A**) Pulmonary procedure room with anteroom allowing visual and intercom communication between the staff and patient with high-flow exhaust (exterior). (**B**) Pulmonary procedure room with anteroom allowing visual and intercom communication between the staff and patient with high-flow exhaust (interior). (**C**) Pulmonary procedure Plexiglas chamber in the examination room with high-flow exhaust. (**D**) Pulmonary procedure examination room with high-flow exhaust.

that whenever possible, patients are fully vaccinated as an important risk reduction strategy. Time has revealed that there will be an evolving definition of "fully vaccinated" that will need to consider third doses and/or boosters. Patients undergoing pulmonary procedures may have underlying high-risk conditions and/or be immunocompromised. These patients will require closer attention and possibly nuanced decisions when assessing their level of protection.

As the Delta variant has demonstrated, even fully vaccinated people can be asymptomatic transmitters and/or develop breakthrough infection. This emphasizes the need to understand the transmission risk in the community and to ensure preappointment screening for each patient. Patients should be screened for symptoms and recent exposure to known or suspected patients with COVID-19 before entering health care facilities. If patients screen positive, they should not enter.[11] The accuracy and effectiveness of noncontact thermometers during screening is controversial,[12] and therefore we do not recommend their use. The persisting risk of asymptomatic spread in the community introduces the consideration to screen individual patients with COVID-19 NAAT before higher risk procedures such as AGPs. The workgroup recognizes that there is variability in testing methods and turnaround time in different clinical settings. Although a complete discussion of the optimal specimen source of the sample (eg, nasopharynx vs saliva)[13] is beyond the scope of this document, we do recommend NAAT over other forms. Although there are no uniformly agreed on timelines, a practical approach has been a negative test within 72 hours before the procedure.[14] Illustrating the complex and composite nature of risk reduction, the CDC outlines the uncertainty of added risk reduction with NAAT preprocedure screening in the setting of low

community transmission and fully vaccinated patients while allowing for the possible added value in higher risk procedures or immunocompromised patients.[11]

On arrival to the clinic/facility patients should implement source control measures by wearing a well-fitting mask (ie, N95, KN95, and surgical), observing cough etiquette, observing physical distancing, and minimizing the number of attendants/family members in the procedure room.[11]

Environment of care considerations. Patients should be scheduled for a particular time and date, rather than simply a walk-in or "on demand" protocol. Scheduling will help to ensure that adequate time is allotted for cleaning between patients and to maintain physical distancing between patients. Patients should be encouraged to attend the visit alone or with 1 attendant if necessary. Waiting rooms should have sufficient seating and room to accommodate such recommendations. High-risk procedures should be scheduled for the last procedure of the day whenever possible.

Any health care worker performing or working in the environment of AGPs should be fully vaccinated. Currently, personal protective equipment (PPE) used by health care workers in the room should reflect contact, droplet, and airborne precautions advised by the CDC. These measures include a gown, gloves, fit-tested National Institute of Occupational Safety and Health—approved N95 mask or higher-level respirator, and eye protection. Gloves and gown should be changed between patients along with hand hygiene, and masks and eye protection can be used for an entire shift if unsoiled.[11]

A single room should be used for each patient undergoing AGPs. The number of people in the room (health care providers and patient attendants) and the number of people entering and exiting the room should be minimized. Engineering controls should be used to the greatest extent in the room selected for AGPs. A negative pressure room is optimal. Given that negative pressure rooms are not commonly available, a room that does not share ventilatory mix with other rooms and that has the greatest external air exchange should be selected. Building managers or local heating, ventilation, and air-conditioning specialists may be able to provide the number of air exchanges per hour. Alternatively, if a facility meets the American Institute of Architecture's Guidelines for Design and Construction of Hospitals and Health-Care Facilities from 2001,[15] then patient examination rooms will have a minimum of 6 air exchanges per hour. Knowing air exchange rates helps determine the appropriate interval until the next use of the room.[16] Air exchanges of 6 per hour are estimated to remove 99% of contaminated air in 46 minutes and 99.9% in 69 minutes. Doubling air exchanges to 12 per hour leads to 99% and 99.9% removal in half the time, 23 and 35 minutes, respectively. Measures such as in-room HEPA filtration, added systemic air filtration with a minimum efficiency reporting value of 13 or greater, and UV-C (ultraviolet light in germicidal wavelengths) are COVID-19 risk reduction strategies endorsed by the American Society of Heating, Refrigerating and Air-Conditioning Engineers.[17] However, the American Lung Association does not recommend HEPA filtration.[18] Other *ad hoc* measures such as augmented air exchange directly with the outdoors via window or door, self-contained cubicles, additional filtering, or additional antimicrobial strategies may provide benefit (see Figure 3). However, the impact of *ad hoc* measures is difficult to quantify, and authoritative endorsements are lacking. Alternatively, outdoor space that is suitable for clinical use may be appropriate for risk reduction for AGPs.

