Improved allergen immunotherapy prescription for seasonal allergic rhinitis: an innovative algorithm

Stefania Arasi[1,2], Sveva Castelli[3], Marco Di Fraia[4], Danilo Villalta[5], Salvatore Tripodi[6], Serena Perna[7], Stephanie Dramburg[7], Maria Antonia Brighetti[8], Mariaelisabetta Conte[5], Paola Martelli[5], Ifigenia Sfika[6], Alessandro Travaglini[8], Pier Luigi Verardo[9], Valeria Villella[6], and Paolo Matricardi[7]

[1]Bambino Gesù Children Research Hospital (IRCCS)
[2]Bambino Gesu Pediatric Hospital
[3]Charite Universitatsmedizin Berlin
[4]Sapienza, University of Rome
[5]Pordenone Hospital
[6]Sandro Pertini Hospital
[7]Charitè University Medical Center
[8]University of Rome Tor Vergata
[9]ARPA

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Abstract

Background: Allergen immunotherapy(AIT) is the only disease-modifying treatment with long-term effects in patients with seasonal allergic rhinoconjunctivitis(SAR). Its efficacy depends on the precise identification of the pollen triggering symptoms. However, a diagnostic approach based on retrospective clinical history and sensitization to extracts often does not lead to unequivocal results. Objectives: To assess the usability and impact of a recently established algorithm for a potential clinical decision support system (@IT.2020-DSS) for pollen allergy and its diagnostic steps (including anamnesis, SPT, component resolved diagnosis, CRD, and real-time digital symptom recording, eDiary) on doctor's AIT prescription decisions. Methods: After a concise educational training on the @IT.2020-DSS algorithm, 46 doctors (18allergy specialists, AS, and 28general practitioners, GP) expressed their hypothetical AIT prescription for 10 clinical index cases. Decisions were recorded repeatedly based on different steps of the support algorithm. The usability and perceived impact of the algorithm on individual clinical performance were evaluated. Results: The combined use of CRD and an eDiary increased the hypothetical AIT prescriptions, both among AS and GP ($p<.01$). AIT prescription based on anamnesis and SPT were heterogeneous but converged towards a consensus after the integration of CRD and eDiary information. Doctors considered the algorithm useful and recognized its potential in enhancing traditional diagnostics. Conclusions: The implementation of CRD and eDiary in the @IT2020-DSS algorithm improved consensus on hypothetical AIT prescription for SAR among AS and GP. The hypothesis, that a CDSS for etiological SAR diagnosis and AIT prescription may be useful in real-life clinical practice deserves further investigations.

Keywords

Allergen specific immunotherapy, clinical decision support system, component resolved diagnostics, mobile health, seasonal allergic rhinitis.

Abbreviations

AIT Allergen Specific Immunotherapy

AIT-WS , AIT prescription workshop

ARIA Allergic Rhinitis and its Impact on Asthma

AS, allergy specialists

CDSS Clinical Decision Support System

CRD component resolved diagnosis

eDiary Electronic clinical diary

GP general practitioners

IgE Immunoglobulin E

mHealth mobile Health

NAPT nasal allergen provocation test

SAR Seasonal Allergic Rhinitis

SD Standard Deviation

SPT Skin Prick Test

Conflict of interest

Dr. Matricardi reports grants and personal fees from Euroimmun AG, during the conduct of the study; grants and personal fees from Thermo Fisher Scientific, personal fees from Hycor Biomedical Inc, outside the submitted work. Salvatore Tripodi is cofounder of TPS Production. All other Authors declare no conflicts of interest.

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Introduction

Seasonal rhinoconjunctivitis due to pollen allergy (SAR) affects millions of people around the globe and is particularly prevalent among children[1]. Symptom-relieving drugs can control the disease, but the only disease-modifying treatment with long-term effects is an allergen-specific immunotherapy (AIT)[2,3]. The efficacy of AIT depends on the precise identification of the eliciting pollen inducing IgE sensitization and triggering the patient's symptoms[4-6]. Unfortunately, pinning down the causing allergen is often difficult, especially in Southern European countries, as patients are frequently sensitized to multiple, often cross-reactive, allergenic sources with overlapping pollination seasons[7].

This diagnostic challenge can be confronted with the use of component resolved diagnostics (CRD) in order to identify the eliciting allergen and thereby choose the proper agent for an allergen-specific immunotherapy. Corresponding algorithms on the molecular diagnosis of allergies have been published[8-10]. However, a traditional approach, based exclusively on anamnesis and the use of pollen extracts, is still the most frequently used worldwide[3] and the implementation of molecular diagnostic algorithms – still considered a complex matter by most doctors - is infrequent[10]. Expert systems and software solutions have been proposed as tools to make the adoption of diagnostic algorithms for CRD easier[11]. However, to our knowledge, no informatics tool dedicated to support the implementation of internationally validated algorithms is yet available.

In contrast, a great variety of mobile phone applications has flooded the market, aiming at an improved disease control and quality of life for allergic patients. Unfortunately, only a small number of applications has been clinically validated, but especially in the area of real-time symptom monitoring, the usefulness of mobile devices has been proven[12-16]. Though in the daily clinical practice still most of the patient´s history is being assessed retrospectively, the electronic clinical diary (eDiary) enables the doctor to evaluate individual symptoms and the need for medication prospectively. With the help of software systems, clinical scores can be automatically generated, graphically matching patients´ SMS trajectories with those of the local pollen counts[16,17].

