



Update on the use of allergen challenge chambers in immunotherapy: clinical implications

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Purpose of review

This review aims to reflect on and discuss recent evidence of applicability of allergen exposure chambers (AEC) for allergen immunotherapy studies, especially focussing on validation of AECs, technical documentation and future perspectives.

Recent findings

Publications covered by this review summarize the historical background, current status of research use and validation of AEC systems. It describes identified unmet needs regarding comparability of AEC systems, reproducibility of clinical assessments and correlation of AEC-induced symptoms with scores under natural environmental exposure. Furthermore, new information on technical specifications, for example, dimensions, allergen dispersal and validation procedures is highlighted and future activities of the EAACI AEC task force group regarding harmonization of clinical endpoints are delineated.

Summary

AECs are in use for evaluation of allergic patients for over three decades now. As different systems largely vary regarding technical set up and standard assessments, detailed technical documentation must be available. To gain acceptance of regulatory authorities for pivotal immunotherapy trials conducted with the use of AEC system, harmonization of clinical assessments as well as documentation of correlation of clinical AEC outcomes with environmental exposure clinical scores is required.

Keywords

allergen challenge chamber, allergen immunotherapy, allergic, clinical trials

INTRODUCTION

Allergen immunotherapy (AIT) has been used for treatment of patients with IgE-mediated inhalative allergies for more than 100 years [1], and has been demonstrated to be effective, well tolerated and cost-efficient [2,3]. Being the only disease-modifying treatment option for allergic patients, extensive evidence for preventive capacities and long-term efficacy of AIT has been generated [4]. Several innovations in AIT, such as, for example, personalized approaches by means of synthetic vaccine development programs or biomarker evaluation as a measure of immune response in AIT are currently under investigation [5–7].

Clinical trials conducted with AIT products to gain market approval in Europe have to align with the guideline on the ‘*Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases*’ of the European Medicines Agency (EMA) [8]. For phase II (dose finding and proof of concept) trials, the EMA accepts allergen provocation tests, such as conjunctival, nasal or bronchial challenge tests or challenges under standardized conditions in

allergen exposure chambers (AEC) [8]. However, authorities do not accept allergen provocation tests including AECs for demonstrating efficacy in pivotal trials [8] and an unmet need for further clinical validation has been identified by different key stake holders including authorities, clinicians, methodologists and AEC operators [9].

The following provides the reader a thorough overview on the historical background of the technology, the current status of applicability of AEC models for clinical research and future perspectives.

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KEY POINTS

- Allergen exposure chambers were developed decades ago to evaluate allergic patients under reproducible and standardized exposure conditions to minimize confounders in studies of therapeutical interventions in allergic diseases.
- However, different AEC systems all around the world vary regarding technical set up and standard assessments.
- To gain further regulatory acceptance for pivotal AIT trials a detailed documentation of differences between and comparability of different systems is required.
- Research is ongoing to harmonize clinical outcome measures, determine correlation of in-season symptoms with AEC-induced symptoms ('hybrid trial') aimed to demonstrate a sufficient correlation of results revealed by different AECs.

HISTORICAL BACKGROUND OF ALLERGEN EXPOSURE CHAMBERS

AECs were developed in the 80s of the last century in order to examine pollen allergic patients under controlled and reproducible pollen exposure conditions [10]. At that time, models for grass, birch and ragweed pollen as well as dust mites were established. The reproducible allergen climate to which volunteers can be exposed offers advantage compared with natural seasonal pollen exposure, as confounding conditions like rain, temperature and wind can be influencing pollen counts. Low pollen counts during season generate less symptoms in pollen allergic volunteers diminishing the possibility to detect a treatment effect of an investigational compound. Several more advantages and disadvantages of the AEC model were discussed in an European review dated 2011 [11]. In studies using AEC treatment effects of antiallergic compounds like antihistamines or corticosteroids are equally determined as clinical efficacy of AIT. Furthermore, molecular mechanisms of allergic reactions like mediator release and time course of cell and mediator synergism can be evaluated. The AEC model was approved and accepted by the competent authorities Food and Drug Administration (FDA) and EMA for phase II immunotherapy trials and suggested by EMA for conducting dose-finding trials of immunotherapeutic products [8].

However, the EMA also stated that for pivotal phase III trials in AIT, AECs 'deemed to be a promising tool for the evaluation of efficacy' but requires further clinical validation [7]. To address this claim, the EAACI gained a task force initiative in 2015 constituting international representatives from regulatory authorities, experts in the field of AIT, clinicians,

methodologists and AEC operators. A first Position Paper aimed to pave the way to internationally harmonize concepts of AECs and enhance their broader use in clinical trials. Unmet needs were identified and suggestions were made for procedures for technical and clinical validation processes useful to fulfil the regulatory requirements [9].

