



# Medical devices in allergy practice

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## ABSTRACT

Medical devices provide people with some health benefits in terms of diagnosis, prevention, treatment, and monitoring of disease processes. Different medical specialties use varieties of medical devices more or less specific for them. Allergology is an interdisciplinary field of medical science and teaches that allergic reactions are of systemic nature but can express themselves at the level of different organs across the life cycle of an individual. Subsequently, medical devices used in allergology could be regarded as: 1) general, servicing the integral diagnostic and management principles and features of allergology, and 2) organ specific, which are shared by organ specific disciplines like pulmonology, otorhinolaryngology, dermatology, and others. The present position paper of the World Allergy Organization (WAO) is meant to be the first integral document providing structured information on medical devices in allergology used in daily routine but also needed for sophisticated diagnostic purposes and modern disease management. It is supposed to contribute to the transformation of the health care system into integrated care pathways for interrelated comorbidities.

**Keywords:** Medical devices, Allergy, Allergology, Allergy diagnosis, Skin tests, Asthma, Lung function tests, m-health, Airway inflammation, Allergic rhinitis

## INTRODUCTION

The simple and straight forward definition of a medical device is any device intended to be used for medical purposes. Based on that, there are a myriad of items which fall within this scope and are used for diagnostic or disease management purposes. A broader general feature that renders devices "medical" is that they provide people with some health benefits and are supposed to improve

their health-related quality of life (HRQoL). They differ by way of the medical field they are used in; or, changing the perspective, the different branches of medicine make use of a variety of medical devices more or less specific for them. As most clinical disciplines derive their names from one or more related organs they are specialized in, the associated medical devices are also organ-specific in most cases.

Allergology is an interdisciplinary field of medical science and teaches that allergic reactions are of systemic nature but can express themselves at the level of different organs across the life cycle of an individual. Subsequently, medical devices used in allergology could be regarded as: 1) general, servicing the integral diagnostic and management principles and features of allergology, and 2) organ specific, which are shared by the corresponding organ-specific disciplines like

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pulmonology, otorhinolaryngology, dermatology, and others (Table 1). Alternatively, medical devices in allergy practice may be classified in terms of the specific pathologic features of the conditions for which they are applied (Table 2).

### What is a “medical device” and what is not

There is a fine line of distinction between medical devices on the one hand, and any other objects, instruments, foods, and auxiliary substances used in everyday life or in healthcare on the other.

While it is clear that scissors on the office desk are not the medical device “scissors” in surgical practice, the difference between medical devices and other products in many other cases may be more obscure. Thus, pharmaceutical formulations fall outside the scope of medical devices despite being used for medical purposes: they contain biologically active compounds which are the result of long meticulous development and need to pass rigid scrutiny for efficacy and safety of the licensing authorities. At the same time, natural products and food additives follow a different track of development and control and are classified as medical devices.

Similarly to pharmaceutical products, laboratory tests are not considered medical devices and are not covered by this overview.

Depending on the health risks they pose, medical devices are categorized into 3 types and respective subtypes. The US Food and Drug Administration (FDA) categorizes medical devices into 1 of 3 classes - Class I, II, or III - based on their risks and the regulatory controls necessary to provide a reasonable assurance of safety and effectiveness.<sup>1</sup> Class I devices generally pose the lowest risk to the patient and/or user, and Class III devices pose the highest risk. In Europe, medical devices are usually regulated by national competent authorities, but the European Medicines Agency (EMA) is also involved in regulating some categories of medical devices in accordance with the recently European Union legislation (Regulation EU 2017/745 on Medical Devices and Regulation EU 2017/746 on In vitro Diagnostic Medical Devices). These regulations, issued in 2017, will be fully applied after a transition period on May 26, 2020 and May 26, 2022, respectively.

EMA distinguishes among medical devices: combination products, medical devices with an ancillary medicinal substance, companion diagnostics, medical devices made of substances that are systemically absorbed, and borderline products.<sup>2</sup> Examples of these categories can also be easily recognized among medical devices of interests for allergology and mentioned in this paper. All medical devices should firstly pass a conformity assessment by a notifying body to receive a Conformité Européenne (CE) mark. Then combination products (such as drugs delivered through inhalers) should be treated as medicines and therefore undergo assessment by EMA as medicines. Notifying bodies should consult EMA for medical devices made of substances that are systemically absorbed and companion diagnostics. EMA can also be consulted by the European Commission for borderline products: medicines or medical devices.

## DEVICES USED FOR ALLERGY DIAGNOSIS AND MONITORING

### Devices for diagnosis of systemic sensitization

#### Skin prick tests

Skin prick test (SPT) is used to detect systemic sensitization to airborne and food allergens, and is used worldwide as first-line diagnostic approach.<sup>3-6</sup> The intradermal test technique is currently limited to the diagnostic work-up of hymenoptera venom and drug allergy. SPT elicits in the skin a visible IgE-mediated wheal and flare reaction that is specific for the allergen tested. The test requires that a minimal amount of an allergen extract containing specific components, both genuine and cross-reacting, to be put into contact with the dermal mast cells by pricking the epidermis. If the mast cells carry on their surface the IgE specific to the component(s) of the allergenic extract, they degranulate and produce the detectable wheal and flare reaction. Thus, to perform SPT, the allergen extract must be put into contact with mast cells by an appropriate device.

The prick devices should be sterile and for one-time use. They can vary in terms of material (plastic or metal), shape (lancet, needle, bifurcated lancet, with or without guard), number (single or multi-puncture devices) and can be prepared as pre-

Medical devices in Allergology	Shared by other specialists	Routinely established/ experimental	Page
<b>Used for diagnosis and monitoring</b>			
Allergy skin tests			
- Skin Prick tests	-	Routinely established	2
- Allergy patch tests	Dermatologists	Routinely established	6
Devices in respiratory allergy			
- Pulmonary function devices	Pulmonologists	Routinely established	7
- Peak expiratory flow meters	Pulmonologists	Routinely established	8
- Plethysmography	Pulmonologists	Routinely established	8
- Carbon monoxide diffusion	Pulmonologists	Routinely established	8
- Fractional expiratory nitric oxide	Pulmonologists	Routinely established	9
- Bronchoscopy	Pulmonologists	Routinely established & Experimental	13
- For sputum assessment	Pulmonologists	Routinely established & experimental	13
- Exhaled breath condensate	Pulmonologists	Experimental	13
- Exhaled breath temperature	Pulmonologists	Experimental	13
- Oscillometry	Pulmonologists	Experimental	14
- For 'omics' research	Pulmonologists	Experimental	13
- Nasal resistance	Otorhinolaryngologists	Experimental	9
- Peak nasal respiratory flow	Otorhinolaryngologists	Routinely established & experimental	9
Devices aimed at allergen avoidance			
- Devices reducing indoor allergens	-	Routinely established	10
- Breathing masks	Pulmonologists	Routinely established	10
- Nasal filters	Otorhinolaryngologists	Routinely established	11
- Mucosal barrier devices	Otorhinolaryngologists	Routinely established	11
Devices for mobile health (mHealth)			11
- Devices for self-assessment	Pulmonologists	Routinely established & Experimental	12
- Devices for treatment assessment	Pulmonologists	Routinely established & experimental	12

(continued)

Medical devices in Allergology	Shared by other specialists	Routinely established/experimental	Page
<b>Used in treatment</b>			
Devices for drug delivery in asthma			14
- Pressurized metered dose inhalers	Pulmonologists	Routinely established	14
- Dry powder inhalers	Pulmonologists	Routinely established	14
- Nebulizers	Pulmonologists	Routinely established	15
- Spacers	Pulmonologists	Routinely established	15
Nasal drug delivery devices			16
- Dropper delivery device	Otorhinolaryngologists	Routinely established	16
- Metered-dose pump sprays	Otorhinolaryngologists	Routinely established	17
- Exhalation delivery desystems	Otorhinolaryngologists	Experimental	17
Energy fields using devices			17
- Rhinophototherapy	Otorhinolaryngologists	Routinely established & Experimental	17
- Laser therapy	Otorhinolaryngologists	Routinely established & Experimental	18
- High intensity ultrasound therapy	Otorhinolaryngologists	Experimental	18
- Radiofrequency turbinoplasty	Otorhinolaryngologists	Experimental	18
- Acupuncture & herbal moxibustion	Otorhinolaryngologists	Routinely established	18
Devices for anaphylaxis management			
- Autoinjectors	-	Routinely established	18

**Table 1. (Continued)** Medical devices used in allergy diagnosis and treatment, shared with other organ specialists

coated with the allergen extract. In this latter case, obviously, no liquid extract solution is needed, and the device directly pricks through the skin. Obviously, there are numerous manufacturers worldwide producing SPT devices, and it is not possible to have an exhaustive list of all of them. The majority of devices have a "guard" around the stinging point that avoids an excessive penetration through the epidermis, limiting the puncture depth to 1 mm. If needles without guard (eg, 23G or insulin syringe needles) are used, the risk of a too deep puncture increases.