The opportunity of mobile Health (mHealth) technology is being used not only to record patients´ data, but also as part of clinical decision support systems (CDSS), created to assist patients, clinicians and pharmacists at the point of care[18-21]. In allergology, several support systems have been created, related to symptom monitoring and a facilitated diagnosis of respiratory allergies[21-22]. In order to create a support tool for the precise prescription of AIT, we identified a diagnostic algorithm based on the use of CRD and eDiaries in combination with local pollen counts as potentially efficient and user-friendly tools to be included in a future clinical decision support system. The purpose of the present study is to assess the effectiveness and usability of this algorithm and its individual tools between two groups of allergy specialists (AS) and general practitioners (GP) in order to facilitate their clinical decision taking with regard to AIT prescription.

Materials and Methods

Study design and population – A workshop ("AIT prescription workshop", AIT-WS) has been organized with 10GP + 11AS at "Ospedale S. Pertini" (Rome, Italy) and with 18GP + 7AS at "Ospedale S. Maria degli Angeli" (Pordenone, Italy). The participants were recruited among those physicians collaborating with each center on a regular base concerning patients suffering from allergic diseases. Each workshop consisted of the following three phases: a) educational training; b) decision taking on clinical cases; and c) feedback survey.

Educational training – During the first part of the AIT-WS, the target, nature and methodology of the diagnostic tools (i.e. questionnaires, SPT, CRD, eDiary) were presented in comprehensive lectures. In detail, three lectures explained the general concepts, specific methodologies and clinical interpretation of the diagnostic tools. A fourth lecture was focused on the procedures for the following workshop module involving clinical cases.

Clinical cases – Among the @IT.2020 pilot study population (n=200), twenty clinical index cases (10 cases for each center) were selected in order to reproduce the local epidemiological scenario[6] and to provide the widest spectrum of allergen(s) among the patients affected by moderate-to-severe SAR[**Table E1**] . The @IT.2020 pilot study population (n=200) has been described in detail elsewhere[23]. Briefly, 101 children ("Ospedale Sandro Pertini", Rome), and 99 adults ("Ospedale S.Maria degli Angeli", Pordenone) underwent a complete diagnostic allergy work-up, including a detailed assessment of the retrospective clinical history, skin prick testing (SPT), blood drawing for IgE determination against allergenic extracts and molecules, a prospective collection of clinical data via mobile phone application and an allergen-specific nasal provocation test (NAPT) with the extract of the AIT-candidate pollen(s) for a subgroup. Among the selected clinical cases, NAPT data were available for 18 of the 20 patients (90%). During the second part of AIT-WS, doctors were asked to express their therapeutic decision concerning their respective 10 clinical index cases.

Therapeutic Decision Taking - Each participating doctor filled a questionnaire reporting his/her own hypothetical AIT decisions on the base of the primary data progressively added. The first decision had to be taken based on the retrospective clinical history and SPT results. An independent second decision was then asked involving the clinical history, SPT and CRD results. Finally, the results of each patient´s symptom monitoring via eDiary during the past pollen season plus pollen counts were shown and doctors decided again on the hypothetical prescription of AIT for every patient.

Feedback survey– Finally, the doctors filled a questionnaire not only on the impact of each given diagnostic tool and its perceived benefits, but also on their role in the doctor´s hypothetical AIT prescription process.

In addition, participants were asked to express their satisfaction level on the entire AIT-WS (tutorial, clinical cases and feedback survey) in terms of content and general organization[**Figure E1**] .

Algorithm for a potential clinical decision support system (CDSS) for pollen allergy– The @IT.2020-DSS tools are based on clinical data progressively considered in three steps: 1) clinical history and SPT (and/or serum sIgE) to allergen extracts; 2) IgE assays to pollen-derived molecular components (component resolved diagnostics, CRD); 3) electronic clinical diary (eDiary)[24]. In the first step, a list of potentially relevant allergens are selected considering the period of allergic symptoms reported by the patient (clinical history, seasonality of AR symptoms) and the SPT reactions ("traditional" diagnosis). In the second step, the list of allergens previously selected is restricted to those confirmed by IgE sensitization to their respective major allergenic proteins (Cup a 1 for cypress, Phl p 1 and/or Phl p 5 for grass, Bet v 1 for birch, Ole e 1 for Olive, Amb a 1 for ragweed, Art v 1 for mugwort, and Alt a 1 for Alternaria). Finally, the list of allergens considered after the second step (anamnesis+SPT+CRD) is further restricted to those whose pollination period, identified by the local aerobiologist, corresponded to moderate-to-severe and/or persistent allergic rhinoconjunctivitis symptoms prospectively registered by the patient during the same period. The three steps of the @IT2020-DSS algorithm can therefore be represented by a "pyramid" scheme for each allergen [**Figure 1a**] generating a precision "target" when combined [**Figure 1b**]. However, the algorithm does not exclude any obtained result based on the described exclusion scheme. In the rare case of positive test results occurring at an advanced stage (e.g. positive IgE to a major molecule of an allergenic source which had been previously excluded on the base of a negative SPT result), the respective allergen is being considered potentially relevant for the next step of the algorithm.

Statistics- Data were summarized as numbers (n) and frequencies (%) if they were categorical and as mean and standard deviation (SD) if quantitative. Percentages of correct hypothetical AIT prescription at each step and for each medical category were computed, taking as comparison reference, for each examined case, the most frequent AIT hypothetical prescription of allergen immunotherapy among allergy specialists at the final stage of CDSS (gold standard). Chi squared test, when conditions were respected or Fisher exact test was used to evaluate the association of categorical data between AS and GP groups. McNemar's test was used to compare difference of frequency within each group. A p-value $< .05$ was considered statistically significant. Statistical analyses were performed with R Core Team (2014), version 3.2.3.

