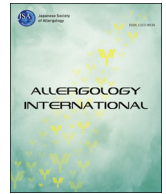




Contents lists available at ScienceDirect

Allergology International

journal homepage: <http://www.elsevier.com/locate/alit>

Invited Review Article

Managing food allergy and anaphylaxis: A new model for an integrated approach

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ARTICLE INFO

Article history:

Received 24 October 2019

Available online xxx

Keywords:

Anaphylaxis
Centres of excellence
Digital health
Education
Food allergy

ABSTRACT

There is an increasing public concern on food allergy and related anaphylactic reactions that occur mainly at the community level. The perception of the disease is huge among parents who believe that 1 out of 20 children suffers from severe food allergy. The discrepancy between this self-reported prevalence and the real one when a food challenge is performed, points out the gap in the implementation of guidelines for clinical practice. Health professionals as well show scarce adherence to the guidelines both at the Emergency Departments and at the primary care level. Anaphylactic reaction are not recognized, adrenaline is under-used and self-injectable devices are not prescribed. Although education and training are limited to local, spontaneous initiatives from patient's organization and few allergists, the data so far available demonstrate that improvement in knowledge and attitudes can be achieved further to a structured program. There is the need to establish good evidence -based practices for educational intervention that should be adopted in the context of public health policies for food allergy. This would imply a change in legislation in many countries to prevent prosecution for liability of lay people administering adrenaline when properly trained. In parallel an integrated clinical care pathway should be developed by multidisciplinary and multi-professional teams in the context of national Centres of Excellence -CoE. These CoE could drive the progression to digital health create, creating networks of CoE for best practices of care and for clinical trials

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"Thinking is easy, acting is difficult, and to put one's thoughts into action is the most difficult thing in the world."

Johann Wolfgang Von Goethe

Introduction

The increase in the incidence and prevalence of food allergy and anaphylaxis is pushing forward to prevent anaphylaxis and fatal reactions –1.81 per million person/years and 3.25 per million person years in children 0–19 year.¹ Fatal food anaphylaxis rarely occurs and the data from the code registries in the UK show a plateau in the incidence.² However in populations with a lower prevalence of food allergy the fatality rate seems to increase.¹

Currently, it appears that there is an increased concern about food allergy in families. It is reported the parents believe that one in 20 children experience food allergy to one or more foods in their lifetime.³ This raises issues from the public health perspective with regard to the perception of the disease, the quality of life, and the economic impact especially if considering that the prevalence rate between self-reported and challenge-verified rate decreases 15-fold. Patients and their families are often puzzled and misled.^{4–7}

In the last 10 years several guidelines for the management of food allergy and anaphylaxis have been published addressing the gaps in knowledge and providing guidance.^{8–10}

However the current scenario is still disappointing as underlined by the disparity of diagnostic pathways and treatments,¹¹ the underuse of adrenaline as first line drug in anaphylaxis, the different scores of severity of allergic reactions in place across the world and overall by the lack of an harmonized approach both at the health care and at the community level.¹² The aims of this article are to review the challenges in diagnosing and managing food allergy and food anaphylaxis with focus on educational

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Peer review under responsibility of Japanese Society of Allergology.

<https://doi.org/10.1016/j.alit.2019.10.004>

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interventions and to provide insights on the role of a multidisciplinary and multiprofessional integrated approach as ultimate lifesaver for the disease.