SPT is largely operator-dependent,<sup>4,7-9</sup> thus it must be performed by well trained personnel. All

the material used must be sterile, and one device for each single allergen must be used (except for the case of multiple-site devices).<sup>4,5</sup> In the commonly used procedure, a drop of the extract is placed on a marked part of the skin; then the device is pushed through the drop and epidermis until the dermis is reached. The SPT procedure should not evoke bleeding.<sup>6</sup> If positive, a wheal and flare reaction appears after 10-20 min, which is typically accompanied by local itching. The most common causes for false negative results are insufficient depth of the prick (so that dermis is not reached) or interference by drugs (most often antihistamines). Causes of false positive results are excessive pressure

Diagnosis/treatment of structural and functional pathologic features	Medical Devices
IgE-mediated sensitization	Skin Prick Test (SPT) devices
	Intradermal test (ID) devices (only for drug allergy and hymenoptera allergy)
Type 4 sensitization	Atopy patch tests
	Patch test for contact sensitivity
Airway pathology and function	Portable respiratory measurement instruments
	Plethysmography and CO diffusion
	Pressurized metered dose inhalers, Dry powder inhalers
Bronchial inflammation	Bronchoscopy
	Induced Sputum
	Fractional Exhaled Nitric Oxide (FeNO)
	Exhaled breath condensate, Exhaled breath temperature
Nasal function and underlying pathologic mechanisms	Peak Nasal Inspiratory Flow (PNIF)
	Nasal Cytology
	Rhinophototherapy, Laser-therapy, Phototherapy
Anaphylaxis	Adrenaline autoinjectors
Devices to avoid allergens	Masks
	Nasal filters
	Barrier enhancing medical devices

**Table 2.** Diagnostic and therapeutic medical devices classified in terms of the specific pathologic processes they are applied for *PMDI*; *DPI*; *r*

(nonspecific irritative reaction) or the presence of dermographism.<sup>4</sup> For those reasons, the SPT is considered highly tester-dependent.

The influence of the specific characteristics of a given device on the results of SPT has been discussed in the literature, but well-designed studies comparing different devices are few, and the results are not conclusive. Fatteh et al compared the SPT results obtained with different devices and reported significant variability among the devices tested.<sup>7</sup> Warner et al found significant differences for all aspects of device performance for all devices they assessed, and also noted that multi-headed devices had a significant intra-device

variability and were more painful than single-prick devices.<sup>10</sup> In this study, multi-headed devices had larger reactions when applied on the back, whereas single devices had larger reactions on the volar surface of arms. One study showed that metal lancets and syringe needles were superior in sensitivity to other devices.<sup>11</sup> Again, another study evaluated the influence of the weight of the devices used (lancets and needles) and concluded that lighter devices could provide more reproducible results.<sup>12</sup> A meta-analysis focusing the diagnostic accuracy of SPT included 7 studies.<sup>13</sup> The pooled estimate of sensitivity and specificity for the test was 88.4 and 77.1%,

respectively, but no specification was provided on the devices used. Of note, it was shown that the SPT devices passing through the drop of allergen extract were equivalent in sensitivity and specificity to the pre-coated lancet (no description was provided of the device used).<sup>14</sup> In children, it was clearly shown that the puncture technique (with or without rotating the prick device at puncture) modifies the results, thus highlighting the relevance of the technique.<sup>15</sup> When intradermal tests and a multi-head device (*Multi-Test II*<sup>®</sup>) were compared, no clear difference in the performance could be established.<sup>16</sup> In another open not randomized study the multi-head SPT had a comparable performance as the dilutional intradermal test.<sup>17</sup>

In addition to the device- and operator-dependency of SPT, the concentration/potency of the allergen extract should be taken into account. There is still a wide variability in the allergen content and the presence of major allergens among commercial extracts, which may contribute to the level of reproducibility and variability of the SPT results.<sup>18-21</sup>

Concerning the safety of the procedure, the risk of systemic adverse events is extremely low. In fact, systemic reactions have been described mostly with scratch and intradermal tests (in particular with drugs or crude food). The estimated occurrence of severe anaphylaxis is less than 1 in 50,000 subjects, with a still lower rate of fatal cases.<sup>22-25</sup> Thus, according to the available literature and case reports, it is suggested that for SPT execution (independent of the device used) only the first-line precautions have to be observed.<sup>26</sup>

SPT remain the first-line diagnostic approach for IgE sensitization. Its value resides in the best cost/benefit ratio, rapidity of response, concordance with biological IgE assays, and safety.<sup>4-8,27</sup> Many different devices for SPT have been proposed over time, with variable and difficult to interpret results. It is clear that there are 3 main variability sources: 1) concentration and potency of the extract; 2) nature of the device (metal, plastic, with/without guard, pre-coated, etc); 3) operators' skill. Looking at the available literature, it is not possible to identify a SPT device as the gold-standard. The recommendation is that each operator should use, when possible, the same

allergenic extracts and the same type of devices. Also, a proper and detailed training in the use of SPT is recommended for all healthcare operators, with a periodic review of the technique.<sup>4-7</sup>

### Allergy patch tests

Patch tests (PT) have undergone a long evolution to still remain the cornerstone of contact dermatitis diagnosis and the technical aspects of the method have been quite well refined and standardized.<sup>28-30</sup> The principle of the test is to evoke a delayed (type IV) reaction after applying on the skin of the patient alleged allergens so as to replicate a natural inflammatory response due to the influx of specifically primed lymphocytes. The tested substances must remain into direct contact with the skin for at least 48 h.<sup>31-33</sup>

The substances to be tested and a negative control (usually vaseline) are inserted into patches and applied by occlusion usually on skin free of lesions on the upper back of the subjects. The site is chosen in order to have a surface large enough to test many substances at the same time. The readings are made at 48 and 72 h after the application and the relevance of any positive tests to the clinical presentation in the individual patient must be considered. Once placed on the skin, PTs are usually kept about 48 h; they can be read at that time-point, or outlined with special markers for a second reading usually done at 72 or 96 h.<sup>34,35</sup>

The basic requirements for a patch-test chamber are an inert material applied to a hypoallergenic tape for providing good occlusion and fixation for at least 48 h. The allergenic substances are embedded in round or square patch chambers of 8-18 mm size which can be of metallic (aluminium) or plastic material (polyethylene).<sup>31</sup> It is not clear, according to the literature if the chambers' size can affect the accuracy of the test.<sup>36,37</sup> There are different patches usually sold in blocks of 5 or 10 chambers included in bands of hypoallergenic adhesive material. When liquid allergens are used, they sometimes require the use of a filter paper to retain them. In recent years, new transparent and water resistant PT have been introduced.

There are numerous pre-defined standard panels of substances (professional, cosmetics, detergents) at national or international level (baseline

series); they vary according to geographical regions according to the decisions of local specialists' societies and are revised periodically.<sup>33,38-41</sup> PTs can be pre-defined and ready to apply, or can be prepared *ex tempore*, choosing only the substances to be tested. In this latter case, there are commercial solutions at pre-specified concentrations that are mounted in patch chambers. There are also individually tailored occupational series with materials contributed by the patient.<sup>42</sup> The allergens are usually diluted in petrolatum, water, or alcohol and rarely with other materials (olive oil, acetone). They are applied at low concentrations that have demonstrated their efficacy.<sup>43</sup> They are deposited with pre-filled syringes with an estimated amount of 20–25 mg for solids (9) and 15 µg for liquids (with micropipette or dropper).<sup>44</sup> There are already pre-charged commercial PT that are easy to use and save time (eg, T.R.U.E. Test).<sup>45</sup>

Although there are many commercialized devices for PT (for review see Jonker et al),<sup>34</sup> there are no studies comparing the devices, *per se*; thus, no experimentally supported recommendation for choosing a specific device can be made so far.<sup>32,46-48</sup>

Atopy Patch Tests are used to study atopic dermatitis in relation to environmental foods or allergens. The chambers used are recommended to be large (12 mm).<sup>49</sup>

Photopatch tests (PhPT) are used to assess photosensitivity reactions and are applied in duplicate on the skin; one of them will be irradiated with UV radiation, usually A (UVA), and the other will remain non-irradiated.<sup>50</sup> These allergens are usually related to sunscreens, plants, non-steroidal anti-inflammatory drugs (NSAIDs), and others that require sun exposure to trigger dermatitis. Results will be reported as negative (both negative areas), positive PhPT (when there is positivity only in the irradiated area), allergic contact dermatitis (when the positivity appears in both and of equal intensity) and allergic photoaggravated contact dermatitis (when both are positive but with greater intensity in the irradiated area).