Results

Study population– The study included 46 physicians: 21 (AS, n=11; GP, n=10) attending the AIT-WS in Rome and 25 (AS, n=7; GP, n=18) in Pordenone. All participants were present throughout the entire AIT-WS, completed the full set of surveys, and provided informed written consent. For demographic characteristics of the respondents, please see**Table 1.** No relevant differences were detected in terms of gender and age. Physicians were asked about the duration of their previous work experience with allergic patients and no relevant differences were found among the groups (mean±SD, years; AS, 15.4±8.9 and 19.0±6.1; GP, 22.6±11.9 and 25.4±9.5, respectively in Rome and Pordenone). Most of the AS (100% and 86%) and a minority of the GP (30% and 39%) were familiar with the concept of CRD; and similarly, 82-86% of the AS and 10%-17% of the GP, have used CRD as a diagnostic tool in pollinosis, respectively in Rome and Pordenone. Furthermore, the results show that 64% (n=7) and 71% (n=5) of AS, as well as 60% (n=6) and 50% (n=9) out of the GP had previous knowledge about electronic clinical diaries. However, only part of them have already used an eDiary in their own clinical practice: most of the physicians with previous experience being AS (46%, n=5, and 43%, n=3) and only a few GP (20%, n=2, and 22%, n=4, respectively in Rome and Pordenone). Some respondents declared previous knowledge of CDSS (AS 18% and 43%; GP 10% and 17%) but none indicated any previous experience with them in the management of pollinosis patients [**Table 1**] .

Spectrum of clinically relevant pollen(s) and hypothetical AIT prescription results – The pollen(s) identified as clinically relevant according to guidelines[2] and considering the information sequentially added through the potential CDSS tools are shown in **Table E2** together with the most frequent allergen source(s) selected by allergy specialists on the basis of primary data[**Table E1**] for hypothetical AIT pres-

cription (if any). In patients with only one relevant allergen source, the AIT agent most frequently prescribed by AS coincided with the pollen identified as clinically relevant according to guidelines taking into account the information obtained through all potential CDSS tools (i.e. history+SPT+CRD+eDiary) (n=8) [**Table E2**] . When this procedure (i.e. after considering the full set of information given: history+SPT+CRD+eDiary) led to the identification of two allergens (n=6), one or both of them have been also prescribed by the allergy specialists. In the case of no (n=2) or [?] 4 (n=4) clinically relevant allergens, no AIT has been prescribed, with one exception (case 4, Rome)[**Table E2**] . Eighteen patients (90%) underwent nasal provocation testing with one or more pollen(s) among the clinically relevant ones. The NAPT results were all positive, confirming the final decision based on the full set of information considered for a CDSS.

Trend and concordance between AS and GP in hypothetical AIT prescription – For each step of the algorithm and each medical category (i.e. AS and GP), the hypothetical AIT prescription was compared per individual case to the most frequent AIT prescription decided by AS at the final step (i.e. history+SPT+CRD+eDiary), as "gold standard". In both groups (AS and GP), the hypothetical prescription of AIT changed significantly through the three diagnostic steps proposed in our "pyramid" model ($p<.01$), as shown in **Figure 2** . Through this evolution, the AIT decisions harmonized within the AS groups and GP groups ($p<.01$) [**Figure 2**] . In particular, taking into account the total amount of available choices (n=110 and n=70 for Rome and Pordenone respectively), 54% (Rome) and 59% (Pordenone) of AITs prescribed by AS after the first step of CDSS corresponded to the gold standard choice of AIT. These percentages increased to 66% (Rome) and 83% (Pordenone) when AS expressed their AIT hypothetical prescriptions considering also CRD data, and furtherly to 86% (Rome) and 87% (Pordenone) including also eDiary results. An analogous trend was observed among GP. Considering the total amount of available choices (n=100 and n=180 for Rome and Pordenone, respectively), the percentages of correct prescriptions of AIT increased from 37% and 39% to 57% and 63%, for Rome and Pordenone, respectively, after considering CRD data, in addition to anamnesis and SPT results. When also eDiary data were evaluated, these percentages among GP increased to 79% (Rome) and 83% (Pordenone). Furthermore, the hypothetical AIT prescriptions of GP became consistently closer to those of the AS: finally, no statistically significant differences could be observed between both groups [**Figure E2**] .

CRD and eDiary impact on AIT prescription by participating doctors – Overall, the number of hypothetical AIT prescriptions increased when, in addition to anamnesis and SPT, physicians considered also the CRD, and finally also eDiary results [**Figure 3 and Table E3**] . This general trend was observed in both GP (hypothetical AIT prescription: Rome, 25%56%63%; Pordenone, 29%59%72%) and AS (Rome, 49%71%65%; Pordenone, 53%77%87%) [**Figure 3 and Table E3**] . At individual level it was possible to count only a few cases with an inverse trend: 2/10 cases in Rome (for both medical categories) and 2/10 cases in Pordenone (only for GP) [**Table E3**] .

Furthermore, we evaluated if any change occurred in the number of potential AIT prescription(s) and in its composition (if applicable) on the basis of anamnesis and SPT (only), by adding data referred to CRD and eDiary [**Table E4**] . Specifically, for each clinical case we considered the most frequent decision taken by each medical category (i.e. AS and GP) at each step of the @IT.2020 algorithm.

In particular, when evaluated only on the basis of anamnesis and SPT, 40% (4/10) and 0% (0/10) of clinical cases presented in Rome would have received a potential AIT prescription according to AS and GP, respectively. Among patients considered eligible for AIT prescription (n=4) by AS, 25% (1/4) would have received a hypothetical AIT prescription with a different composition after considering CRD results and 50% (2/4) when eDiary was considered in addition to the previous information in comparison to the most prevalent composition at the first step (i.e. anamnesis and SPT). In Pordenone, 5 (50%) and 2 (20%) of patients would have received a hypothetical AIT prescription according to AS and GP, respectively. Only one (20%) would have received a hypothetical AIT prescription with a different composition after CRD data and two (40%) after considering CRD and eDiary results[**Table E4**] .