After completing the procedure, hand hygiene should be accomplished and appropriate disinfection of surfaces and equipment should be performed with 70% isopropyl alcohol or alternative agents recommended by equipment manufacturers.[16] Finally, the room should remain closed and unoccupied for the appropriate interval as discussed above.

Spirometry

Performing spirometry in the office setting has long been a foundational part of the diagnosis and care of patients with asthma. For example, the National Heart Lung and Blood Institute (NHLBI) Expert Panel Report-3 Guidelines for Asthma note that physicians have a "poor ability to assess the degree of airflow obstruction" and recommend the use of spirometry for diagnostic purposes as well as periodic monitoring.[19] However, the forced exhalation performed by patients during spirometry raises the concern for generation of aerosol particles, potentially putting health care personnel supervising spirometry at risk for infection with SARS-CoV-2. The CDC and OSHA do not consider spirometry as an AGP, whereas the ATS does.[9,20,21] The American Lung Association does not classify testing but offers specific guidance on the performance of spirometry during COVID-19.[18] This illustrates the lack of consensus on a list of AGPs for the health care setting. Work published by the ATS has demonstrated generation of significantly elevated amounts of 0.3 μm particles generated at the point of origin for tidal breathing, forced vital capacity (FVC) maneuvers, and maximal voluntary ventilation maneuvers. However, the elevation returned to ambient levels within 1.5 ft of the point of origin.[22] This reinforces the importance of physical distancing when possible. Also, it is not well established if aerosols from certain procedures are infectious.[23] The exact amount and significance of aerosol generation with pulmonary function testing (PFT) is not fully known. Despite the uncertainty, there is a possibility that infectious aerosols remain airborne in the room for an extended time after conducting spirometry.

Spirometry specific risk reduction considerations. Although spirometry monitoring is indeed an important tool in asthma management, obtaining these data reflexively at every clinic visit must be re-examined in the current environment. We recommend limiting spirometry measurements to patients where the results are likely to influence ongoing treatment such as poor perceivers, and when changing medications. In patients with mild and/or stable disease, we recommend reconsidering the need for spirometry while relying on the history and physical examination. When spirometry is indicated for management or diagnostic purposes, multiple risk reduction precautions should be used.

When performing the test, the technician should sit in the same direction as the patient and attempt to remain as physically distant as practical from the exhalation port. It remains critical for the technician to guide and evaluate the test and patient in real time to ensure good technique and reliable results. To assist pediatric patients performing spirometry, the use of party favors, video incentives like blowing out the candles, or video chat with remote spirometry may be employed.

Although spirometry machines are not sterile, precautions can be used to decrease the risk and spread of infection. In-line bacterial/viral filters should be used as they help minimize the risk from exhaled air contaminating the spirometer and the room. Disposable nose clips should be used and discarded after each patient use. After each patient, equipment should be cleaned with 70% isopropyl

FIGURE 4. Metered dose inhaler with a single-use valved holding chamber. Example shown is: https://www.macgill.com/products/respiratory/peak-flow-meters-spacers/liteaire-dual-valved-holding-chamber.html. The arrow points to the valved holding chamber.

alcohol (or equivalent) or the disinfectant recommended by the manufacturer.

If reversibility testing is required, follow the recommendations outlined below for nebulization procedures.

Home monitoring strategies. Encouraging peak flow monitoring at home in patients who are not already doing so may provide valuable clinical data, particularly in patients being monitored via telemedicine without the ability for in-person examination and full spirometry. Although peak flow data do not replace spirometry and are not suitable for initial assessment of lung function, they do have utility in longitudinal monitoring and potential early detection of exacerbation. Peak flow measurement can be added to symptom-based monitoring in a supportive self-management strategy for asthma, with a large meta-analysis supporting a self-management approach.[24] Peak flow monitoring can also be useful in assessing response to treatment, detection of exacerbation in poor perceivers, and monitoring recovery from exacerbation.[25] On the downside, peak flow testing is effort dependent so it may have limited utility in some patients.

There are a burgeoning number of home spirometry devices available to measure FEV_1 and FVC. Some have associated smart phone apps that facilitate real-time video coaching. Emerging data show that these devices can be a diagnostic tool used in the accurate measurement of lung function. In one pilot study specific to asthma, repeated measures with a home spirometry device agreed closely with measurements taken with standard in-clinic spirometry.[26] Home spirometry has also been demonstrated to be feasible and to provide valid data in idiopathic pulmonary fibrosis,[27] although another study found a poor correlation between home and office spirometry.[28] If home spirometry is instituted, results should be frequently correlated with office spirometry to assure reliability during exacerbations. Additional research to determine best practices is needed.