Food anaphylaxis and anaphylactic triggers

The main food allergen triggers in children are ubiquitous food proteins cow's milk, egg, wheat, fish, soy, peanut, tree nuts and shellfish. Adults reports display drugs and insect venoms as the most common allergens; undetected triggers represent up to 20% of anaphylactic reactions.^{13–16} Overall food allergy is the most common trigger of anaphylaxis in the community.^{17,13} The cross-contamination in the food preparation chain, the difficulty to detect the food allergens in labels of ingredients and the need to always carry adrenaline increase the burden of the patient and the families resulting in severe psychological impact.¹⁸

Challenges in diagnosis

The gold standard of diagnosis of food allergy is still the oral food challenge. However the procedure itself is burdensome and requires a team of skilled health professionals (including nurses, dietitians) with expertise in dealing with oral challenges and facilities that ensure the safety of the patients. Molecular allergology with the use of component resolved diagnostics (CRD) is helpful for identifying the patients at major risk of reaction in a probability risk model. The epitope mapping further refines profiling the patient but it is still limited to sophisticated research lab.^{19–21} Therefore, so far only the OFC can confirm or exclude the diagnosis with certainty.

The lack of the recommended requirements in many countries⁹ with a shortage of allergy services dealing with food allergy has as a consequence a misdiagnosis of food allergy and the missed recognition of the patient at risk of severe reactions. Anaphylaxis diagnosis is still a challenge, due to the lack of operational diagnostic criteria accepted worldwide able to catch precisely the several symptoms of anaphylaxis from the onset and their severity. A

proposal from NIAID/FAAN for criteria in the emergency setting dated back 2006²² as well as others²³ have not yet been fully validated among both emergency physicians and the allergist community.²⁴

The severity of a reaction differs between individuals and in the same individual between episodes. In addition it appears that the several stakeholders use different definitions and severity criteria for anaphylaxis.^{12,25} The most recent efforts focus on the development of less heterogeneous and more harmonized, simplified scores for allergic reactions to be adapted in several settings i.e. for the emergency department, the allergy clinic, the community and food industry. The main goal would be to provide an appropriate recognition of acute episode of anaphylaxis implementing a therapeutic strategy according to the severity (Table 1).¹²

A set of quality indicators for anaphylaxis management should be established in order to ensure that the health care providers are empowered to adopt and follow best standard of practice in the clinical setting.²⁶

Challenges in the treatment

The well-known cornerstone of managing food anaphylaxis is the complete *avoidance of the food allergen*. This goal is however hard to be accomplished. It is well known that half of the children who experience food allergy reactions, present inadvertent accidental allergen exposure within the next 2 years.²⁷ Therefore the patient and his/her family should be instructed on an appropriate management of severe reactions. The adrenaline (auto-injector) then becomes the first line therapy in all food allergy anaphylactic reactions and should be made available timely for all patients at risk.^{28,29} However the use of adrenaline and the prescriptions of auto-injectors are just one piece of the puzzle and there is a striking evidence of the under recognition and mismanagement of anaphylaxis at the emergency departments, primary care and community level, worldwide.^{30–34,13,15,35,10}

The reports of many death and near fatal reactions in the lay community^{2,36} well describe that the patient often was not

Table 1
Need for a harmonized severity scoring of acute allergic reactions according to different stakeholders Stakeholder.

Stakeholder	Purpose	Essentials of the system
Patients and their carers	Risk awareness, recognition of symptoms of allergic reaction, recognition of seriousness and decision of type of self-treatment, and reassurance.	Requires a simple, easy-to-remember system to facilitate direct linkage of presentation to management.
Emergency department, family doctors, and other healthcare professionals	Assessment for acute and long-term management according to their competences, decisions about need to refer to specialist, and educational purposes.	Requires a simple, easy-to-remember system to facilitate emergency management.
Allergy healthcare specialists	Assessment for acute and long-term management, risk assessment, and education of patients.	To document the reaction in detail to allow documentation and communication.
Food industry	Increase awareness on anaphylaxis, risk assessment of products, and risk management	Client-facing sectors (eg, restaurants) need a simple framework to manage allergic reactions. Risk assessors and managers need numerical scores that can be incorporated into probabilistic models of allergen risk.
Public health authorities	Increase awareness on anaphylaxis, to assess outcomes of health policies, funding allocation, health policy prioritization, and cost-effectiveness assessment, improve allergic reaction codification, facilitate epinephrine availability, education on anaphylaxis management for lay people (eg, teachers, children day carers, and airline cabin crew).	Require a simple, easy-to-understand system that can be used by nonhealthcare professionals. For regulators, a more sophisticated numerical score incorporating probabilistic models of allergen risk would be required.
Food, hospitality, and catering industrie	Increase awareness on anaphylaxis, risk assessment of products, and risk management.	The food industry (eg, restaurants) needs a simple framework to manage allergic reactions. Risk assessors and managers need numerical scores that can be incorporated in probabilistic models of allergen risk.
Researchers	Harmonize terminology in observational and interventional studies, aid comparison of data, and interpretation of mechanistic studies.	System needs to document the reaction with increased granularity to allow definition, segmentation, and analysis.