There are many other auxiliary devices used in patch testing helping the positioning of the

chambers and the documentation of the results, summarized in García-Abujeta.<sup>51</sup>

### Diagnostic devices in respiratory allergy

Devices used for respiratory allergy disorders in general are used to assess the functional capacity of different parts of the respiratory system, from nasal patency to the capacity of alveo-capillary membrane to provide adequate exchange of gases between the respiratory and cardiovascular systems. These devices are more organ specific than disease specific and are used also in otorhinolaryngology and pulmonology. Because the results of the measurement done with these devices are not disease specific, they can be used only to support the clinical diagnosis and not to make one. They also can support the management of allergic disorders, as they are sensitive to change due to therapeutic interventions. Allergic disorders can impair the function of the respiratory system in different ways depending on the part of the respiratory system they affect and the type of allergic reaction.<sup>52</sup> Based on the underlying pathology, different devices can be used either on their own or in combination to evaluate the state of the airways from nose to small airways or alveoli.<sup>53,54</sup> The most commonly used devices are the spirometers to assess pulmonary function, while the ones measuring nasal patency are least commonly used, most probably because of the poor correlation with the clinical presentation.<sup>55</sup>

### Pulmonary function test devices

Pulmonary function test devices, or spirometers, are medical devices that measure dynamic lung volumes and flows by recording the changes in volume over time during maximal (forced or slow) inspiration and expiration. There is a high degree of standardization prescribed by the leading pulmonology societies, the European Respiratory Society (ERS) and the American Thoracic Society (ATS), for the technical characteristics of the devices, the maneuvers of inhalation and exhalation, and the proper assessment of the measurement.<sup>56-58</sup> The devices use different techniques to measure volume over time: 1) direct measurement of volume, and 2) indirect measurement of volume by measuring the flow using different techniques. Either way a calibration to a standardized volume (3L) is needed. Flow can be measured using: 1)

the difference in pressures before and after the barrier (the so called resistance net), 2) ultrasound, or 3) a propeller device; the last one can be used as a pre-calibrated single use part for the spirometer.<sup>57,59</sup> These devices measure 3 volumes: tidal volume (VT), inspiratory reserve volume (IRV), and expiratory reserve volume (ERV), the sum of which give the vital capacity (VC) or forced vital capacity (FVC), depending on the maneuver used – slow or forced expiration. When using a forced maneuver, the forced expiratory volume in 1 s (FEV1) is also calculated as the measure of obstruction. As the flows are also measured, standardized flows are also calculated: peak expiratory flow (PEF), and forced expiratory flows (FEF) at 25%, 50%, and 75% of FVC.<sup>57</sup> After assessing the technical validity of the measurement, the results are then compared with the reference values, GLL, and expressed as z-values and percentage of a predicted normal.<sup>60,61</sup> Two distinctive pathological patterns are recognized based on this: obstructive and restrictive.<sup>60</sup> Obstructive pattern is a characteristic of allergic asthma, but can be present also in allergic alveolitis.<sup>62</sup> As asthma is characterized with reversible obstruction, spirometry can be used in combination with short- or long- acting bronchodilators or corticosteroids to do a pharmacodynamics test or as a monitoring tool to assess the effectiveness of treatment or disease control.<sup>63</sup> Pulmonary function testing is also recommended in patients with allergic rhinitis or other allergic disorders (atopic dermatitis or food allergy), because up to 30% of patients suffering from these conditions may also have unrecognized asthma.<sup>64</sup> With the advances in technology, pocket, handheld, and smartphone supported devices (spirometers) are available on the market for a reasonable price to be used for home monitoring, but they can be used in highly compliant patients, although more standardization is needed.<sup>59,65</sup> When a restrictive pattern is present, further diagnostics (body plethysmography and/or CO diffusion) are recommended.<sup>60</sup>

#### Peak expiratory flow meters

Peak expiratory flow meters are simple, handheld personal devices that measure the maximal peak expiratory flow (PEF) that represents just a

single point of the flow-volume curve recorded during forced spirometry.<sup>57,66</sup> PEF results are expressed in L/min and reflect the airway patency mostly associated with the large conductive airways, and only in a small proportion of the mid-airways; they also account for the strength of the expiratory muscles which exert extrathoracic pressure of the airways.<sup>7</sup> PEF is highly associated with the level of effort, so reliable results can be expected from adherent and compliant patients.<sup>66,67</sup> PEF-meters can be used both to support the diagnosis of asthma and for monitoring purposes. It is also recommended as the part of the Asthma Action Plan (AAP) to assess risk of exacerbations and for treatment adjustments to preserve and maintain control of the disease.<sup>63,66,68</sup> Once individual patients establish their personal best result, green, yellow and red marks can be added on the scale of the devices, allowing self-assessment of the need to updose the treatment or to seek medical advice in accordance with the written AAP.<sup>63,66</sup> There are both mechanical and electronic devices present on the market, the latter storing the separate attempts in digital format for review by the consulting physician.<sup>67</sup>

#### Plethysmography - carbon monoxide diffusion

Body plethysmography and carbon monoxide (CO) diffusion measuring devices assess additional lung function parameters like static lung volumes and capacities: residual volume (RV), total lung capacity (TLC), functional residual capacity (FRC). They use 2 different methods to evaluate the restrictive pattern suggested on spirometry.<sup>69,70</sup> The downside of both methods is the expensive equipment and the need for highly specialized and trained staff, confining them to tertiary healthcare level premises. Another limitation of body plethysmography is that it measures all the air in the chest, thus overestimating the TLC, especially in aerophagia; conversely CO diffusion underestimates TLC in severe airways obstruction or when non-ventilated or poorly ventilated areas in the lungs exist.<sup>69</sup> These shortcomings derive from the methods of measurement. Body plethysmography uses the principle of Boyle-Mariotte to assess FRC by calculating it from the volume of gas in the body box, the pressure in the body box, and the pressure at the mouth (representing alveolar pressure) on the level of FRC



using a shutter. It additionally measures the mechanical properties of the lung and airways – resistance and compliance.<sup>71</sup> A proper assessment of RV is crucial to distinguish between real restriction (loss of lung volume) and hyperinflation (increase in RV due to obstruction, primarily on the level of small airways).<sup>60</sup> CO diffusion measures TLC using the dilution of an inert gas (helium or methane) along with a low concentration of CO.<sup>70</sup> This mixture is inhaled from the level of RV (after complete exhalation) to the TLC. Expired concentration of the inert gas is measured with the fall in concentration being proportional to the RV.<sup>70</sup> The method additionally measures the fall in CO concentration after the breath hold of 10 s when CO concentration additionally decreases (besides dilution) because of diffusion through the alveo-capillary membrane, thus providing the information about the diffusion capacity of the lungs.<sup>70,72</sup> Diffusion capacity can be significantly decreased in allergic alveolitis, and CO diffusion represents a significant part of the diagnostic process in this disorder.<sup>62</sup>