Although the workgroup cannot make a specific recommendation for instituting a home spirometry program based on current evidence, this is a promising strategy. Issues related to legal, privacy, and access issues must be considered with home monitoring strategies, particularly with home spirometers that rely on connections to software applications running on smartphones. Bronchodilator reversibility studies add an additional layer of complexity and may not be fully feasible at this time until more knowledge is gained regarding best practices and quality control.

Fractional exhaled nitric oxide testing

The concentration of FeNO test is a diagnostic tool in the evaluation and management of asthma. FeNO is a quantitative biomarker of type 2 airway inflammation that is useful for evaluating patients with chronic cough and for determining corticosteroid responsiveness in patients with underlying eosinophilic asthma.[29] The testing characteristics of FeNO are favorable because it is noninvasive, can easily be repeated, and requires a simpler technique than other pulmonary tests. Furthermore, FeNO has not been identified as an AGP by the CDC, ATS, OSHA, and other national and international organizations including the latest NHLBI asthma guidelines.[23] FeNO testing requires a deep inhalation to TLC followed by slow and constant exhalation into an analyzer at a rate of 0.05 L/s.[30] Because there is no forced exhalation maneuver with FeNO testing, the test is not known to trigger cough in an otherwise healthy patient. The viral transmission risks with FeNO are likely lower than spirometry given that an FVC is not required, though the exact risk is unknown. These characteristics allow for the use of FeNO routinely in clinical practice. However, FeNO is not a "stand alone" diagnostic standard but rather an evaluation and management option if history, physical examination, and spirometry do not permit sufficient management.[31]

FeNO specific risk reduction considerations. As FeNO testing is typically performed in conjunction with other pulmonary tests, the location should be the same for all pulmonary testing as this limits patient movement in a facility. The timing and order of pulmonary tests should be considered and deliberate when scheduling. Before COVID-19, the timing of pulmonary tests was determined by the impact of testing maneuvers on airway caliber and lung volumes. In the era of COVID-19, the generation of aerosols through forced expiratory techniques should be considered foremost. Tests that involve tidal breathing or slow exhalation (eg, FeNO) should be performed before tests that require a forced exhalation maneuver (eg, spirometry) to decrease exposure of aerosolized particles to patients and health care workers.

Because the exact risk of viral transmission is unknown, it is reasonable to conduct the test similarly to other pulmonary procedures. Single-patient, high-efficiency, in-line filters with FeNO testing prevent bacteria and viruses from being transported into the breathing circuit and thus reduce viral transmission.

Patient selection for FeNO testing is also important as there may be alternatives for evaluation. FeNO levels are particularly useful in categorizing type 2 inflammation in patients with lung disease. Although less specific, blood eosinophil count is an alternative test to consider if FeNO testing cannot be performed.[32] In the setting of high COVID-19 community transmission, where a pause in pulmonary procedures has been recommended, this biomarker should be considered as an alternative to FeNO testing.

Nebulized treatments

Nebulization in the office setting generally occurs as either a diagnostic or therapeutic procedure. This section will limit discussion to nebulization in the diagnostic setting used to assess bronchodilator responsiveness. Methacholine challenge is addressed in a following section.

By design, nebulized therapies produce aerosols containing medications in particle sizes that vary widely but are generally

FIGURE 5. Nebulizer with a 1-way valve and expiratory filters.

targeted in the 1-5 μm range.[33] In the setting of nebulized therapy, most of the aerosolized particles are medical aerosols defined as medication from the chamber not the patient. Unless contaminated, medication aerosols pose no risk. Risk of medication contamination in the chamber can be minimized by using a proper aseptic technique in preparing the chamber and by using appropriate filters, 1-way valves, and/or design to prevent patient-contaminated material from entering the chamber during expiration. There are also fugitive aerosols defined as aerosols released during expiration. Fugitive aerosols can be medication aerosols directly from the chamber or exhaled aerosols from the patient. Up to 50% of the aerosolization from a nebulized treatment is from fugitive emissions. Fugitive emissions can last indoors for several hours.[34] However, it is not known what proportional amount of medical versus patient-derived emissions make up fugitive aerosols. Furthermore, the risk of viral transmission with fugitive aerosols is unknown. Goldstein et al[35] performed a broad search of 2416 references to identify 22 studies meeting review criteria to examine the risk of viral transmission with nebulized treatment. The results were confounded by different nebulization types, varied levels of PPE, and design inconsistencies. The authors were unable to quantify a risk for nebulized therapy, but they could not rule out that nebulized therapies may increase viral transmission.[35]