Several claims have been elaborated and formulated in this Position Paper. First, it was requested that reproducibility of findings between studies should be shown for each system and comparability of clinical outcomes in one facility to those in another facility being technically different should be determined.

Secondly, it was highlighted as an unmet need that the comparability of AEC data with data reported under natural exposure in field trials should be better investigated and correlated. Currently, it is not feasible to sufficiently quantify the natural environmental allergen exposure of each individual. A so called 'hybrid study design' evaluating patients under environmental exposure conditions, for example, during pollen season, and additionally out of season in a standardized AEC challenge could solve this issue and convince regulators and other stakeholders regarding the value of 'pivotal' signals of efficacy in both the scenarios [9].

To achieve at least a minimal level of harmonization, it was agreed to establish (if not in place yet) a standardized documentation in each AEC system. To validate different allergen models technically, airborne allergen concentration, diameter of the allergenic particles pollen grain counts (and method), spatial homogeneity and temporal stability of the exposure as well as climatic conditions should be documented and monitored, and anti-static, nonadhering, easy to clean materials (i.e. wall materials, seats) and well defined cleaning procedures should be installed. Data serving this claim has been presented in a current report of the task force [12²²] as outlined below.

Furthermore, to harmonize clinical study outcomes, it was agreed to use standardized and clinically relevant outcomes, evaluate the outcomes at the plateau-phase of the challenge, justify single-versus-serial challenges, justify low versus high doses in challenges and specify safety measures and SOPs on patient selection [9].

CURRENT STATUS OF USE AND VALIDATION OF ALLERGEN EXPOSURE CHAMBERS

Currently grass and ragweed pollen, tree pollen, Japanese cedar pollen, house dust mite and cat epithelia serve as routine allergen sources for AEC

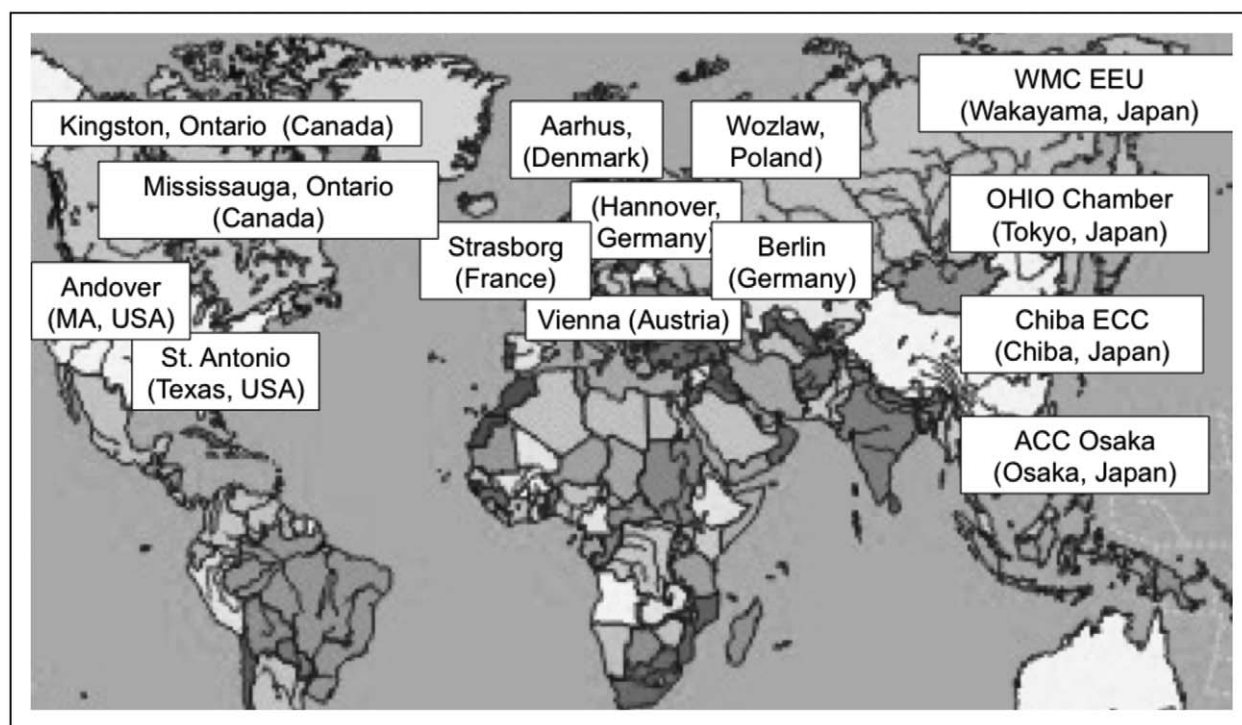


FIGURE 1. Overview of currently operative allergen exposure chambers. Data from [13] (with kind permission from Dustr).

challenges. Available AECs are located in Europe (Germany, Austria, Belgium, France, Poland), North America (USA and Canada) and Asia (Japan) [9] (Fig. 1).