Feedback survey on doctors' perception regarding diagnostic tools – Doctors filled a questionnaire on the role of each diagnostic tool or step in their own decisions expressed in the AIT-prescription survey.

Additionally, their opinion on the algorithm proposed for our innovative CDSS has been assessed. All physicians considered the application of a CDSS useful and recognized its potential in ameliorating the traditional diagnostic procedures [**Figure 4, Table E5**] . There was agreement also concerning the role of molecular diagnostics in improving the accuracy of AIT prescription (100%). The reliability of the retrospective assessment of clinical histories was assessed lacking (70-100%) and optimizable by an electronic clinical diary (82-100%). In addition, all respondents judged the latter as easier to be filled by patients and to be interpreted by physicians in comparison to a paper diary. Furthermore, the majority of doctors agreed on a potential role of an electronic diary in the diagnostics of other allergic diseases (e.g. asthma and food allergy). Significant discrepancies were registered between the two medical categories (AS vs GP) in one center (Pordenone) concerning the physicians' opinion on eligibility to AIT of patients sensitized to more than four aeroallergens ($p = .03$). Participants were overall satisfied by the workshop (tutorial, clinical cases and feedback survey) in terms of content and general organization [**Figure 4**] .

Discussion

In the AIT-workshop involving 46 doctors dealing with patients seeking care for seasonal allergic rhinitis, we found that the measurement of serum specific IgE to the major allergenic molecules of pollens (CRD) and the use of an eDiary significantly improved the accuracy of AIT prescription, not only among AS, but also in the group of GP.

In fact, when AS combined the "traditional approach" (anamnesis and SPT and/or IgE to pollen extracts) with these diagnostic tools (CRD and eDiary), they frequently modified and harmonized their AIT decision. The same trend was observed in the group of GP, who improved their clinical decision up to reproducing the standards of AS.

We have previously reported[6] in another cohort (n=1271), that the inclusion of CRD in the diagnostic algorithm led to a change in AIT prescription for 44% of the patients. This might be explained by the presence of highly cross-reactive molecules from unrelated allergenic sources (e.g. profilins, polcalcins and LTPs), which may contribute to a confounding SPT-reactivity to extracts. Once this interference is ruled out by CRD, the clinical decision taking is simplified, especially for patients with various positive SPT results. Still, the clinical significance of individual sensitization profiles remains to be proven before prescribing the correct treatment. In order to overcome the inaccuracy of a retrospective symptom monitoring, the present study successfully assessed the use of digital symptom and medication recording. The access to this real-time clinical information increased the diagnostic precision of the GP and AS significantly.

In general, it is estimated that only a restricted minority (2-6%) of eligible patients currently receives AIT[25]. One reason for this condition may be the fact that most patients with seasonal allergic rhinoconjunctivitis are polysensitized[26]. The choice of the correct allergen for immunotherapy appears then often difficult, which may be the cause for clinicians to refrain from this therapeutic option. Yet, the differentiation between a pure polysensitization in mono-allergic patients and real poly-allergic subjects is fundamental, as an AIT prescription for the former is clearly recommended[2]. We found that also allergy specialists were more inclined to prescribe AIT when CRD and eDiary information were added to clinical history and SPT data. Therefore, more patients could benefit of AIT, which is currently the only disease-modifying treatment for SAR.

Our study may have several implications for the clinical practice. Even though CRD and eDiary have been available for more than one decade, guidelines for AIT have not yet adopted these diagnostic approaches. Our findings suggest that a more precise description of the patient's sensitization profile before an AIT prescription should be taken into account. There is a need of controlled studies comparing the efficacy of AIT in patients in whom the therapeutic decision was based on SPT results vs SPT and CRD vs SPT, CRD and eDiary. Cost-benefit studies should also evaluate whether the immediate additional costs, implied by molecular analysis, are justified in the long-term period. Further, it is important to underline that the aim of CDSS should never be to replace a healthcare professional, but to enhance clinical routine by facilitating basic decisions and proper patient allocation at a primary care level.

We have to acknowledge some limitations of our study. First, the sample size is small, though 10% of

whole population (200 patients) as suggested for pilot studies[27]. Second, our conclusions apply to settings with high pollen exposure for prolonged, seasonal periods, such as those of Mediterranean countries and the study should be repeated in other geographic areas on larger scale. Third, the forms filled by doctors were anonymous, so no sub-group analyses could be performed.

In conclusion, our findings suggest that in countries with high and prolonged exposure to various allergenic pollen sources, a clinical decision support system involving CRD and eDiary can improve the diagnostic precision of doctors in the clinical routine significantly. On one side, it can be useful in improving the diagnostic accuracy of AS with a positive impact on the therapeutic management and proper AIT prescriptions. On the other side, it can reinforce the crucial link between GP and AS by a more conscious referral to specialists by GP, which calls for a proper GP's training and investigations regarding GP's perceptions and expectations during the referral process. This conclusion might be useful to update national and international guidelines on the prescription of AIT in SAR. The hypotheses, that the precise identification of the proper allergen for AIT also improves its clinical efficacy, as well as cost-effectiveness, deserves to be tested.