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prescribed adrenaline, if prescribed often didn't receive any training as well a reinforced advice on the need to carry adrenaline all time. In parallel the most used drugs for an anaphylactic reaction in the Emergency Departments are anti-histamines and steroids,^{13,37} the primary care physicians often underestimate the severity of the reaction reported by the patient and don't have time to deliver any detailed instruction and the allergists' adherence to guideline from regulatory bodies (European Medicine Agency -EMA) in recommending prescribing 2 self-injectors is very scarce.^{10,38}

A promising treatment for food allergy and food anaphylaxis is currently represented by food allergy immunotherapy. Increasing the threshold of reactivity to inadvertent exposure through desensitization has shown to reduce the risk of anaphylaxis due to ingestion of small amounts of food allergen i.e. cross-contamination. The ultimate goal to achieve tolerance when the desensitization protocol is stopped i.e off-treatment, might be possible in the next future especially if combining food allergen-specific immunotherapy and new generation biologics. Results from on-going clinical trials will hopefully provide further opportunities for a cure of food allergy.

However once again, these procedures should be performed only in allergy centers specialized in the procedure with a trained team taking care of the multifaceted aspects of food allergy.^{39,40}

For example a dietitian trained in food allergy is crucial in proper undertaking of food challenge and desensitization protocols. Furthermore a trained dedicated dietitian represent the link between the clinical setting and the community, in guiding the correct avoidance of food allergens at home, in reading labels, in suggesting free allergens recipes and what actions to take when patients eat out or travel. However in a survey the dietitians self-reported moderate to low proficiency in key areas: "less than 20% understand the steps in food allergy diagnosis, how to create oral food challenges for diagnosis or develop elimination diets, evaluate safe food in school and hospital; training for dietitians to management food allergies are greatly needed".⁴¹ All inclusive these highlight a world-wide lack of awareness and recognition of the

food allergy and anaphylaxis individual and social impact. May be in order to deal at the best with these unmet needs, the educational programs for anaphylaxis could be designed within the context of comprehensive plan for a "chronic life-long disease" with "acute episodes". The model of an integrated care pathway developed for other chronic diseases would fit well to food allergy and food anaphylaxis. It would allowing also to take benefit from other stakeholders such a dedicated psychologist addressing also the poor quality of life of the patients and their psychological distress.

Challenges in educational programs: structured educational programs

The structure of the educational interventions published so far is very different across the studies not allowing any comparison regarding the efficacy of the several interventions (Table 2a, b).

The educational programs and related materials were initially designed by the allergy patient's working groups and focused on pre and post-test improvements on specific areas; knowledge and skills in the proper use of *adrenaline auto-injectors* by patients and parents.^{42,43}

Further to the publication of the guidelines emphasizing the role of the quality of life educational structured programs were developed embracing approaching 4 specific areas: understanding food allergies, recognizing signs and symptoms, treatment with *adrenaline auto-injectors* device and reading food labels (Fig. 1).⁴⁴⁻⁴⁶ Studies conducted by allergy services usually select a broader global strategy: the educational programs focus on the community needs, mainly in school where anaphylactic reactions take place from 10%⁴⁷ up to 25%, the importance of a tailored action plan and the stakeholders (parents, school teachers) empowerment to prevent and treat food allergy in several context's including school is essential.¹⁴

Overall it appears that providing information improve the knowledge of the target population regarding the management of acute allergic reactions. In one longitudinal prospective and

Table 2a
Intervention anaphylaxis educational programs for health professionals.