Adult patients suffering from allergic rhinitis, conjunctivitis and asthma can be exposed not only to investigate mechanisms of allergic reaction in more detail but also to assess the efficacy and tolerability of antiallergic treatment compounds. Only in AIT studies, acceptance of AEC models is limited to phase II clinical trials including proof of concept, dose determination, onset and duration of action protocols as well as tolerability and safety. For all other evaluations, for example, of pharmaceutical compounds, AECs can be used without limitations.

As mentioned above, harmonization of systems is intended to advance acceptance of regulatory bodies for the use of AECs in pivotal (phase III) immunotherapy trials. After having identified unmet needs for future elaboration [9], the EAACI task force group proceeded with a compilation of technical specifications of the different systems in a second phase of the task force project. Recently, information on different technical aspects were collected from all researchers working with AECs worldwide [12^{***}]. This EAACI task force report provides an overview of these technical standards and as such provides comprehensive insights into the technical set ups of AEC facilities around the world (Fig. 2).

Dimensions and structure of contributing AECs were described, specialized working staff was specified, air flow, air processing, and operating conditions were discussed as well as particle dispersal and pollen/particle counting. Along with the depiction of safety and noncontamination measures a short section on precautions concerning SARS CoV 2 safety measures has also been added. Information on tested allergens/substances and technical validation procedures was provided by each researcher but respective data are only partly published yet [14–23]. Procedures for symptom assessments are only mentioned in this first task force report of the planned series and will be elaborated in detail during the upcoming phase 3 of the task force project.

FUTURE PERSPECTIVES OF CLINICAL ENDPOINTS EVALUATED IN ALLERGEN EXPOSURE CHAMBERS

Methods used in allergen exposure chambers

Study participants are traditionally examined in a symptom-free interval out of season, as antiallergic concomitant drugs must be omitted before and during the provocation session in order not to compromise study results. In the context of a field study, during which the patients are observed for a longer period of time (weeks or months) under natural