The OSHA does not include nebulized therapy among AGPs.[21] The CDC has included nebulized administration within its section on AGPs but acknowledges a lack of consensus and insufficient supporting data, whereas the ATS lists nebulized therapy as aerosol generating without caveat.[9,36] The CDC adds the caveat that "based on limited available data, it is uncertain whether aerosols generated from some procedures may be infectious" that include nebulizer administration. Further commentary considers that increased risk could possibly come from the aerosols or from the increased contact between health care providers and patients during nebulization.[32] Although no comparison data are available, it is possible that the performance of the FVC maneuvers for spirometry and/or any associated cough may present similar or greater risk of transmission than nebulized therapy.

Nebulization specific risk reduction considerations. The uncertainty but possibility of viral transmission with nebulized therapy has led many national and international professional medical associations to recommend that nebulized therapy be included among the procedures that should be limited during this pandemic.[37] The recommendations vary in restrictive language, patient selection and screening, and infection control measures.[14] In the setting of elevated community transmission rates, the CDC and many other national and international professional organizations recommend that nebulized therapy should only be performed when essential.[14,36] As a result, nebulized bronchodilator responsiveness testing or therapeutic nebulized treatment should only be performed when essential and should be limited to those patients who cannot successfully use a metered dose inhaler (MDI) with a 1-way valved holding chamber.

Most patients able to adequately understand and perform spirometry should be able to understand and use an MDI with a valved holding chamber. Delivery of 4 to 8 puffs of albuterol from an MDI with a valved holding chamber has been shown equivalent to nebulized albuterol in the assessment of bronchodilator responsiveness and in the acute treatment setting for patients of a wide range of ages.[38,39] Although no head-to-head comparisons of viral transmission have been performed, the use of an MDI with a valved holding chamber has theoretical advantages that lower the risk of transmission. With an MDI, no additional aerosolized material is created beyond that which occurs with tidal breathing. The time for the patient to be without a mask to administer the MDI should be significantly shorter than a nebulized treatment. For practical and cost considerations, cardboard, single-use, disposable, valved holding chambers are available (see Figure 4). With scheduled diagnostic testing, patients can be prescribed and/or reminded to bring their own MDI for testing. If an MDI is provided by the clinic/PFT laboratory, single use for 1 patient unless full sterilization can be performed (see protocols in reference).[40] In the rare circumstance that an MDI with a valved holding chamber is not appropriate and nebulized therapy is selected, additional risk reduction should be undertaken. A nebulizer with an in-line bacterial/viral exhalation port filter and 1-way valve should be used (see Figure 5).[41] The 1-way valve prevents contamination of the aerosol medication. The in-line, bacterial/viral exhalation port filter is designed to capture the exhaled aerosol particles and limit the amount of potentially infectious aerosol that enters the room during the treatment. The effectiveness of these measures on reducing viral transmission is unknown. Similarly, the use of a mesh nebulizer to decrease time or a breath-actuated nebulizer to decrease risk for backflow may decrease the risk of infection from reduced aerosol dispersion or backflow, but the effectiveness of these methods is also unknown.

Methacholine challenge

Airway hyperresponsiveness is a characteristic feature of asthma, and the methacholine challenge test is a direct inhalation bronchoprovocation test that is widely used clinically to document and quantitate airway hyperresponsiveness.[42,43] Methacholine, a synthetic derivative of the neurotransmitter acetylcholine, directly stimulates airway smooth muscle via muscarinic (M3) receptors when inhaled.[44] Methacholine challenge testing is often considered for patients with possible asthma symptoms and for which spirometry has not established or eliminated the diagnosis. Cut points have been established so that methacholine challenge testing is highly sensitive and has a high negative predictive value. Moreover, methacholine challenge testing is more useful for excluding a

TABLE I. Unanswered questions

COVID-19 testing
• What is the optimal role of NAAT testing before pulmonary procedures? Does patient and staff vaccination affect the need for testing?
• If COVID-19 preprocedure testing is deemed necessary, will point-of-care in-office tests with improved sensitivity/specificity be an option?
• How will the changing local prevalence of COVID-19 impact the requirement for preprocedure testing in the future?
• As new variants emerge where the current vaccines show less efficacy, how will preprocedure testing requirements change?
COVID-19 vaccination status
• What does "fully-vaccinated" mean long term with regard to transmission during pulmonary procedures?
• How will vaccination status be assessed in the future vs current honors system or vaccine card—will a national vaccine registry with a secure app interface be developed?
Clinical practice issues
• Who will cover the ongoing costs associated with preprocedure COVID-19 testing, PPE, etc long term?