Joyce E. ¹¹	2008	Survey and development of specific educational program needs and preference. Knowledge and Treatment 1 h PowerPoint presentation	Primary Care Physicians Emergency Medicine Providers	Pre and post-test scores increased from 38% (correct mean) to 64% after. >95% increased their comfort with recognition and management of FA	Improvement	Knowledge Treatment
Hernandez-Trujillo V. ⁶⁴	2013	Knowledge 3-minute presentation base on the AAAAI-AWC, Randomized control study	Residents in general pediatrics	Pre-test and post-test and follow-up test 4 weeks later. Increased in recognize anaphylaxis symptoms, recall name of AAI and doses available. The intervention group was more likely to identify severe or fatal anaphylaxis.	Improvement	Knowledge
Juhee L. ⁶⁵	2018	Knowledge Anaphylaxis diagnostic criteria Adrenaline first line therapy Implement Practice Discharge Chart outline diagnostic criteria & 1 st Line Therapy implementation of the clinical pathway	Emergency Department Staff Residents Nurses Physicians	Applying IM adrenaline using diagnosis criteria in less than 10 min from arrival. Hospitalizations rate decreased in 60% Discharge after 4 h. of observation without risk factor for biphasic reaction Discharge 85.4% with adrenaline AAI in hand and use training Referred to Allergy department for follow up within 1-3 months	Improvement	Knowledge Treatment

Table 2b

Intervention anaphylaxis educational programs for patients, parents, caregivers, and restaurants.

Sicherer S. ⁴³	2012	Knowledge Treatment AAI pre-post Training One Day Course and Online Resources	Patients & Caregivers preferences	18% correctly perform prior training and increased to 95% after. (mean scores increased from 3.4 to 5.9) Reduction anaphylactic reaction from 1.77 to 0.42 annual person year	Improvement	Treatment
Polloni L. ⁴⁹	2013	Knowledge Thoughts Feelings Pre-Post Course 12 months Period 2 h Intensive session	Teacher & Principals	Total Score increased from mean 6.6 to 8.9 Statistics significant.	Improvement	Knowledge Psychological parameters.
Murphy K. ⁶⁶	2014	Milwaukee Public Schools Emergency Anaphylaxis Training Plan. Knowledge AAI effective administration technique Identify potential sources of stress and anxiety related to implementation of the protocol. Importance of debriefing after an emergency.	School Nurses	Pre-test and post-test evaluation improved awareness of the anaphylaxis symptoms, greater confidence in their ability to respond effectively to an anaphylaxis.	Improvement	Knowledge Treatment
Sasaki K. ⁶⁷	2015	Series of workshops The effects were evaluated base on the Self-Efficacy 3 sessions: FA Knowledge Mechanisms Signs and symptoms Prevention Treatment of reactions Systematic workflow and individual roles in emergency AAI practical training Q&A session	School personnel Nurses, Teachers, Childcare workers	Increased Self-efficacy.	Improvement	Psychological parameters.
Wahl A. ⁶⁸	2015	Assess effectiveness of in-person training program (development, implementation, evaluation). Knowledge about FA Improving self-confidence: Preventing, Recognizing Treating FA reactions. Skills Treating FA reactions using AAI 45 min standardized presentation and post-test evaluation. Online survey follows up and phone interview.	Schools personnel, Childcare providers in: Summer camps School nurse School transportation Community Educational settings Government agencies	55% have prior treatment. 94% felt more confident in their ability allergy reaction as a result of the presentation. 66% were likely to changes the way they management FA. 88% were not likely to change because they already follow best practices.	Improvement	Knowledge Treatment
Brockow K. ⁴⁶	2015	Knowledge Emergency management skill Psychological parameters Randomized control Trail 2 days conference	Patients & Caregivers	Knowledge Intervention increased 3,2% vs. Control (0,7%) Treatment Intervention increase 8,7% vs. control (1,2%) Psychological Intervention -1,9% vs. control (-0,7%) less anxiety Base line and 3 months assessment	Improvement	Knowledge Treatment skills Psychological parameters.

