and studies have been established to address pediatric/transitional aspects (All-Age-Asthma-Cohort [13] and Children's Respiratory and Environmental Workgroup Birth Cohort [14]) as well as molecular endotype persistence/evolution in adults (Cohort for Reality and Evolution of Adult Asthma in Korea [15] and Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes [16]), to name only a few. It is thus evident that one-size-fits-all treatment approaches are inherently flawed, and deeper understanding of the heterogeneous (targetable) molecular mechanisms in asthma is imperative. ■

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High-Flow Aerosol-Dispersing versus Aerosol-Generating Procedures

Hypoxemia is the main symptom and primary reason for hospital admission among patients with coronavirus disease (COVID-19), and oxygen therapy is the mainstay therapy to treat hypoxemia. Among 10,054 patients with COVID-19 admitted to ICUs in the United Kingdom during the pandemic, more than 70% required advanced respiratory support, including high-flow nasal cannula (HFNC) oxygen therapy, noninvasive (NIV) and invasive ventilation, and extracorporeal membrane oxygenation (1).

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HFNC and NIV have been categorized as aerosol-generating procedures, based on the hypothesis that high-velocity gas flows may promote aerosolization of patients' secretions containing viable virus, which may then be dispersed in the environment and be inhaled by healthcare workers (2). Indeed, retrospective studies assessing risk factors of nosocomial transmission of the severe acute respiratory syndrome (SARS) observed that healthcare workers caring for patients with SARS treated by NIV had a twofold higher risk of infection transmission than those who did not (3). However, the exact infection transmission route, that is, aerosol versus contact or other routes, was not investigated.

In this issue of the *Journal*, Gaeckle and colleagues (pp. 1115–1124) provide evidence that the difference of the aerosol particle concentrations generated by various oxygenation devices is clinically insignificant and probably negligible, compared

Table 1. Comparison of Different Methods Used to Investigate Aerosol Generation and Dispersion

	Imaging			Aerosol Particle Concentrations
	Smoke Light Detection (6, 7)	**Schlieren Imaging (8)**	**Laser Light Scattering (9)**	
Description	Smoke particles (0.1–2.5 μm) are mixed in exhaled gas to highlight the exhaled flow. The exhalation plume is then illuminated by a laser light sheet to enable measurements	Use of a *Schlieren* mirror to visualize the flow of fluid of varying density, human-exhaled flow differing from the surrounding air in density	A green laser is transformed into a light sheet, and a camera is used to record the light-scattering events when droplets encounter the light sheet. The size of the droplets is estimated from ultra-high-resolution recordings	Use of an aerosol particle sizer to measure the concentrations of aerosol particles of different sizes (0.3–20 μm) in ambient air
Advantage	Visualizes the gas or aerosol movement during breathing and quantifies the distance of exhaled gas or aerosol			Quantifies the concentrations of aerosol particle ranges in the room air at a specific sampling distance from the patient
Disadvantage	Smoke only represents a small part of aerosol particle range (2.5 μm). Does not reflect the movement of large bioaerosol particles generated during coughing and sneezing. *In vitro* limited method	Does not quantify the concentrations and sizes of the exhaled particles	The size of the droplets is estimated; it mainly counts large droplets, and thus it is limited for small particle quantification	Does not show the movement of aerosol particles, requires sufficient time to clear aerosol particles between interventions, and is very sensitive to background noise
	No measurement of the virus load contained in the aerosol nor its infectious potential			

with the intersubject variability of patient-generated bioaerosols (4). So far, three additional methods have been implemented to assess respiratory aerosol generation and/or dispersion (Table 1).

Using light detection of smoke dispersion technology, the distances at which oxygen devices disperse exhaled smoke, including nasal cannula, simple mask, Venturi mask, nonrebreathing mask, HFNC, NIV, and bag-valve-mask ventilation, were measured (5–7). Smoke dispersion distance was similar among the tested devices. Smoke dispersion distance appeared greater during HFNC therapy (6) when the nasal prongs were malpositioned or with loose connection, and during NIV when a vented mask was used (7). Schlieren imaging (8) and laser light scattering (9) have also been used to visualize the movement of exhaled gas and droplets, and to quantify their dispersion distance from patients, which may indirectly investigate the transmission risk of different medical procedures in a complementary way to smoke detection technology.