NAAT, Nucleic acid amplification test; *PPE*, personal protective equipment.

diagnosis of asthma than for establishing one because its negative predictive power is greater than its positive predictive power.[43,45]

Recommended methacholine challenge protocols include a tidal breathing method (1- or 2-minute) and a 5-breath dosimeter method.[42,43] Both protocols are identical except for the method of inhalation. In both protocols, (1) baseline spirometry is performed, (2) increasing concentrations of methacholine are administered via a nebulizer, and (3) FEV_1 is measured 30 to 90 seconds after each nebulization dose is completed. If the FEV_1 falls more than 20% from baseline or the highest methacholine concentration has been given, inhaled albuterol is administered, and spirometry is repeated after 10 minutes. In the tidal breathing method, each dose of methacholine (doubling doses starting at 0.031 mg/mL increasing to 16 mg/mL) is administered via a nebulizer while the patient is tidal breathing for the 1- or 2-minute time period. In the 5-breath dosimeter method, each dose of methacholine (quadrupling doses starting at 0.0625 mg/mL increasing to 16 mg/mL) is administered while the patient takes 5 inspiratory capacity inhalations (5 seconds to complete the inhalation and hold the breath at TLC for another 5 seconds) over a time period of no longer than 2 minutes.[46] Inhaled methacholine causes bronchoconstriction, and transient symptoms may include coughing, wheezing, dyspnea, and chest tightness.[44]

Given the multiple forced respiratory maneuvers, nebulized doses of methacholine, and resulting adverse respiratory symptoms, methacholine challenge testing results in evident aerosolization into the environment. It has the worst risk/benefit ratio among standard lung function tests that could be performed during the SARS-CoV-2 (COVID-19) pandemic.[46] Indeed, an international survey,[47] including 52 countries with the majority of respondents being allergists, demonstrated that approximately 90% of respondents had stopped performing methacholine challenge testing during the COVID-19 pandemic. As for the remaining period of the pandemic, most respondents had no specific timeline to resume methacholine challenge testing, and 63% of responders stated that lung function tests should be restricted to selected patients and only performed in health care facilities that have adapted to new safety requirements. Furthermore, only 17% of responders believed that the number of lung function tests should remain like that before the pandemic.[47]

One published study aimed to investigate aerosol generation during methacholine challenge testing and other breathing maneuvers. Subat et al[48] compared small particle generation with 2 different nebulizer devices and a dosimeter, each with and without a viral filter. This study was performed in a highly controlled, nearly particle-free, sealed room representing a simulated procedure area (74 × 36 × 36 inches). Two devices continuously sampled the ambient air during the procedure in which 5 healthy participants simulated methacholine challenge testing using nebulized saline and 3 simulated FVC maneuvers with and without a viral filter. The testing maneuvers were associated with substantial production of small particles (up to 50,000 particles/cc), with a predominance of ultrafine particles (0.02-1 μm). Of note, small particles (≤5 μm) remain airborne longer, potentially increasing spread.[49] The addition of a viral filter resulted in significant reductions in small particle generation with all devices used, although this reduction was significantly different between delivery systems.[48]

These findings support the view that methacholine challenge testing likely poses a particularly significant infectious risk when compared with other lung function tests.

Methacholine challenge specific risk reduction considerations. Methacholine challenge testing is associated with a substantial risk for transmitting pulmonary viruses such as SARS-CoV2. These risks underscore guidelines from several national and international professional organizations that advise limiting methacholine challenge and other lung function tests to only essential treatment decisions. Furthermore, if methacholine challenge is performed, then all appropriate risk reduction measures previously outlined in the environment of care, spirometry, and nebulized treatments should be implemented to minimize the risk for health care workers and patients.[14]

FUTURE CONSIDERATIONS

Prevalence and transmission rates of COVID-19 and the occurrence of new viral variants in the community are important parameters in determining future alterations/relaxation of risk reduction strategies. Advances in testing and understanding of vaccine efficacy parameters will play a role in assessing patient risk and assigning risk reduction. The duration of vaccine efficacy, including second and third boosters, has already complicated and changed the definition of "fully vaccinated." It may be possible to return to more selective and relaxed risk reduction strategies when the CDC defined community risk of transmission is low. The CDC has considered a future state where the local transmission rate is low, and a patient is fully vaccinated that will make preprocedure COVID-19 testing unnecessary. In that scenario, prescreening for symptoms and exposure will be considered sufficient.[11]