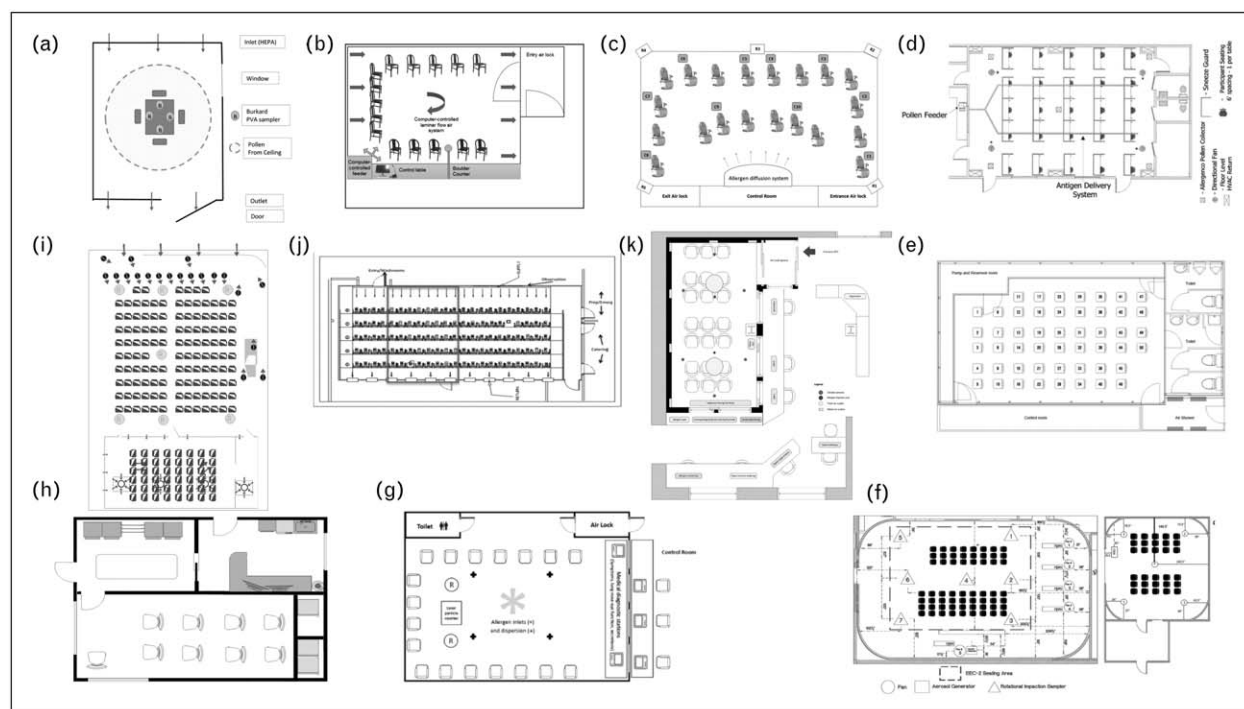


FIGURE 2. Schematic description of allergen exposure chamber models, presented in clockwise order. (a) Aarhus AEC; (b) ALL-MED AEC; (c) ALYATEC EEC [20 seats and 10 particle counters (C1–C10)]. Allergen particles are dispersed in the EEC through six outlets (arrows). R1–R5 correspond to air extraction outlets; (d) Biogenics AEC; (e) CHIBAUNIV AEC; (f) Cliaantha AEC-2 and AEC-3; (g) Fraunhofer Allergen Challenge Chamber (+ denotes pollen inlets from the ceiling, * denotes dispersion by ceiling ventilator, R denotes Rotorod samplers); (h) GA2LEN chamber [participants enter the chamber from the observation room (top right) crossing the changing room, where they are given protective clothing (top left). There are nine separate seats in the provocation room]; (i) Kingston EEU and HD EEU; (j) RED MAPLE TRIALS AEC (participants enter from a gowning area at the upper left and are observed through a large window at the upper right. The arrows at the top of the figure indicate allergen entry, and the arrows at the bottom indicate allergen exit through HEPA filters. Zone 2 is indicated by a rectangle); (k) Vienna Challenge Chamber (VCC, AAR, active anterior rhinomanometry). Data from [12] (with kind permission from Wiley). AEC, allergen exposure chamber.

exposure, an interruption of the concomitant medication is prohibited by itself for ethical reasons. This is, therefore, included and evaluated according to predefined criteria. Decisive for pivotal studies is the collection of subjective symptom data under natural exposure to pollen allergens: for this purpose, the cardinal symptoms of allergic rhinitis (sneezing, nasal itching, rhinorrhea and nasal obstruction) are determined by means of 4 point Likert scores collected at regular intervals and compared with the symptoms before the start of treatment [8,24]. Depending on the study design, conjunctival and bronchial symptoms are also documented and evaluated. It is now good clinical practice to also determine the quality of life by means of a standardized and validated questionnaire at different time points during the study, and thus to determine the clinical significance of the success of the treatment [24]. In AEC studies, which are accepted as pivotal studies for pharmaceutical products by the authorities, symptoms are not only subjectively collected during

the provocation chamber session but also objectified with different measuring methods if possible. For example, the subjective symptom ‘rhinorrhea’ can be quantified by quantitative recording of the nasal secretion or the subjective symptom ‘nasal obstruction’ by means of nasal air flow measurement.

Unmet needs encompassing allergen exposure chamber operators, clinicians and authorities

In a next phase of the EAACI task force project, a thorough review of clinical outcome measures used by the different research groups will be elaborated. Each assessment will be evaluated regarding scientific and regulatory rationale, clinical usefulness and practicability in terms of reliability and robustness of results based on a Delphi consensus process of experts in the field.

Along with this, studies are planned involving several AECs in a multicenter approach to document

inter-chamber variability of clinical outcomes and demonstrate correlation of results as discussed above [25,26]. Also, further activity will be posed on a consensus for hybrid design models of AIT clinical development programs in AEC models as requested by regulatory authorities [27].

CONCLUSION

The value of an AEC model for the evaluation of treatment options in allergic diseases allows the investigation and quantitative determination of clinical effects under controlled conditions (humidity, temperature, allergen-exposure) in a reproductive manner. Regardless of the environmental exposure and other confounding factors, the evaluation of the safety and clinical efficacy in phase 2 and phase 3 studies is possible in general. Recent international recommendations have underlined the unmet need for better standardizing intra-chamber procedures, testing interchamber comparability and further investigating the correlation to natural exposure. The level of evidence concerning the validity and reliability of AEC systems is increasing, including comparability of AEC models, reproducibility of clinical effects at different time points and possible extrapolation to the natural exposure of patients. Further development in the field will increase the knowledge of phenotypes of allergic diseases, investigate effects of therapeutic interventions under standardized conditions and as such may also foster clinical development of products in AIT.

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Conflicts of interest

P.U.Z.: scientific director of the Vienna Challenge Chamber.

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