Chokshi N. ⁶⁹	2015	Didactic session (1 school education workshop) FA general knowledge Recognition of FA, Education of parent and children Assess type reactions Assess suitability of response Skills Practice session AAI training School avoidance strategies Development individualized school policy. * Adrenaline availability in schools	School Nurses	Increased availability of AAI in FA children and sustained over 2 years.	Improvement	Knowledge Treatment
Contreras-Porta J. ⁷⁰	2016	Pre-test and post-test Study questionnaire. 2 weekends workshop (4 h total) Workshop 1 Knowledge (40 items) FA general knowledge Symptoms Diagnosis Treatment Workshop 2 (Daily life 22 items) Labeling Cooking School Latex & medicines ³	Parents' of children with food allergies & caregivers	94.56% completed the study (174/184) McNemar's Test Significant improvement: 72.5% (29/40 items) Workshop 1, 83.3% (15/18) Workshop 2 63.6% (14/2) * Lower increased on labeling.	Improvement	Knowledge
Lanser B. ⁴⁵	2016	4 Area Understanding Food Allergy Recognizing signs and symptoms Treatment functional demonstration of AAI use Food labeling 1 h presentation	Patients & Parents	Increased 54%–83% in pre-test and post-test program.	Improvement Benefit	Knowledge Treatment Action plan
Gonzalez-Mancebo E. ⁵⁴	2018	4 Areas Conference General concept (Epidemiology, problems in education, diagnosis and prevention) Diagnosis and Prevention Treatment (AAI, emergency action plan) Practical workshop (AAI, Administration training, role play)	School Teachers Cooks Dinning rooms monitors	From 25.5% to 96.6% pre and post evaluation improvement	Improvement	Knowledge Treatment Action plan
Dumeier H. ⁷¹	2018	Educational session (survey before, after session and 4-12vWeeks) Knowledge & Clinical skills	Preschool teachers	Well-prepared. Increased from 11% to 88% Would apply AAI increased 2/3 Sustained effect 4–12 weeks after session.	Improvement	Knowledge Treatment
Dyer A. ⁷²	2018	Interview 1) Emergency situation 2) Risk reduction/prevention 3) Coordination of care 4) AAI 5) Social support 6) Administrative guidelines 7) Education Transition from high school to college with food Allergies	Stakeholders College campus Patients	Transition to college for student with FA may be improved by providing support for: 1) Notification of others (student's networks), 2) Cleary-defined roles and responsibilities 3) Increasing campus awareness	a) Understand patient challenges b) Perceived responsibilities of community stakeholders c) Facilitators and inhibitors of smooth transition to collage	Knowledge Action plan

(continued on next page)

Table 2b (continued)

2018	E-learning Platform 9 modules 6 common background 3 specific for school 3 specific for restaurants Intended Learning Outcomes General Concepts Diagnosis Treatment Labeling Prevention 4 weeks to completed (45–60 min)	School Personnel Restaurant	Data not show	Improvement	Knowledge Treatment Action plan
2019	Canon N. ⁷³ Randomized case–control groups.	School Personnel	Intervention group increased knowledge scores 19.58%	Improvement	Knowledge

case–control study in a tertiary allergy clinic provided evidence of a reduction of frequency and severity of reactions up to 60-fold further to an appropriate use of the management plan.⁴⁸

More recently the attention has been devoted to the role of psychological interventions in dealing with the quality of life, anxiety, stress, behavioral problems, self-efficacy management in patients and their families.^{49–54}