#### Nasal resistance/peak nasal inspiratory flow

Nasal patency can be assessed using different techniques, all of which have a significant shortcoming: they lack significant association with the clinical presentation, ie, the pathological signs and symptoms.<sup>55,73,74</sup> This is the reason why they are seldom used in clinical practice and are rarely used in clinical trials. Basically, 3 different types of devices are used to assess nasal patency: rhinomanometers, acoustic rhinometers, and peak nasal inspiratory flow (PNIF)-meters.<sup>73-77</sup> The first two instruments assess each of the nostrils separately, while PNIF provides an integral result for both nostrils at the same time. The shortcoming from assessing the separate nostrils is based in the nasal cycle that changes the dominating nostril every 2-4 h significantly changing the nostrils' patency in turns. This can also be because of the change of the posture.<sup>78</sup> A confounder with the PNIF could be the collapse of the *alae nasi* during forced inspiration.<sup>55,77</sup> Rhinomanometry can be anterior or posterior, and it uses 1 blocked nostril as a sampling site for pressure and measures the flow from the active one that the patients breathe

through during the measurement, repeating the procedure with the alternative nostril. The resistance is calculated based on the flow measured at a standardized pressure for each nostril. Calculating the total nasal resistance is a way to overcome nasal cycle changes because the total nasal resistance stays approximately the same even during the nasal cycle change.<sup>75</sup> Acoustic rhinometry uses sound waves and their rebounding to assess the cross-sectional area and length of the nasal cavity, thus providing information on its structure and dimensions. The problem is the low level of standardization of this method.<sup>75</sup> PNIF is a cheaper handheld device that can be used for daily individual measurements but is rarely used in routine practice.<sup>55,77</sup> The latest study confirmed the low association between PNIF and the levels of baseline nasal symptoms assessed by a validated questionnaire, but on the other hand showed a comparable measure of clinically significant change after intervention.<sup>79</sup> Most recently, visual analog scale (VAS) was validated to assess the severity of the nasal symptoms, and a mobile app on a smart phone can now be used to guide management of allergic rhinitis.<sup>80</sup>

#### Fractional expiratory nitric oxide

Nitric oxide (NO) acts as a bronchodilator and is produced in highest quantities from the nasal mucosa from paranasal sinuses having a significant role in the homeostasis of the respiratory system.<sup>81</sup> It has also been shown that NO production could be significantly increased by inducible NO synthase in association with allergic/eosinophilic inflammation.<sup>82</sup> NO production can also be suppressed in certain conditions, like cystic fibrosis (CF), primary ciliary dyskinesia (PCD), or in untreated gastroesophageal/laryngopharyngeal reflux disorders.<sup>83</sup> The commercial devices measure fractional exhaled nitric oxide (FeNO) using a higher precision chemiluminescence method and an electrochemical method, smaller and less expensive devices, requiring, though, consumables. The measured FeNO concentrations are rather low, in part per billion (ppb) and require careful calibration of the devices. The measured level of FeNO is dependent on the flow rate during exhalation, so an ATS/ERS standard of expiratory flow rate of 50 ml/s is recommended

for the measurement.<sup>84,85</sup> Different flows can be used to assess the fractions originating from different parts of the airways, but for now only for research purposes. The devices are well standardized and regularly used in clinical practice.<sup>85</sup> Some devices are modified to measure nasal FeNO, and also FeNO in air sampled from non-cooperative or patients on assisted ventilation.<sup>84,86</sup> These devices can be used to support the diagnosis of allergic/eosinophilic inflammatory disorder (asthma, allergic rhinitis), to monitor/guide the adherence and effectiveness of treatment, and for screening of patients with CF and PCD on the basis of a negative result.<sup>83,86,87</sup>

## DEVICES AIMED AT ALLERGEN AVOIDANCE

### Allergen avoidance as a fundamental approach in allergology

Allergen avoidance is one of the cardinal principles in the management of allergic diseases.<sup>88</sup> This involves any measures taken to minimize the contact between the allergens of the ambient environment and respective mucosal surfaces and skin of the human organism. The approaches to achieve this goal range from simple cleaning methods to reduce the dust and allergen levels indoors, to filtration and ventilation systems of residential and office buildings.<sup>89</sup> Universal appliances and reagents used for trivial household hygiene do not pertain to the category of medical devices, as opposed to the specifically tailored tools and non-pharmacological compounds used to protect subjects with sensitization to indoor and outdoor allergens.

### Medical devices used to mitigate the effects of indoor allergens

House dust is invariably present in all dwellings. Its ubiquitous components are different species of live mites and their metabolites, moulds, fungi, cockroach, and pet (where relevant) allergens which cause allergic sensitization and subsequent clinical symptoms of asthma, rhinitis, or atopic dermatitis in predisposed subjects.<sup>90-92</sup> Interventions aiming to eliminate house dust mites or to reduce exposure to their antigens are usually centered at bedrooms, where mites find

optimal temperature, humidity, and food (human epithelia) for their development in the beds and the associated linen/beddings. The methods used to this end comprise general measures to reduce indoor relative humidity through ventilation,<sup>89</sup> removing allergen carrying materials from floors and furniture (including fluffy toys), vacuuming with HEPA (High Efficiency Particulate Air) filters,<sup>93</sup> ionizers,<sup>94</sup> freezing and hot washing ( $\geq 55$  °C), spraying with acaricides.<sup>95</sup> While all of these interventions bring about indoor allergen reduction, little clinical benefit has been achieved with any one of the separate methods in sensitized subjects. Therefore, it has been recommended that patients do not resort to a single preventive method aimed at reducing allergen exposure.<sup>96</sup>

Most devices used for allergen elimination are not specifically designed for the allergy practice. Among those, which are actively promoted for direct sales to subjects with asthma, allergic rhinitis, and atopic dermatitis for use in their homes as individual medical devices, are beddings made of fabrics, meant to impede the development of mite colonies. There is an industry manufacturing impermeable covers and encasings of mattresses and pillows whose fabric and zippers would not let through dust mites, their metabolites and eggs.<sup>97</sup> Despite the controversies about their clinical usefulness, these products maintain a steady presence on the medical devices' market as evidenced by the long list of companies selling them on Internet.

### Breathing masks

Covering the face with handkerchiefs, scarves, and veils is the simple-most instinctive way of self-protection from any visible or perceived air-born hazards that may penetrate the airways. Historically, cloth masks attached over the mouth and nose were worn on mass scale as a (questionably effective) protective means during the global influenza epidemics in the twentieth century. Still now medical staff and patients wear disposable cloth masks, also known as "medical" or "hygiene" masks, to cut the likelihood of contracting or passing on air-transmitted infections.<sup>98</sup> In the last decades face masks became increasingly popular first in Asia, but subsequently spreading elsewhere, as a means against air pollution.

Basically, a breathing mask is a shield made from fibrous material (cotton, microfiber, woven cloth, plastic, or even paper) meant to trap allergens, particulate matter, microbes, and gaseous irritants. In addition, masks can also temper the inspired air and thus prevent attack of cold and dry air induced bronchospasm. The more sophisticated models containing special cartridges and valves can retain also fine particle of less than 2.5  $\mu\text{m}$  and also some gaseous components.

It is conceivable that breathing masks could be protective against allergens. Surprisingly, there are not many studies testing how effective masks are against common outdoor allergens like pollens. Actually, a study on subjects with Japanese cedar pollinosis found a statistically significant decrease in clinical symptoms despite the fact that the number of pollen particles in the nasal cavity and on the conjunctiva was unchanged by wearing a facemask and eyeglasses.<sup>99</sup> By all means, face masks can provide protection of the airways and conjunctiva in different occupational settings. Specifically designed studies are required to characterize the efficacy of a given model of a breathing mask in reducing the amount of inhaled allergens and the clinical symptoms.

#### Nasal filters

In essence, nasal filters are meant to sieve away particulate matter when inhaled through the nose. Their key component is a membrane that removes particles by means of interception and impaction, which is placed in each nostril's anterior vestibule and kept in place by a frame.<sup>100</sup> They are disposable and are engineered in a way so that the inevitable increase of air resistance across the filtering membrane is below the level of perception of the subject. Nasal filters act as invisible breathing masks confined to the nose and still have to prove their utility and benefits like clinical effectiveness, convenience, comfort, and safety at acceptable cost.<sup>101,102</sup>

#### Mucosal barrier enhancement devices

Barrier-enforcing measures protecting the nasal mucosa and blocking contact with potentially harmful substances such as allergens and particulate matter can be implemented: these may be viewed as a means to achieve allergen avoidance,

and, arguably, that all patients may be recommended to use such an approach.<sup>103</sup> Ideally, if implemented properly, this strategy could make the use of any other therapeutic action unnecessary. Attempts have been made to use different substances as barrier enhancers. These include cellulose derivatives,<sup>104,105</sup> white vaseline, allergen blocker creams,<sup>106-108</sup> lipid based ointment,<sup>108</sup> microemulsion,<sup>109,110</sup> liposomal formulation,<sup>111</sup> and seawater gel.<sup>112</sup> Many of the listed approaches had not progressed to the stage of commercialization. Among these, a powder microcrystalline hydroxypropyl-methylcellulose formulation has been developed into a patented medical device and backed up by over 20 clinical studies.<sup>113</sup> However, not all derivatives from the broad variety of cellulose derivatives can offer nasal protection as demonstrated by a liquid nasal spray, which was not proven efficacious in a nasal challenge test model.<sup>114</sup>

### MOBILE APPROACHES (MHEALTH)

We are witnessing an amazing technological development that can be referred to as a "mobile revolution; it is characterized by a widespread use of connected mobile devices such as smartphones, tablets, and laptops. These tools are modifying many aspects of our lives including health care. "Mobile-health", or "mHealth", refers to this set of mobile health applications, and the World Health Organization (WHO) has stated that mHealth has the potential for changing the overall process of healthcare worldwide.<sup>115</sup> The availability of powerful processors, ever-growing memory capacity, user friendly tools, and penetration of the Internet in all populated areas across the globe have given rise to a new health culture and behaviors and allow the monitoring, storage and sharing of clinical data, promoting self-assessment and altering patient/physician communication.