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Legend to figures

Figure 1 – Algorithm for a potential Clinical Decision Support System (CDSS) for pollen allergy . A, ¡¡Pyramid model¿¿. The four steps of the diagnostic algorithm of @IT2020.DSS develops vertically as a "pyramid". Only the pollens that have passed the previous step are considered at the next one. This approach might find applicability on large scale. However, its usefulness is particularly relevant in Mediterranean area, burdened by high aereobiological complexity and polisensitization prevalence. There, recognizing the true clinically relevant sensitization(s) and prescribing the appropriate AIT at individual level, in the perspective of a precision medicine, is particularly challenging. In most clinical cases, excluding step by step more and more pollens, the "pyramid" algorithm proceed from a large basis towards a narrow top, allowing the recognition of the only one or a few relevant pollen(s) among the many putative considered by the traditional diagnostic approach. Modified from Matricardi PM et al[22]. **B, The octagonal "dartboard".** Each of the 8 pyramids referred to one of the main local airborne allergenic sources is graphically represented

as one of the 8 regular triangles constituting the octagonal "dartboard". As in a dartboard, the algorithm aims to hit the target, that is identifying the clinically relevant pollen(s).Step by step, the algorithm proceeds from the basis up to the top of each pyramid, which is also from the outer edge towards the core of the dartboard. Allergen excluded are turned off and only the selected allergen remain colored with a more intense tone in the same colour gamma. At the end, the target will take the color of the only relevant allergen(s).

AIT , Allergen Immunotherapy; **eDiary** , electronic clinical diary; **CRD** , Component-resolved diagnosis;**NAPT** , nasal allergen provocation test; **sIgE** , serum specific Immunoglobulin E; **SPT** , Skin Prick Tests.

Figure 2 – Concordance (%) of the "virtual" prescription of allergen immunotherapy with the most prevalent final decision among allergy specialists for each medical category (allergy specialists and general practitioners) at each of the three diagnostic steps proposed in our "pyramid" model in Rome (**A**) and Pordenone (**B**).

CRD , component resolved diagnostics; eDiary , electronic clinical diary; Hx , clinical history; SPT , skin prick test. Chi squared test, when condition were respected or Fisher exact test was used to evaluate the association of categorical data between allergy specialists and general practitioners groups. McNemar's test was used to compare difference of frequency within each group. *P $<$ .05, **P $<$.01, ***P $<$.001.

Figure 3. Frequency of hypothetical AIT prescriptions decided by allergists or general practitioners at each diagnostic step proposed in our "pyramid" model (i.e. clinical history and skin prick test; clinical history, skin prick test and molecular diagnostics; clinical history, skin prick test, molecular diagnostics and electronic diary) in (A) Rome and (B) Pordenone study centers.

CRD , component resolved diagnostics; **eDiary** , electronic clinical diary; **Hx** , clinical history; **SPT** , skin prick test.

(A) Percentages are calculated on total amount of 110 cases for allergy specialists and 100 cases for not-allergists in Rome. (B) Percentages are calculated on total amount of 70 cases for allergy specialists and 180 cases for general practitioners in Pordenone.

Figure 4 – Answers to the "feedback survey" among allergy specialists and general practitioners for each clinical center in the context of the diagnostics of pollinosis for Rome (**A**) and Pordenone (**B**). Fisher test was used to evaluate the association of categorical data between independent groups (*p-value $<$ .05). SS Sensitization to more than four aeroallergens. CDSS, clinical decision support system; CRD , component resolved diagnostics; eDiary , electronic clinical diary.

Figure 1

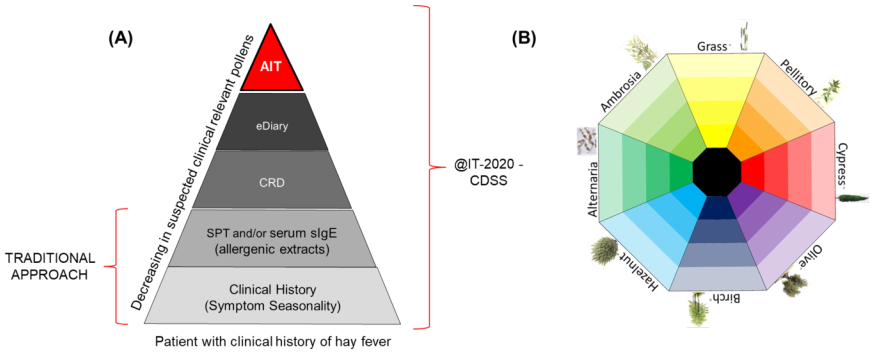

Figure 2

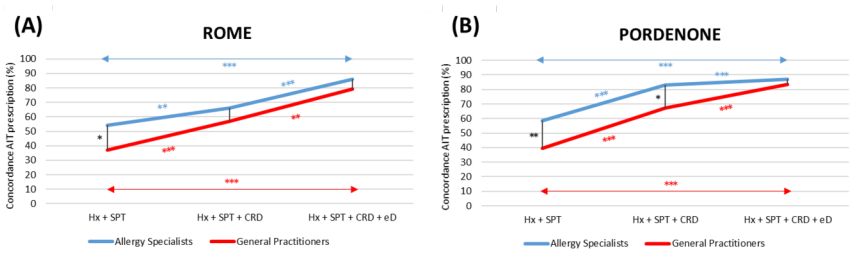

Figure 3

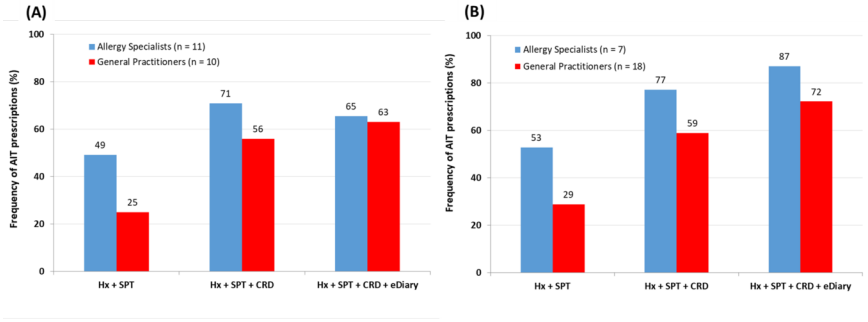

Figure 4. Answers to the "feedback survey" among allergy specialists and general practitioners for each clinical center [Rome **(A)**and Pordenone **(B)** , respectively] in the context of the diagnostics of pollinosis