The CDC defines community transmission as low when the 7-day average of new cases per 100,000 is <10 and the community NAAT positivity rate is less than 5%. At the beginning of 2022, over 90% of the counties in the United States continue to have high or substantial transmission rates.[5] Assessing the infectious risk of patients is also important, but it is not well standardized. Lower patient transmission risk is supported by full vaccination, negative symptom/exposure screening, and a recent negative COVID-19 test. Immunocompetent patients who are fully vaccinated against COVID-19 and have negative symptom/exposure screening are lower risk. Availability of reliable, affordable, single-patient, real-time COVID-19 tests with rapid

results for in-clinic use would help identify low-risk patients. There may not be a full and permanent return to the prepandemic state of risk reduction. In the future, even when practices can return to more relaxed infection control, there will remain a need to quickly scale up risk reduction strategies procedures in response to elevated risk scenarios. Such scenarios might include spikes in community disease transmission (COVID-19 ± variants, future pathogens, and possibly influenza). They likely will include care for higher risk patients, for example, those who are unvaccinated, have multiple comorbidities, are over 65 years old, are residents in congregate settings, or with immunodeficiency. As a result, preparedness and vigilance will remain important and further research is needed to clarify remaining questions (see Table I). There is still a need for consensus on the risk of COVID-19 infection posed by aerosolization with pulmonary procedures.[21] Finally, although nebulizers are already commonly used at home, the use of other portable home testing devices (eg, FeNO) may be considered a long-term strategy to reduce the need for in-clinic testing.

CONCLUSIONS

The COVID-19 pandemic has led to several challenges in providing health care services particularly among people living with respiratory diseases. When we begin to slowly transition toward the postpandemic era, health care providers will continue to adjust and adapt how pulmonary procedures and treatments are delivered. Although this workgroup report provides recommendations on how to resume performing procedures such as spirometry, it is not a "one size fits all" approach. Composite considerations of risk will need to be synthesized by providers from elements including assessment of risk reduction for each procedure in their environment of care, knowledge of community transmission levels, and understanding of individual patient risk.

As this workgroup report outlines, the environment of care is important to consider, starting with ensuring that the clinic or office is compliant with the CDC-guided OSHA COVID-19 Emergency Temporary Standards.[48] Whereas some practices may be able to retrofit existing spaces to reduce risk for spirometry or methacholine challenge testing, others may not be able to do this feasibly. If safety standards cannot be met in the current setting, then referral to a nearby hospital-based pulmonary function lab with established protocols could be considered. Some downsides to outsourcing these procedures include long waits for appointments, additional staff to follow-up on results, and a delay in diagnosis or treatment modifications. Once the appropriate care setting for the procedure has been selected, the feasibility of preprocedure COVID testing must be considered. Patients may face challenges with access to convenient testing sites, travel-related affordability, or work/family commitments that impede timely testing. This might make point-of-care testing relevant for certain practices, but the costs (eg, staff time, test kits) and reduced sensitivity with some methods must also be considered.

The prevalence and transmission rates of COVID-19 in the community are constantly changing. Providers that are performing these procedures and treatments need to monitor community infection rates using local prevalence data as well as guidance from the CDC and local health departments. Risk reduction and infection control procedures will vary depending on the intersection of community, patient, and specific procedure considerations.

Unfortunately, but predictably, variants of COVID-19 have emerged. Some variants are more contagious and some potentially more lethal. Asymptomatic transmission and breakthrough infections are occurring in fully vaccinated people. Emergence of novel variants remains likely in the future given the climate of vaccine hesitancy in the United States, and there is no assurance that current vaccines will provide adequate protection. The allergy/asthma/immunology specialist must be a strong advocate for patient vaccination. At present, it is not possible to predict what combination of herd immunity, local viral prevalence and transmissibility, and community vaccination status will be necessary to remove current precautions.

This workgroup report provides recommendations but is not meant to serve as a restrictive guideline on utilization of spirometry, nebulizers, FeNO, and methacholine challenge testing during the COVID-19 pandemic. These procedures should be performed in patients when determined to be clinically necessary and when adequate risk reduction measures are in place. As the COVID-19 pandemic is a moving target, the recommendations outlined here may require modification in the future, but they remain our current advice on performing these procedures and treatments. There may never be a return to "normal." Considerations for the future include a need to determine the responsibility and sharing of costs associated with added infection control and risk reduction measures, and to assess the long-term impact of delayed accurate diagnosis for patients with chronic respiratory disease. The need for individual providers to use their clinical judgment to decide who should undergo pulmonary procedures and in what setting will always be required as we navigate this pandemic.