These processes lead to a radical change in the diagnostic algorithms and in the long-term management of chronic diseases.<sup>116</sup> It is envisaged that current procedures and services will be reconsidered, leading to a greater appropriateness at all stages of the healthcare process. The above mentioned evolution is in line

with the development of a personalized approach (precision medicine), that includes a tailored action based on individual genetic pattern and clinical data.<sup>117</sup>

### Self-assessment

Mobile applications (known by the abbreviation “apps”) for health are software created for smartphones and tablets, whose function is to monitor the symptoms and clinical parameters, allowing patients to check their health status. They also improve patients’ adherence to treatment and enhance their communication with healthcare providers or physicians. The results of a recent review showed that in 2018 there were 325,000 mobile health apps available to smartphone owners worldwide with an additional 200 health apps being launched daily.<sup>118</sup>

Many wearable devices (bracelets, watches, bandages, bands) detect through the use of special sensors specific physical parameters (ie, heart rate, respiratory sounds), level of physical activity (ie, number of steps performed, hours of inactivity), sleep (hours of sleep, REM sleep, nocturnal awakenings, snoring), and allow self-monitoring of biological parameters in daily life in a passive and non-intrusive manner.<sup>119</sup> Furthermore, wearable sensors allow matching exposure to environmental triggers (ie, pollutants or allergens) to the patient’s physiological data.

### Mobile-based treatment assessment

Technology is transforming inhalers from tools for drug administration to instruments of care. The incorporation of modern electronic components into inhaler devices is aimed to reduce inhalation errors, to improve patient adherence, and to monitor and manage patients’ disease states.<sup>120</sup>

The first built-in inhaler monitoring technology, that essentially allowed recording of the inhaler activation, was developed in the 1980s.<sup>120</sup>

Developers have pursued different strategies; while Adherium Smart Inhaler Tracker, able to store the dates and times of inhaler actuations, is compatible with several inhaler types, eg. SmartTurbo<sup>®</sup>, SmartDisk<sup>®</sup>, and SmartTrack<sup>®</sup> (Adherium), the Propeller Health device was the first to incorporate Global Positioning System

(GPS) functionality, in order use the geo-location to map potential triggers of exacerbations or the use of rescue medication due to symptoms. Several devices, such as Care TRx<sup>®</sup>, Sensohaler<sup>®</sup>, Inspiromatic<sup>®</sup>, T-Haler<sup>®</sup>, and X-haloHome<sup>®</sup> are capable of monitoring lung functional parameters such as peak expiratory flow (PEF) and inhalation flow and volumetric flow rate and exhaled breath temperature.

The smart inhalers are provided with dose-memory and dose-reminder functions with a positive effect on adherence.<sup>121,122</sup> The clinical benefits of this approach, in terms of reduction of number of oral steroids bursts and hospital admissions, have been shown.<sup>123</sup>

Digital health developments have also shown great utility in the management of device errors, and are now able to provide detailed feedback on patients’ device competence.<sup>120</sup> The SmartMist<sup>™</sup> and MDILog<sup>™</sup> have both included sensing capabilities to facilitate the assessment of inhalation technique. The latter one is provided by an accelerometer for the detection of inhaler shaking and a sensitive temperature sensor for the assessment of inhalation. Furthermore, Amiko<sup>®</sup> is able to monitor loading, inhalation, inspiratory time, and orientation.<sup>124</sup> Inhalation detection technologies can be used to coach patients on correct device technique. Apps are under development which have the potential to correct inhaler errors with, for example, pop-up instructional videos based on real-time measurements.

The above mentioned technologies, along with other innovative e-health developments, have the potential to reduce the resource burden on healthcare systems and provide optimal and personalized asthma management to patients.<sup>125</sup>

Technologies and innovations are relevant to improve public and individual health and they offer real opportunities to improve chronic disease management, increase the appropriateness of treatment choices, and lower costs, keeping the patient at the center of the care process.

## OTHER DIAGNOSTIC APPROACHES INVOLVING MEDICAL DEVICES

The substantial economic impact respiratory allergies pose on society has prompted intensive research involving the use of different medical devices. These devices have been used or specially developed as part of methods aimed at improving diagnosis and disease management. Following is a listing of investigational methods and implicated medical devices not routinely applied in clinical practice, with short commentaries on the prospects they offer.

### Bronchoscopy

Historically bronchoscopy with biopsies and bronchoalveolar lavage, eventually combined with bronchial allergen challenges, made possible the formulation of the present understanding that a common feature of all phenotypes of asthma is airway inflammation driven by different mechanisms defining different disease endotypes.<sup>126-128</sup> Nowadays, there are different modifications of the bronchoscopy equipment combined with ultrasonography, electromagnetic guidance, and high resolution imaging techniques, which allow high precision diagnostic procedures reaching much deeper in the lung periphery.<sup>129</sup> On the basis of bronchoscopy, bronchothermoplasty has been developed as a therapeutic method in severe asthma.<sup>129</sup>

### Sputum

Induction and examination of sputum have been developed as a non-invasive proxy to the bronchoscopic methods.<sup>130-133</sup> The medical devices associated with examination of sputum are nebulizers for induction of sputum with hypertonic saline solutions and laboratory equipment including standard and cyto-centrifuges for assessment of the fluid-phase and cellular components of sputum. The sputum associated methods are time-consuming, expensive, and requiring sophisticated lab equipment, so they are mostly confined to highly specialized centres.

### Exhaled breath condensate

Collection and examination of exhaled breath condensate (EBC) is another non-invasive method to assess biomarkers deriving from the

intrathoracic airway contained in the epithelial lining fluid.<sup>85,134,135</sup> It makes use of collection devices, the principle of which is passing exhaled air through a cooling chamber so that the breath vapor and droplets from the epithelial lining fluid of the airways containing volatile organic compounds are sampled during tidal breathing of the examined subject. After collection, the EBC samples are further processed to identify biomarker profiles useable for the diagnosis and management of airway diseases.

### The "-omics" approach

Genomics, proteomics, metabolomics, and other "-omic" methods measure compounds of different specificities contained in the exhaled breath/EBC and can be referred to as breathomics.<sup>136</sup> They rely on different modifications of liquid chromatography and/or mass-spectrometry for identification of compounds associated with different pathological processes in the airways and the creation of libraries of molecules as well characterized biomarkers.<sup>107</sup> The clinical utility of these molecular approaches has yet to be demonstrated, as the replicability of the results obtained from different research teams is rather low.

### Exhaled breath temperature

Measurement of exhaled breath temperature (EBT) has been suggested as a non-invasive method to detect inflammatory processes in the airways as a result of increased blood flow within the airway walls.<sup>137-139</sup> As EBT values are within a narrow range, the thermometers designed for the purpose of assessing it need to be precise and very sensitive. EBT increases linearly over the pediatric age range and seems to be influenced by gender, but not by height and body weight.<sup>140</sup> When interpreting EBT in subjects with alleged airway pathology, the possibilities of tissue destruction (chronic obstructive pulmonary disease, cystic fibrosis) or excessive bronchial obstruction and air trapping (severe asthma) need to be considered, as these conditions drive EBT down.<sup>141</sup> A prominent advantage of the method is to assess EBT when patients are in a steady state of their disease and to use this "personal best" to monitor them and guide their treatment. Individual devices outfitted with

microprocessors and memory have been created, which can be used for personalized monitoring and disease management by telemedicine.<sup>142</sup>

## Oscillometry

Impulse oscillometry (IOS) is a noninvasive method, which uses sound waves to measure respiratory mechanics.<sup>143,144</sup> It is based on the principle of forced oscillation technique (FOT), which superimposes sound waves of different low frequencies upon the breathing maneuver of the tested subject. The IOS/FOT methods are patient-friendly since they require minimal cooperation and thus can be applied in children, very elderly people, and subjects who are on ventilators. FOT and IOS measurements use equipment of different construction and can detect subtle changes in the small airway function even in the setting of normal spirometry. A limitation of the oscillometry methods is the broad variability of the results and need to further validation.