Those technologies measuring the dispersion and/or emission of exhaled aerosol or gas are representative of bioaerosol dispersion. However, dispersion must be distinguished from bioaerosol generation, and the potential increased risk of aerosol-mediated infection transmission. The latter is related to the viable viral load disseminated through the aerosol route (10, 11). So far, the virus load of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the aerosol generated from cough or contained in exhaled breath from patients with COVID-19 has not been reported (11), although SARS-CoV-2 was reported to be viable in room air for 3 hours (12). The virus load required to induce infection transmission in humans also remains speculative.

Currently, the measurements of the size and concentration of the bioaerosol particles are important complementary information to dispersion measurements (Table 1). Particle concentration is potentially directly related to the viral load, whereas the particle size impacts the trajectories of aerosol particles: large particles quickly settle down at close distance, and fine particles ($\leqslant$5 μm) that are compatible with healthcare provider inhalation remain in suspension for prolonged periods of time (10).

Gaeckle and colleagues' measurements of particle concentrations at 5 cm from the healthy volunteer's mouth during normal breathing, talking, deep breathing, and coughing were overall insignificantly different across all the test scenarios, including breathing room air or using various oxygen devices (nasal cannula, face mask, HFNC, and NIV) (4). Interestingly, the authors reported lower concentrations of particles with HFNC at 50 L/min and NIV, compared with breathing room air or with a nasal cannula at 4 L/min. Regardless of the types of oxygen devices, coughing was observed to generate higher concentrations of aerosol particles than other breathing patterns.

Their findings confirm that oxygen administration devices are potential aerosol-dispersing procedures, but not aerosol-generating procedures (10). The lower aerosol concentrations detected when using devices with high-velocity gas flow (HFNC, NIV) may be explained either by subject-generated aerosols being dispersed farther away than the measurement location in close vicinity of the subject or by the high gas flow actually opposing exhalation of patient-generated bioaerosol. Whether the particle concentrations, particularly the large particles, at a farther distance from the subject would be higher with HFNC or NIV than breathing room air or using a low-flow nasal cannula remains to be investigated. Regardless, the likelihood is limited that HFNC generates and disperses large amounts of aerosol particles; thus, the risk of dispersing large amounts of virus is relatively low. Of note, the results may only be generalized in similar settings with high-level room ventilation (15 times per hour). Moreover, this room ventilation setting might help quickly clean the

room air between interventions, resulting in low probability of contamination between sequential experimental conditions. Sufficient time to ensure that the particle concentrations return to baseline is necessary between interventions in future studies, especially if frequent air exchange is not available.

Optimal respiratory management of patients suffering from COVID-19 pneumonia is debated; the potential benefits of early intubation, NIV, and HFNC, to be put into balance with the potential risk of bioaerosol generation and dispersion, are controversial; and practice is heterogeneous between units and over time during the pandemic spread (13, 14). As evidence is accumulating against a significantly increased bioaerosol generation associated with the use of HFNC and NIV, clinicians may consider those therapeutic options as they do when caring for patients with hypoxemia without COVID-19, not overemphasizing the potential theoretical risk of increased infectious transmission. In any case, personal protective equipment should be worn by professionals caring for patients with suspected or confirmed COVID-19.

Beyond bioaerosol generation and dispersion, the crucial question that needs to be answered remains the infectious potential of the virus carried by the bioaerosols generated by the patients or various procedures and its relative quantitative importance compared with other routes of viral dissemination such as surface contact. ■

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Invasive Pulmonary Aspergillosis in Ventilator-associated Pneumonia: The Hidden Enemy?

Ventilator-associated pneumonia (VAP) is one of the most important hospital-acquired infections in mechanically ventilated patients. It has a major impact in terms of morbidity, mortality, and health costs.

The microbiology of bacterial VAP has been well established by studies using standard quantitative or semiquantitative microbiological techniques in either distal (BAL) or proximal samples (endotracheal aspirates) (1). The few studies to include rapid molecular techniques have demonstrated an increased rate of microbial diagnoses compared with standard methods (2).

Fungi, and especially *Aspergillus* species, are recognized as a potential cause of VAP in nonimmunosuppressed patients. However, the most recent guidelines do not provide recommendations for their suspicion and diagnosis (3, 4), nor do

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