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
2. Centers for Disease Control and Prevention. How COVID-19 spreads. Accessed October 2, 2021. https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/how-covid-spreads.html
3. Harding H, Broom A, Broom J. Aerosol-generating procedures and infective risk to healthcare workers from SARS-CoV-2: the limits of the evidence. J Hospital Infect 2020;105:717-25.
4. Frangos SA. ACOEM advises suspension of routine occupational spirometry testing during COVID-19 pandemic. Accessed March 25, 2020. https://myemail.constantcontact.com/ACOEM-Advises-Suspension-of-Routine-Occupational-Spirometry-Testing-During-COVID-19-Pandemic.html?soid=1102647720683&aid=idWxyX21cJ4
5. Center for Disease Control and Prevention. COVID data tracker. Accessed October 2, 2021. https://covid.cdc.gov/covid-data-tracker/#datatracker-home
6. Center for Disease Control and Prevention. Symptoms of COVID-19. Accessed October 2, 2021. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html
7. Wilson NM, Norton A, Young FP, Collins DW. Airborne transmission of severe acute respiratory syndrome coronavirus-2 to healthcare workers: a narrative review. Anaesthesia 2020;75:1086-95.
8. Bazant MZ, Bush JWM. A guideline to limit indoor airborne transmission of COVID-19. Proc Natl Acad Sci U S A 2021;118:e2018995118.
9. Wilson KC, Kaminsky DA, Michaurd G, Sharma S, Nici L, Folz RJ, et al. Restoring pulmonary and sleep services as the COVID-19 pandemic lessens. From an Association of Pulmonary, Critical Care, and Sleep Division Directors and the American Thoracic Society-coordinated task force. Ann Am Thorac Soc 2021;17:1343-51.
10. Greening NJ, Larsson P, Ljungström E, Siddiqui S, Olin A-C. Small droplet emission in exhaled breath during different breathing maneuvers: implications for clinical lung function testing during COVID-19. Allergy 2021;76:915-7.
11. Center for Disease Control and Prevention. Interim infection prevention and control recommendations for health care personnel during the coronavirus