## DEVICES USED FOR TREATMENT

### Asthma drug delivery by inhalation devices

Drugs delivered through inhalation go directly to the lungs, by-passing the systemic circulation, thus achieving a rapid local effect at lower doses and with fewer adverse events. These benefits have rendered inhalation therapy a preferred route of drug administration for many respiratory conditions. In the last 3 decades, all types of devices for drug delivery by inhalation have evolved and diversified into a wide array of models incorporating different concepts. At present, more than 250 inhaler devices licensed for drug delivering in chronic respiratory disorders. The effectiveness of the inhaled route of administration is related with the appropriate choice and correct use of an inhaler device.<sup>145</sup>

#### Pressurized metered dose inhalers

Historically, pressurized metered dose inhalers (pMDIs) were the first introduced in clinical practice and are the most commonly used pocket-sized devices for delivery of fixed doses of aerosolized drug into the airways. Metered dose inhalers offer multiple advantages such as portability, no need of an external power source, and release of fixed-doses uniformly over time.<sup>146</sup>

A pMDI is a pressurized system comprising in a metal container a mixture of propellants, flavouring agents, surfactants, preservatives, and active drug comprising approximately 1% of the total contents. The drug delivery through the pMDIs takes place when the mixture is released from the delivery device through a metering valve and stem which fits into the design of an actuator plastic boot. Small changes in the actuator design can affect the aerosol characteristics and the shape of the jet plume.<sup>146</sup>

pMDIs emit the dose at high velocity, which makes premature deposition in the oropharynx probable. They require careful coordination of actuation and inhalation, requiring demonstration, active training and repeated follow-up by the attending healthcare professionals. pMDI needs vigorous shaking in case of suspensions.<sup>147</sup> (4) Classical pMDIs deposit the array of their droplets mainly in the central airways, so that only 10–15% of dose is reached to the lung; devices designed to generate extrafine aerosol could deliver it more to the periphery.<sup>148</sup> Breath actuated devices have also been launched on the market, which omit the coordination between actuation of the device and the inhalation.<sup>149</sup>

#### Dry powder inhalers

Dry powder inhalers (DPIs) are breath actuated devices which contain medication in the form of powder and deliver micronized dry particles with specified characteristics to the respiratory airways on inhalation. The energy emitted from the patient's inspiratory airflow is the driving force for powder dispersion from the device.<sup>150</sup> DPIs are actuated with the onset of the inhalation and require minimal coordination on the part of the patient. When reaching the intrathoracic airways, the dry powder formulation is subjected to larger dispersion forces and splits into individual particles.<sup>151</sup> As opposed to pMDIs, which have similar characteristics despite the different manufacturers, DPIs are mostly “company-specific” and follow different inhalation protocols. Comparative studies have been performed to outline the differences between the different models.<sup>146</sup> This requires acquiring of special skills by the patients when using different DPIs. In general, a faster airflow is necessary for the increase in the particle split and the stronger

impactions achieve a higher fine particle fraction reaching deeper into the airways. However, a very rapid airflow may increase the deposition in the region of oropharynx and thus reduce the delivery of the drug to the lungs.<sup>151</sup> The performance of the DPI system depends on performance of powder formulation and the inhaler device. The modern devices are being designed for different powder formulations, single or multiple DPIs.<sup>152</sup> In single-dose DPIs, the dose is formulated inside individual capsules. The mechanism of a single dose delivery is that the patient must load the device with 1 capsule before each administration. The multi-unit dose DPIs have the advantage that before administration of each dose it does not have to be reloaded, as it utilizes the factory-metered and sealed doses packaged so that the device can hold multiple doses at the same time.<sup>153</sup>

### Nebulizers

Aerosol therapy-nebulizers transform liquid drug formulation into aerosol of desired characteristics to be inhaled into the respiratory tract. They have a role in the treatment of asthma and have particular value in treating subjects with very low lung volumes as in severe asthma exacerbations, but also in young children and elderly, in ventilated, non-conscious patients, and, in general, in those who are unable to use pMDIs or DPIs.<sup>146,154</sup> Nebulizers contain a medication reservoir, nebulizing mechanisms, and mouthpiece or facemask.<sup>155</sup> They can generate a spectrum of droplets (ideally in the range from 1 to 5  $\mu\text{m}$ ), the finest of which can reach deep into the lungs.<sup>156</sup> There are 3 main types of nebulizers: jet-driven, ultrasonic, and mesh-nebulizers.

Jet nebulizers are the most commonly used drug delivery devices for pulmonary diseases in emergency settings, utilizing the gas flow from a compressor.<sup>157</sup> The main issues with jet nebulizers are the noise that some of them generate, the requirement for a compressor to generate the aerosol, and the temperature drop of the liquid in the nebulizer chamber caused by liquid evaporation in the nebulized droplets.<sup>146</sup>

Ultrasonic nebulizers are generally preferred to jet nebulizers. High frequency ultrasonic waves generate aerosolized particles through the

required vibration range of (1.2-2.4 MHz) by a piezo-electric crystal. The vibration mechanism is then transferred to the liquid formulation, which further produces a fountain of liquid-drug consisting of larger and smaller droplets. The smaller droplets are stored inside the chamber of the nebulizer which is inhaled by the patient. The larger droplets are recovered into the liquid drug reservoir.<sup>154</sup> Ultrasonic nebulizers are more expensive and increase the temperature of the nebulized drug solution; therefore, they are considered inappropriate to nebulize thermolabile compounds. They are also less efficient in nebulizing viscous liquids and suspensions than jet nebulizers, due to the reduced force they use, and are, therefore indicated to nebulize only solutions.<sup>146</sup>

Mesh nebulizers were developed to overcome the problems associated with jet and ultrasonic nebulizers. Mesh nebulizers contain a mesh or a membrane with a range of perforated micron-sized openings through which the liquid medication is forced. The diameter of droplet is defined by the size of the openings, usually between 1 and 6  $\mu\text{m}$ . These nebulizers produce small-sized particles compared to jet and ultrasonic nebulizers. They are portable (work on batteries), produce a substantial fine particle fraction, and have increased output efficiency and short treatment time.<sup>155</sup>

The liquid formulations used in nebulizers are less expensive and are easier to develop compared to pMDIs and DPIs. Different compatible drug solutions can be mixed and nebulized at the same time. The droplet size and the dose emitted by a device can be altered by a change in the viscosity of the solution and that nebulizer settings should be optimized for each medication.<sup>146</sup> On the negative side, nebulizers should be assembled, loaded with medication, and disassembled and cleaned every time they are used.<sup>158</sup>

### Spacers

The space chambers, or spacers, are devices designed to improve the performance of the metered dose Inhaler (pMDI) by increasing the distance between the pressurized device and the patient's mouth and decreasing the velocity of the droplets. They also cause evaporation of

propellants, diminishing the unpleasant sensation produced by the evaporation of the solvent in the oral cavity. As a result, spacers decrease the oropharyngeal droplet impact and deposition, thus minimizing the ensuing local unwanted effects. They have been shown to decrease systemic bioavailability and to increase drug deposition in the lungs.<sup>159</sup> The spacers separate the nozzle of the pMDI from the patient's mouth with the larger particles sticking on the walls of the spacer; subsequently, a smaller amount of drug adheres to the oropharynx, reducing the possible side effects.<sup>160</sup> The correct use of a spacer chamber largely solves the common and potentially critical problem of the lack of coordination of the activation of the MDI with the onset of inhalation.<sup>161</sup> Most spacers have a valve system so that air only circulates in the direction of inhalation, closing when the individual exhales and thus diverting the exhaled air out of the chamber; they should be provided with a mask when used in children under 5 years of age and in elderly people with difficulties in collaboration/understanding.<sup>162</sup> In acute asthma, treatment with beta-agonists administered by using spacers is at least as effective as those administered by nebulizers.<sup>163</sup> The use of spacers remains an alternative with good cost-effectiveness and in those patients unable to achieve sufficient inspiratory flow.<sup>164</sup> However, the administered dose, the pulmonary deposition/oropharyngeal deposition ratio and the dependence on coordination between activation and inspiration differ considerably between the various available spacers.<sup>165</sup>