ELECTRONIC REPOSITORY

Improved allergen immunotherapy prescription for seasonal allergic rhinitis: an innovative algorithm

Stefania Arasi[1,2,3], MD, PhD, Sveva Castelli[1], MD, Marco Di Fraia[1], MD, Danilo Villalta[4], MD, Salvatore Tripodi[5], MD, Serena Perna[1], MSc, Stephanie Dramburg[1], MD, Maria Antonia Brighetti[6], Mariaelisabetta Conte[4], MD, Paola Martelli[4], MD, Ifigenia Sfika[5], MD, Alessandro Travaglini[6], Pier Luigi Verardo[7], Valeria Villella[5], MD, and Paolo Maria Matricardi[1*], MD.

From the:

[1] Dept. of Pediatric Pneumology, Immunology and Critical Care Medicine, Charité Universitätsmedizin - Berlin, Berlin, Germany

[2] Dept of Pediatrics, Unit of Allergy, University of Messina, Messina, Italy

[3] Predictive and Preventive Medicine Research Unit, Multifactorial and Systemic Diseases Research Area, Pediatric Allergology Unit, Bambino Gesù Children's Hospital IRCCS, Rome, Italy

[4] Immunology and Allergy Unit, "S. Maria degli Angeli" Hospital, Pordenone, Italy

[5] Pediatric Allergology Unit, Sandro Pertini Hospital, Rome, Italy

[6] Dept. of Biology, University of Rome "Tor Vergata", Rome, Italy

[7] Center of Aerobiology, ARPA, Pordenone, Italy

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[*]Corresponding author:

Stefania Arasi MD, PhD

Pediatric Allergology Unit,

Bambino Gesù Hospital (IRCCS),

Piazza S. Onofrio, 00161 Rome, Italy

Short title : Innovative algorithm for AIT prescription

Legend to figures

Figure E1 – Allergen Immunotherapy Workshop- Feedback Survey

Figure E2 – Concordance of the hypothetical prescription of allergen immunotherapy with the most prevalent final decision among allergy specialists at each diagnostic step (clinical history and skin prick test; clinical history, skin prick test and molecular diagnostics; clinical history, skin prick test, molecular diagnostics and electronic diary) proposed in our "pyramid" model in Rome and Pordenone for each medical category (allergy specialists and general practitioners).**CRD** , component resolved diagnostics; **eDiary** , electronic clinical diary; **Hx,** clinical history; **SPT** , skin prick test. *the most prevalent final decision among allergy specialists.

Table E1. Primary data of the clinical cases shown in the workshops

ROME

CASE	Age (y)	Gender	Calendar *	Allergic co-morbidities	Family hystory	Perennial aeroallergens[‡]	SPT (mm)[†]	Extracts (kU/L)[§]	Major allergenic proteins (kU/L)[§]	Profilin(s)[§]	CCD (kU/L)[§]
1	13	M	Mar -Sep	_	AR (f, s); AA (m)	CAT, DOG	GRA(10.5; 8.5); PAR(6); FAG(4); OLE(4); CYP(3); HAZ(3); CAT(6); DOG(3.5)	GRA(90; 2.4)	Phl p 1 (80)	Phl p12 (17.4)	1
2	13	F	Mar - Jun; Sep- Oct	_	AR (f)	_	OLE(6.5); GRA(4. 5; 5.5)	GRA(2.4; -)	Phl p 1 (9.5)	_	_
3	15	F	Mar - May; Sep- Oct	AA, OAS	AR (f, m)	HDM, CAT, DOG	PAR(11.5); GRA(3.5; 4); CYP(3); HDM(8.5); CAT(6.5); DOG(7)	PAR(83); GRA(1.7)	Par j 2 (100)	_	1
4	10	F	Apr -Jun; Sep	AA	_	_	PAR(10.5); GRA(11; 5.5); OLE(9.5); ALT(9); FAG(3)	PAR(94); GRA(100); OLE(11.4); ALT(21)	Par j 2 (100); Phl p 1 (100); Cyn d 1 (24); Ole e 1 (32); Alt a 1 (68)	Phl p 12 (0.5); Bet v 2 (21)	_
5	16	F	Mar- May; Sep- Oct	AA	A (f), AA (f); AR (f, m)	HDM	PAR(6); OLE(6); GRA(4. 5; 2); CYP(3); HDM(6.3)	PAR(41); OLE(0.4)	Par j 2 (58); Ole e 1 (5.5)	_	_
6	11	M	Feb - May	_	_	HDM, CAT	OLE(5); HDM(5); CAT(5)	OLE(1.7)	Ole e 1 (28)	_	_
7	13	F	Feb - Aug	_	_	HDM, CAT, DOG	GRA(8. 6.5); ALT(7.5); HDM(5); CAT(8.5); DOG(4)	GRA(100); ALT(23)	Phl p 1 (100); Cyn d 1 (59); Alt a 1 (97)	_	_
8	12	F	Mar-May; Sep-Nov	AA, OAS	AR (f, s)	HDM, CAT, DOG	ALT(11); GRA(8; 9); CYP(8.5); OLE(9); PAR(5); HDM(13); CAT(7.5); DOG(5.5)	GRA(100; 83); OLE(55); ALT(6.5); CYP(0.1)	Phl p 1 (100); Cyn d 1 (94); Ole e 1 (100); Alt a 1 (92); Cup a 1 (15.4)	_	4
9	11	M	Apr -Jun; Sep - Oct	_	_	HDM, CAT, DOG	GRA(9. 5; 7.5); OLE(7); PAR(3); HDM(6); CAT(4); DOG(4)	GRA(100; 59); OLE(2.4)	Phl p 1 (100); Cyn d 1 (70); Ole e 1 (28)	_	4
10	13	M	Apr -Jun; Nov - Dec	AA, E	AR (f)	HDM, CAT	PAR(6.5); OLE(6); HDM(6.5); CAT(3.5)	PAR(70); OLE(2. 1)	Par j 2 (99); Ole e 1 (46)	_	_