The implementation of adequate education in not clinical settings would allow to efficiently address the knowledge gap of food allergy in patients, family members, caregivers i.e. schools and also improving awareness in the restaurants. The knowledge about signs and symptoms by school personnel would increase prompt identification of acute episodes and appropriate and timely use of adrenaline auto injectors. Emergency action plans with simple steps -wise design are essential at school. There is however a huge demand for a more in depth courses with the aim to highlight the food allergens, the elimination diet, signs and symptoms of food allergy and anaphylactic reaction to the school personnel and to show how to activate and use the *adrenaline auto-injector device*. The emergency protocol or action plan should be locally adapted and legally regulated by authorities. The validation of operational diagnostic criteria at the emergency department would improve education in the recognition of the initial symptoms of anaphylaxis for a punctual identification of severe patients and earlier use of adrenaline.

The achievement of specific knowledge from the primary care physicians and pediatricians on when and how to prescribe, an adrenaline device and further proper referral to the allergy service is crucial to prevent recurrences of the reaction and possibly even the first severe reaction.

A summary of the educational programmes performed at the community level (parents and teachers), school nurses, at the emergency department and for other healthcare professional (primary care, residents in pediatrics) is provided in Table 2a and b. Despite the studies limitations –selected population, conducted in only one specific allergy center, surveys with low rates of response, few with control or randomized population and only one prospective study. The available data outline the pathway to develop robust evidence for establishing good practices for an effective education.

How can we move forward

It appears quite clear that the evidence summarized in the Guidelines recommendations is not yet fully translated in the clinical practice and that we need to design a comprehensive plan which serves to build a safety network around the food allergic patient.

In addition there is a need for good quality data on the epidemiology of food allergy reactions setting registries and acquiring information from the real world. Can the new technologies help? Today the technology is part of our daily lifestyle raising questions about what do patients and parents with food allergy search in the Internet and what do they do with the information. The study in one specific allergy center in USA went through these items with an online survey; despite a low response rate, they reported the underestimated proportion of patients who use and follow online health information; most of them searched for advice on management, almost half of them searched for clinical trials, and a few, for referral to medical centers or diagnosis. Half of them searched in food allergy websites, and less in social media. A shocking finding was that 2/3 of patient and parents follow online advice, and when a mismatch is seen between medical and online advice the majority will follow the former health advice, but unfortunately some still will follow online advice. Health professionals should improve