### Choice of optimal inhalation device in asthma

Inhaled corticosteroids are the most effective drugs used in asthma to control airway inflammation and reduce bronchial hyperresponsiveness, reducing the severity of asthma.<sup>166</sup> The response to the clinical therapy in asthma depends on the patient's age and the ability to use an inhaler of a particular type. Children below 5 years of age present difficulties for aerosol delivery due to anatomic, physiological, and emotional factors.<sup>167</sup> Generally, it is important to evaluate the ability of the patient to use a specific inhaler or mouthpiece, generate optimal inspiratory drive, and coordinate breathing when using the

inhaler.<sup>168</sup> Demonstration and training are of paramount importance to achieving adequate inhaler technique, maximal adherence to treatment and, subsequently, optimal control of asthma.<sup>169,170</sup>

### Rhinitis: intranasal devices

#### Nasal drug delivery devices

The nasal cavity is a strategic gateway for drug delivery in conventional topical pharmacotherapy of sino-nasal diseases such as allergic and non-allergic rhinitis and rhinosinusitis, but also for drugs intended for systemic circulation.<sup>171</sup> Optimal nasal drug delivery is hindered partly by the intrinsic geometry of the nose and its functional properties, namely the nasal valve and the cyclic physio-morphological alteration of its turbinates, respectively. In other words, the incongruity between the nasal inlet geometry and the different nasal plumes causes only a fraction of the drug to be deposited in the target area.<sup>172</sup> Consequently, *in vitro* and *in vivo* studies are required to determine which nasal delivery drug device (NDDD) optimally matches the drug formulation, be it a solution, suspension, emulsion, or powder.<sup>173</sup> In general, NDDD containing topical steroid aerosols are mainly mechanically triggered (pump sprays). Infrequently they can be electrically powered (eg, nebulizer) or gas propellant-driven (eg, atomizer).<sup>174</sup> A NDDD containing topical steroid (budesonide) in powder form has been devised and marketed in Europe for AR, vasomotor rhinitis, and nasal polyps, but studies suggest no superiority over its aerosol form in terms of polyp and nasal symptom scores.<sup>175</sup> There is some degree of dissatisfaction expressed by most current NDDD users because of their inconvenient and embarrassing use in public due to immediate liquid run-off and unpleasant post-nasal drip down to throat.<sup>176</sup> More recently, a breath powered aerosol formulation of fluticasone propionate (FP) has been developed in a bi-directional NDDD that seems to overcome drawbacks inherent to most nasal sprays (see below).

#### Nasal dropper delivery devices

Single-use pre-filled pipettes are NDDDs which use the "blow-fill-seal" technology and still exist for



some OTC nasal medications such as decongestants and saline. The drug is prefilled in a small single use plastic container and is squeezed directly into the nose under direct vision. Similarly, drugs can be instilled into the nose from a small multiple-use glass or plastic canister using a glass dropper. One advantage is no requirement of any preservatives due to the aseptic manufacturing process, but care should be taken not to introduce nasal secretions and microorganism into the container by backflow when the pressure is released. Recently, they have been advocated for delivering steroid formulation into the middle meatus of patients with nasal polyps, but they require the head down position.<sup>177,178</sup>

#### *Metered-dose pump sprays*

Metered-dose pump sprays (MDPS) predominate the NDDD market. As stated previously, the mechanism is finger-actuated which mounts a metered dose of nasal drugs in spray form from a non-pressurized container. *In vitro* testing confirms high reproducibility of the generated dose. However, the deposition pattern of drug particles in the nose is complex and depends on the physical properties of the device. Studies suggest most particles about the anterior 2-cm non-ciliated part of the nasal vestibule and much of the remaining particles get past the nasal valve along the floor of the nose with inadequate dispersion along the rest of nasal and sinus cavities.<sup>179,180</sup> This phenomenon can be further aggravated by forceful sniffing, which deploys the drug quickly into nasopharynx. A fluticasone furoate formulation has been recently designed in a pump spray with a new short tip and a side actuated NDDD to minimize trauma to the nasal mucosa.

MDPS devices generally require preservatives, typically benzalkonium chloride; however, few devices which use a collapsible bag and a movable piston design can be devoid of preservatives. Moreover, such an arrangement enables the patient to use the spray in any head position, particularly suitable for patients with neck problems. Other designs incorporating an air filter into MDPS can also secure a preservative-free aseptic aerosol.<sup>174</sup> As benzalkonium chloride has been regarded safe for chronic use in the nasal mucosa the additional cost incurred on relatively sophisticated preservative-free MDPS seems debatable.<sup>181</sup>

#### *Nasal exhalation delivery systems*

Nasal exhalation delivery systems (EDS) are designed to reliably and effectively deliver medications, such as steroids, higher and deeper into the nasal passages than intranasal sprays and can be adapted to any type of dispersion technology for both liquids and powders.<sup>182</sup> Its unique bi-directional mechanism causes the patient's exhaled breath to be directed into a mouthpiece and instantaneously converted through a sealing nosepiece into a proportional nasal pressure that effectively propels the drug beyond the nasal valve so as to deposit it in high/deep sites in the nasal passages. Furthermore, when the patient exhales against the resistance of the mouthpiece, the positive oropharyngeal pressure elevates the soft palate and can isolate the nose from the mouth and lungs, hence minimizing systemic absorption of the drug whenever swallowed. Also the mechanism assures patent communication behind the nasal septum, allowing air (and drug formulation) to escape through the opposite nostril – thus, the name “bi-directional”. Additionally, the design of the device allows firm sliding of the nosepiece into one nostril, sealing it firmly and hence expanding mechanically the narrow slit-shaped part of the nasal triangular valve.<sup>183-185</sup>

Recent large scale studies have suggested efficacy and safety of an EDS-fluticasone formulation (EDS-FLU) in chronic rhinosinusitis patients with and without polyps, expressed as decreased Sino Nasal Outcome Test scores as well as improvement in nasal polyp score in majority (60%) of patients. Recently a 60-70% decrease of the indication for surgery has been reported following EDS-FLU use.<sup>183,184</sup> Xhance (fluticasone propionate), which uses this new delivery system, is currently approved for the treatment of nasal polyps in adults. It has shown promising results in adults and is currently undergoing evaluation in pediatric patients.<sup>186</sup>

#### *Medical devices using energy fields for allergic rhinitis treatment*

##### *Rhinophototherapy*

Devices beaming inside the nose certain wavelengths of visible and infrared light have been shown to reduce the symptoms and improve

HRQoL subjects with allergic rhinitis to both outdoor and indoor allergens.<sup>187-190</sup>

### *Laser therapy*

Attempts of using conventional laser treatment for allergic rhinitis have been initiated in the 1990s. The technology has now been refined, and 810 nm diode laser has been demonstrated to offer relief of symptoms to allergic rhinitis sufferers when applied before or during the Japanese cedar pollen season.<sup>191,192</sup>

### *High-intensity focused ultrasound therapy*

Devices generating ultrasound with specific characteristics have been found to be effective in reducing eosinophil loaded tissues and structures in the nasal cavity, to reduce inferior turbinate hypertrophy and improve ventilation.<sup>193,194</sup>

### *Radiofrequency turbinoplasty*

Devices generating radiofrequencies with specific characteristic have been proposed as alternative to conventional surgical approaches ablating inferior turbinates and improving rhinitis symptoms.<sup>195,196</sup>

### *Acupuncture and herbal moxibustion\**

Traditional Chinese medicine uses these approaches presumably interfering with the energetic state of the nasal tissues to improve symptoms and HRQoL of rhinitis sufferers and reduce the recurrence of exacerbation episodes.<sup>197-200</sup>

## **Devices for anaphylaxis management**

Anaphylaxis is a severe generalized hypersensitivity reaction that is rapid in onset and may cause death. Anaphylaxis management is mainly based on preventing a reaction and treating each anaphylactic episode.<sup>201</sup> Epinephrine (adrenaline) can be life-saving when administered as soon as possible once anaphylaxis is recognized, namely in community settings including schools, workplaces, and recreational facilities, although several barriers

to access this treatment, namely in schools, were identified.<sup>202</sup>

When indicated, clinicians should prescribe an epinephrine (adrenaline) auto-injector (EAI/AAI), teach how to use it by means of training devices, and review the procedure in every appointment. Patients should have a written action plan that explains how to recognize the symptoms and how to act in case of anaphylaxis. Any patient who has an EAI device should seek immediate medical care for further monitoring and treatment, as the anaphylactic reaction might have ongoing life-threatening effects, like a biphasic reaction.<sup>203</sup>

All over the world there are a limited number of EAI/AAI, and in more than 2/3 of countries patients do not have access to them in the local pharmaceutical market, namely in low- and middle-income countries.<sup>204,205</sup>

### *Main types of devices (autoinjectors)*

The EAI/AAI can be divided into two classes: true auto-injectors, which when activated, extend a needle in the thigh and automatically administer an intra-muscular dose of epinephrine, and pre-filled single-dose syringes that work similarly to traditional syringes. The device comes pre-loaded with a premeasured dose of epinephrine, the needle is uncovered and inserted in the muscle, and the patient/caregiver presses a plunger to administer the medication (eg, Symjepi by Sandoz/Adamis Pharmaceuticals, in two doses, 0.15 and 0.30 mg).