disease-2019 (COVID-19) pandemic. Accessed October 2, 2021. https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html
12. Aggarwal N, Garg M, Dwarakanathan V, Gautam N, Kumar SS, Jadon RS, et al. Diagnostic accuracy of non-contact infrared thermometers and thermal scanners: a systematic review and meta-analysis. J Travel Med 2020;27:taaa193.
13. Butler-Laporte G, Lawandi A, Schiller I, Yao M, Dendukuri N, McDonald EG, et al. Comparison of saliva and nasopharyngeal swab nucleic acid amplification testing for detection of SARS-CoV-2: a systematic review and meta-analysis. JAMA Intern Med 2021;181:353-60.
14. Crimi C, Impellizzeri P, Campisi R, Nolasco S, Spanevello A, Crimi N. Practical considerations for spirometry during the COVID-19 outbreak: literature review and insights. Pulmonology 2021;27:438-47.
15. The Center for Health Design. Guidelines for design and construction of hospitals and health care facilities. Accessed May 9, 2021. https://www.healthdesign.org/knowledge-repository/guidelines-design-and-construction-hospitals-and-health-care-facilities-2001
16. Centers for Disease Control and Prevention. Appendix B. Air—guidelines for environmental infection control in health-care facilities. 2003. Accessed May 9, 2021. https://www.cdc.gov/infectioncontrol/guidelines/environmental/appendix/air.html
17. American Society of Heating, Refrigerating, and Air-Conditioning Engineers. Epidemic Task Force: core recommendations for reducing airborne infectious aerosol exposure. Accessed October 2, 2021. https://www.ashrae.org/file%20library/technical%20resources/covid-19/core-recommendations-for-reducing-airborn-infectious-aerosol-esposure.pdf
18. American Lung Association. American Lung Association guidance on performance of spirometry during and after the pandemic. Accessed October 2, 2021. https://www.lung.org/getmedia/db83d857-3642-4ec0-a120-405d44f98711/considerations-for-conducting-spirometry-during-and-after-covid19-07062020-(002).pdf
19. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma—summary report 2007. J Allergy Clin Immunol 2007;120(Suppl):94-138.
20. Zepp JA, Alvira CM. Nanoparticle delivery of angiogenic gene therapy. Save the vessels, save the lung. Am J Respir Crit Care Med 2020;202:13-4.
21. Occupational Safety and Health Administration. OSHA COVID-19 emergency temporary standard. Accessed October 2, 2021. https://www.osha.gov/coronavirus/ets
22. Helgeson SA, Lim KG, Lee AS, Niven AS, Patel NM. Aerosol generation during spirometry. Ann Am Thorac Soc 2020;17:1637-9.
23. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. PLoS One 2012;7:e35797.
24. Pinnock H, Parke HL, Panagioti M, Daines L, Pearce G, Epiphaniou E, et al. Systematic meta-review of supported self-management for asthma: a healthcare perspective. BMC Med 2017;15:64.
25. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2021. Accessed April 9, 2022. https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf
26. Huang C, Izmailova ES, Jackson N, Ellis R, Bhatia G, Ruddy M, et al. Remote FEV1 monitoring in asthma patients: a pilot study. Clin Transl Sci 2021;14:529-35.
27. Noth I, Cottin V, Chaudhuri N, Corte TJ, Johannson KA, Wijsenbeek M, et al. Home spirometry in patients with idiopathic pulmonary fibrosis: data from the INMARK trial. Eur Respir J 2021;58:2001518.
28. Gardiner F, Pizzichini E, Bailes Z, Peachey G, Zarankaite A, Chaudhuri R, et al. A comparison of clinic versus home spirometry in the CAPTAIN study. Am J Respir Crit Care Med 2021;203:A134.
29. Khatri SB, Iaccarino JM, Barochia A, Soghier I, Akuthota P, Brady A, et al. Use of fractional exhaled nitric oxide to guide the treatment of asthma: an official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med 2021;204:97-109.
30. American Thoracic Society; European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med 2005;171:912-30.
31. Cloutier MM, Baptist AP, Blake KV, Brooks EG, Bryant-Stevens T, DiMango E, et al. 2020 focused updates to the asthma management guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. J Allergy Clin Immunol 2020;146:1217-70.
32. Silkoff PE, Laviolette M, Singh D, FitzGerald JM, Kelsen S, Backer V, et al. Identification of airway mucosal type 2 inflammation by using clinical biomarkers in asthmatic patients. J Allergy Clin Immunol 2017;140:710-9.
33. Ong KY, Tan TL, Chan AKW, Tan KLL, Koh MS. Managing asthma in the COVID-19 pandemic and current recommendations from professional bodies: a review. J Asthma 2021;58:1536-43.
34. Ari A. Practical strategies for a safe and effective delivery of aerosolized medications to patients with COVID-19. Respir Med 2020;167:105987.
35. Goldstein KM, Ghadimi K, Mystakelis H, Kong Y, Meng T, Cantrell S, et al. Risk of transmitting coronavirus disease 2019 during nebulizer treatment: a systematic review. J Aerosol Med Pulm Drug Deliv 2021;34:155-70.
36. Centers for Disease Control and Prevention. Clinical questions about COVID-19: questions and answers. Accessed October 2, 2021. https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html
37. Jackson T, Deibert D, Wyatt G, Durand-Moreau Q, Adisesh A, Khunti K, et al. Classification of aerosol-generating procedures: a rapid systematic review. BMJ Open Resp Res 2020;7:e000730.
38. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.
39. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest 2005;127:335-71.
40. Elbeddini A. Sterilization plan of the used metered dose inhalers (MDI) to avoid wastage amid COVID-19 pandemic drug shortage. J Pharm Policy Pract 2020;13:19.
41. Ari A. Promoting safe and effective use of aerosol devices in covid-19: risks and suggestions for viral transmission. Expert Opin Drug Deliv 2020;17:1509-13.
42. Cockcroft DW, Davis B. Direct and indirect challenges in the clinical assessment of asthma. Ann Allergy Asthma Immunol 2009;103:363-70.
43. Cockcroft DW. Methacholine challenge testing in the diagnosis of asthma. Chest 2020;158:433-4.
44. Coates AL, Wanger J, Cockcroft DW, Culver BH, Carlsen K-H, Diamant Z, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017;49:1601526.
45. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing—1999. Am J Respir Crit Care Med 2000;161:309-29.
46. Milanese M, Corsico AG, Bellofiore S, Carrozzi L, Di Marco F, Lovene B, et al. Suggestions for lung function testing in the context of COVID-19. Respir Med 2021;177:106292.
47. Eguiluz-Gracia I, van den Berge M, Boccabella C, Bonini M, Caruso C, Couto M, et al. Real-life impact of COVID-19 pandemic lockdown on the management of pediatric and adult asthma: a survey by the EAACI Asthma Section. Allergy 2021;76:2776-84.
48. Subat Y, Sajgalik P, Hainy M, Torgerud K, Guntupalli SK, Helgeson S, et al. Aerosol generation during methacholine challenge testing: clinical implications during the COVID-19 pandemic. Am J Respir Crit Care Med 2021;203:A4473.
49. Somsen GA, van Rijn C, Kooij S, Bem RA, Bonn D. Small droplet aerosols in poorly ventilated spaces and SARS-CoV-2 transmission. Lancet Respir Med 2020;8:658-9.