PORDENONE

CASE	Age (y)	Gender	Calendar *	Allergic co-morbidities	Family hystory	Perennial aeroallergens[‡]	SPT (mm)[†]	Extracts (kU/L)[§]	Major allergenic proteins (kU/L)[§]	Profilin(s)[§]	CCD (kU/L)[§]
1	24	F	Apr -Jun	OAS	AR (f, s)	_	GRA(12.5; 12.5)	GRA (>100; 55)	Phl p 1 (91); Cyn d 1 (57)	Phl p12 (8.5); Bet v 2 (45)	_
2	52	M	Feb - Apr	_	_	_	CYP(10.5); HAZ(10); BIR(7.5); GRA(3)	BIR (2.4); CYP (0.35)	Cup a 1 (23)	_	_
3	15	F	Mar - May	_	_	HDM, CAT	GRA(11; 11); OLE(11.5); CYP(6); BIR(5.5); HAZ(5); HDM(5.5); CAT(5)	GRA(98; 31); BIR(21); CYP(3.1); OLE(2.4)	Phl p 1 (97); Cyn d 1 (42); Cor a 1 (10); Bet v 1 (85)	_	_
4	46	F	Apr - Oct	OAS	OAS (m)	CAT, DOG	ALT(10); PAR(54); GRA(0.7; 0); DOG(15); CAT(5)	PAR (68); ALT (19)	Par j 2 (68); Alt a 1 (19)	_	_
5	48	F	Mar - Jun	_	AR (s)	_	GRA(8; 8); HAZ(3.5); OLE(3.5)	GRA (37; 3.4); OLE (3.5); BIR (2.4)	Phl p 1 (37); Cyn d 1 (3.4); Ole e 1 (4); Cor a 1 (0.43); Bet v 1 (0)	_	_
6	18	F	Apr - May	_	A (m, s); AR (m, s)	CAT	HAZ(7.5); BIR(3.1); GRA(3.5; 3.5)	BIR (3.1)	Bet v 1 (2.4); Cor a 1 (0.43)	_	_
7	18	M	Apr - Jul	_	_	_	GRA(7; 7); CYP(3)	GRA(65; 19); CYP (0.35)	Phl p 1 (58); Cyn d 1 (28); Cup a 1 (7.5)	_	_
8	18	M	Apr -Jun	AA	_	CAT	BIR(4); GRA(4); CAT(4.5)	BIR(11); GRA(37;3.4)	Phl p 1 (44); Cyn d 1 (6.5); Cor a 1 (3.1); Bet v 1 (3.1)	_	_
9	45	M	Apr -Jun	_	_	HDM	GRA(10; 10); HDM(11)	GRA (>100; 3.1)	Phl p 1 (86); Cyn d 1 (3.1)	_	_
10	44	M	Jan - Dec	OAS	_	HDM	BIR(8); OLE(8); GRA(8; 8); HAZ(7); PAR(6); CYP(4);HDM (8)	PAR(95); GRA(65; 5.5); BIR(40); CYP(21); HAZ(7); OLE(8)	Cup a 1 (84); Bet v 1 (73); Phl p 1 (66); Cyn d 1 (7.5); Ole e 1 (56); Cor a 1 (8.5)	_	_

A, anaphylaxis; ***AA***, allergic asthma; ***ALT***, Alternaria; ***AR***, allergic rhinitis; ***BIR***, birch; ***CAT***, cat epithelium; ***CRD***, component resolved diagnosis; ***CYP***, cypressus; ***DOG***, dog epithelium; ***E***, eczema; ***F***, female; ***f***, father; ***FAG***, fagaceae; ***GRA***, grass (Phleum pratense; Cynodon dactylon); ***HAZ***, hazel tree; ***HDM***, house dust mite; ***M***, male; ***m***, mother; ***na***, not applicable; ***OAS***, oral allergic syndrome; ***OLE***, olive tree; ***PAR***, pellitory; ***RAG***, Ragweed; ***s***, sibling(s); ***SPT***, skin prick test.

* month(s) with allergic rhinitis symptoms reported by the patient. All patients presented a persistent and severe/moderate allergic rhinitis according to ARIA classification except case 6 in Rome whose symptoms were intermittent.

† cutaneous sensitization to dust and/or dog and/or cat, if any (mean wheal ≥ 3mm).

‡ cutaneous sensitization to standard panel (mean wheal ≥ 3mm)

§ ESEF assay, sIgE ≥ 0.35 kU/L. The levels of IgE to pollacins were negative in all samples.