Two premeasured fixed doses of EAI, 0.15 mg and 0.3 mg, are currently available (eg, EpiPen (0.30 mg) and EpiPen Jr (0.15 mg) Mylan/MEDA; Teva's generic versions of EpiPen and EpiPen Jr; Auvi-Q by Kaléo (auto-injector available in 0.15 mg and 0.30 mg doses; when activated, a voice prompt steps through the administration process); Anapen 0.15 mg and 0.30 mg auto-injectors by Lincoln Medical; Jext 0.15 mg and 0.30 mg auto-injectors by ALK-Abello; and Adrenaclick 0.15 mg and 0.30 mg auto-injectors by Amedra Pharmaceuticals). In a limited number of countries there is also available a device with an additional epinephrine dose of 0.50 mg (Emerade 0.15 mg, 0.30 mg and 0.50 mg by Medeca Pharma).

Although several guidelines suggest that children weighing 7.5-25 kg should be prescribed

\* Moxibustion: from **moxa** - a flammable substance or material obtained from the leaves of certain Chinese and Japanese worm-wood plants, especially *Artemisia moxa*; it is placed on the skin usually in the form of a cone or cylinder and ignited.

with the 0.15 mg dose and children from 25 to 30 Kg and adults must receive the EAI with 0.30 mg dose,<sup>206-208</sup> recently an additional EAI approved by the FDA is now available for infants weighing between 7.5 and 15 kg, with an epinephrine dose of 0.10 mg (Auvi-Q by Kaléo).

### Indications and prescription

The prescription of an EAI/AAI can facilitate timely epinephrine injection in community settings for patients with anaphylaxis, and also, under particular circumstances, in patients with high-risk to anaphylaxis. EAI are indicated in patients including those with a history of anaphylaxis who can be re-exposed to their triggers, such as foods, drugs, stinging insects, or exercise, and those with idiopathic anaphylaxis.

The EAI prescription can also be considered and indicated in patients at increased risk of anaphylaxis who might not yet have experienced it, including those with food (for instance patients with previous history of severe generalized acute urticaria, that reacted to trace amounts of a food, or had food allergy and concomitant asthma), and insect allergy (for instance children with a history of generalized urticaria after an insect sting), namely when living in areas with difficult access to emergency medical facilities.

There are no absolute contraindications for intra-muscular epinephrine use in severe/emergency allergic conditions.

The patients/caregivers must receive sufficient education/training about EAI use, included in a written action plan, and the technique must be reviewed in each appointment and also in the pharmacy when the device is dispensed.<sup>209</sup> Once again a lot of opportunities for improvement were identified in the quality of care that must be provided to these patients,<sup>210</sup> and both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) recommended several measures, including the introduction of educational material, to ensure that patients and caregivers can use EAI successfully.

The companies that market EAI have been asked by EMA to develop more effective educational material for patients, as well as for healthcare professionals, to ensure their optimal use. This

includes a training device with which patients can practice, audio-visual material to show in detail how the device is to be used, and a checklist for prescribers to ensure that sufficient information is given to the patient before they use the EAI. The product information of adrenaline auto-injectors has also been updated with further warnings and precautions, including a recommendation that some patients should be prescribed with 2 auto-injectors which they should carry at all times and a recommendation for family members, caregivers, or school staff to be trained on how to use the auto-injector.<sup>211</sup>

It is advised not to store EAI under conditions of excessive heat or cold (eg, in a car or beach bag in summer time). Manufacturers recommend keeping them at 20° to 25 °C (68°-77 °F), with limited time exposures allowed from 15° to 30 °C. Degradation of the epinephrine solution in EAI can occur without visible discoloration or precipitates. It is beneficial to check EAI expiration dates and renew prescriptions in a timely manner. However, if the only EAI available during an episode of anaphylaxis is past the expiration date, it can be used in preference to no epinephrine injection at all.<sup>30</sup>

According to recent investigation, almost all EAI are still potent a long time after expiration date. In a recent study, 80% of the devices tested at least 2 years after the expiration date still retained 90% or more of the initial epinephrine dose, indicating that they were still effective under the FDA rules that require that an EAI in the expiration date must contain 90% or more of the epinephrine original labeled dose; after 6 months of the expiration date all the AIE devices had 100% of the dose, and 12 months after, the devices still had 95% of the original dose.<sup>212</sup>

Although the devices were not used to treat acute anaphylaxis episodes, these data can support extension changes in the expiration dating guidance that is currently of 18 months from the manufacturing process. Nevertheless, nowadays, we strongly recommend that patients should use the EAI as labeled, including with the strict respect for the expiry date.

## CONCLUDING STATEMENT

All practitioners in the field of allergology have the privilege to be broad specialists with the requirement to be familiar with the subtleties of a multidisciplinary medical field. This involves knowledge and skills about the wide spectrum of medical devices used in daily routine, but also needed for sophisticated diagnostic purposes and modern disease management. This is in line with the necessity to support the transformation of the health care system into integrated care pathways for interrelated comorbidities.<sup>64</sup> This position paper of the World Allergy Organization (WAO) is meant to be the first integral document serving to provide structured information on medical devices in allergology. It can be regarded as a kind manual to help patient-centered care.

### Abbreviations

AAP: Asthma Action Plan; ATS: American Thoracic Society; CE mark: Conformité Européenne mark; CO: Carbon monoxide; DPIs: Dry Powder Inhalers; EAI/AAI: Epinephrine/Adrenaline Auto-Injector; EBC: Exhaled Breath Condensate; EBT: Exhaled Breath Temperature; EDS: Exhalation Delivery Systems; EMA: European Medicines Agency; ERS: European Respiratory Society; ERV: Expiratory Reserve Volume; FDA: Food and Drug Administration; FEF: Forced Expiratory Flows; FeNO: Fractional Exhaled Nitric Oxide; FEV1: Forced Expiratory Volume in 1 second; FOT: Forced Oscillation Technique; FRC: Functional Residual Capacity; FVC: Forced Vital Capacity; GLI: Global Lung Function Initiative; IOS: Impulse Oscillometry; IRV: Inspiratory Reserve Volume; MDPS: Metered-Dose Pump Sprays; NDDD: Nasal Drug Delivery Device; NO: Nitric oxide; PDMI: Pressurized Metered Dose Inhaler; PEF: Peak Expiratory Flow; PhPT: Photopatch tests; PNIF: Peak Nasal Inspiratory Flow; Ppb: part per billion; PT: Patch Tests; RV: Residual Volume; SPT: Skin Prick Test; TLC: Total Lung Capacity; UV: Ultra Violet; VC: Vital Capacity; VT: Tidal Volume; WAO: World Allergy Organization; WHO: World Health Organization

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SB: What is a "device" and what is not

GP: Skin prick tests, Allergy patch tests

JLGA: Allergy patch tests

DP: Diagnostic devices in respiratory allergy

FB: Mobile approaches (m-health)

LD: Other diagnostic approaches involving medical devices; Linguistic upgrade

SGD: Asthma drug delivery by inhalation devices

PR: Rhinitis: intranasal devices

LC: Medical devices using energy fields for allergic rhinitis treatment

MMA: Devices for anaphylaxis management

IA: General outline of the paper; Introduction

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