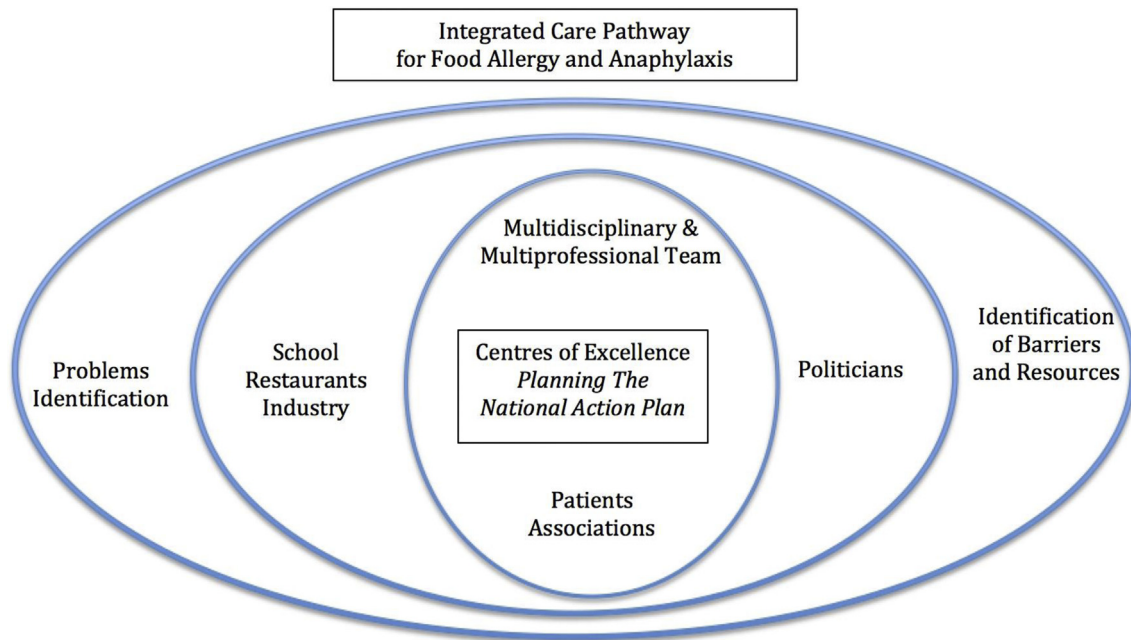


Figure 1. Multidisciplinary action plan for food allergy.

communication with patients, parents and caregivers and be aware of the online available info.⁵⁵

An important approach is a web-based food allergy education program using an e-learning platform to teach the community. A preliminary study integrates specific intended learning outcomes in 7 background modules, with 3 specific modules for school staff or restaurant staff, a total of 9 video modules for each community group, achieving a certificate to those who successfully completed a 4-week period online course. This proof-of-concept study reports only 2 months of surveillance showing efficacy and improvement in all areas.⁵⁶

Some innovative e-learning tool, already developed for other chronic diseases and supported by university platforms, could be translated to allergic diseases and to food allergy facilitating the adoption of best practices.⁵⁷

Likewise, developing apps, mirroring what has been already implemented in allergic rhinitis MASK-ARIA⁵⁸ could help the patients to manage adequately reactions in real time and the allergists/health professionals to monitor the patient and provide support in an innovative telemedicine platform specifically designed for food allergy and anaphylaxis.

However this implies in change in legislation permitting the institutional provision of adrenaline auto-injector at school and for general use. The legislation should be implemented to support mandatory training programs and prevent liability and prosecution of lay people administering adrenaline for anaphylaxis when appropriately trained.^{59,60}

The digital transformation of health care should be an opportunity to not be missed when caring for the food allergic patients. Capturing this cultural change requires setting a clinical standard of care agreed globally and the establishment of coordinating centres who would share best practice of care and research.

Centres of Excellence have been established in different areas of medicine to ensure translating the evidence of science in practice and also to facilitate research in networks for clinical trials. Centres of Excellence for food allergy and anaphylaxis with different expertise tiers, according to each centre facilities, working together

would develop national action plans with health professionals and patients organizations gradually overcoming the challenges and harmonizing care (Fig. 1).

Conclusions

The need to prevent accidental trigger exposure, avoiding anaphylaxis and fatal reactions can be tackled by structured validated educational programs across the community. An effort in providing education would take over the lack of awareness among health professional, and the lack of knowledge, fear, hesitation on adrenaline auto-injectors use, and anxiety in patients, families, health care providers themselves. It should also evolve to focus in the community -school personnel,- all across the education system to include nursery, elementary schools, high school and colleges.

There is the need to develop a multidisciplinary and multi-professional approach which integrates health professionals, nutritionist, dietitians, psychologist, pharmacists, patient organization and food industry.⁶¹ Some examples in other areas such as allergic rhinitis have shown benefits for the implementation of good practices. This process includes developing specific skills for each of this professional in recognizing, diagnosis and appropriately managing food allergy.^{41,62} The progression of health care to digital health should facilitate the integration of competencies and achieve the ultimate life saver of an holistic vision of caring for the food allergic patients⁶³

Conflict of interest

AM received honoraria from Aimmune, DVB, Nestlé-Purina, Nutricia, and Nestlé-Health Institute. DAMH has no conflict of interest.

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