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Table E5 - Feedback on the data primarily used for the hypothetical allergen immunotherapy prescription in the 10 clinical cases by the allergy specialists and the general practitioners.

	ROME		PORDENONE	
Tool(s)	**Allergy Specialists (%)** n= 11	**General practitioners (%)** n= 10	**Allergy Specialists (%)** n= 7	**General practitioners (%)** n= 18
eD	9	10	0	0
CRD	0	20	14	11
SPT,CRD	9	10	0	0
CRD, eD	18	0	14	39
Hx, CRD	0	0	14	0
SPT, eD	0	0	0	6
Hx, SPT,CRD	0	10	14	39
Hx, SPT, eD	0	10	0	0
Hx, CRD, eD	9	0	0	0
SPT,CRD, eD	9	0	0	0
SPT,CRD, eD	9	0	14	0
Hx, SPT,CRD, eD	36	40	29	6

CRD, component resolved diagnosis; **eD**, Electronic clinical diary; **Hx**, clinical history; **SPT**, skin prick test.

Data were summarized as frequencies (%).

*Fisher test was used to evaluate the association of categorical data between independent groups. No significant differences have been assessed between the two medical categories (specialist allergists and general practitioners) in both centers (Rome, p = 0.3; Pordenone, p = 0.5).

7 – Do you think that the traditional retrospective anamnesis is reliable enough?

- ◯ YES
- ◯ Probably YES
- ◯ Probably NO
- ◯ NO

8 – Do you think that a molecular assay targeted only to pollinosis may be useful in the diagnostics of the seasonal allergic rhinitis?

- ◯ YES
- ◯ Probably SI
- ◯ Probably NO
- ◯ NO

9 – Have you seen any pivotal methodological errors during the discussion of the clinical cases and the conduction of the workshop?

- ◯ YES
- ◯ Probably YES
- ◯ Probably NO
- ◯ NO

10 – Do you think that a patient with a true sensitization to more than 4 pollens should be excluded by specific immunotherapy?

- ◯ YES
- ◯ Probably YES
- ◯ Probably NO
- ◯ NO

11 – Do you think that filling in a clinical diary is easier through a smart-phone rather than on traditional paper copybook?

- ◯ YES
- ◯ Probably YES
- ◯ Probably NO
- ◯ NO

12 – Do you think that a medical doctor may interpret an electronic clinical diary more easily and more quickly than clinical diary written on a traditional paper copybook?

- ◯ YES
- ◯ Probably YES
- ◯ Probably NO
- ◯ NO

13 – Do you think that the tutorial preliminary to this survey has been exhaustive and well-leaded?

- ◯ YES
- ◯ Probably YES
- ◯ Probably NO
- ◯ NO

14 – Do you think that mobile-health technology may ameliorate the diagnostics of asthma and/or food allergies?

- ◯ YES
- ◯ Probably YES
- ◯ Probably NO
- ◯ NO

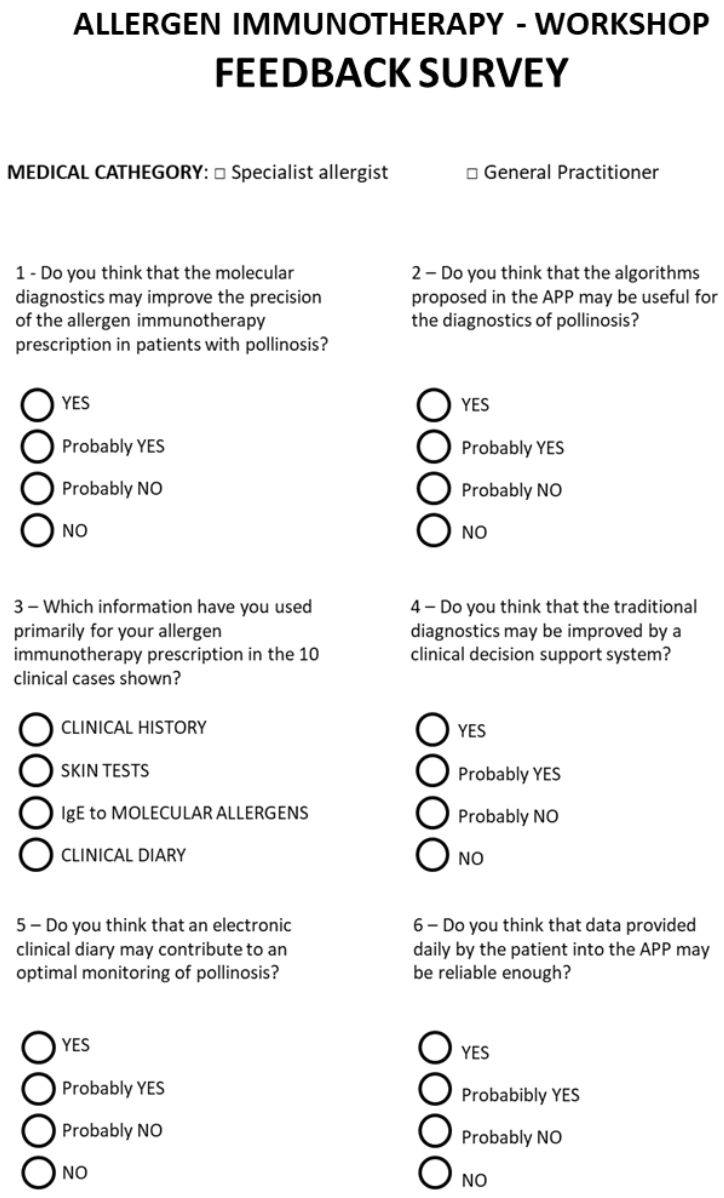

Figure E1

Figure E2

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