



Progress in *Anisakis* Allergy Research: Milestones and Reversals

Alvaro Daschner, Ph.D., M.D.^{1,*} 
Carmen Cuéllar, Ph.D.²

Address

¹²Servicio de Alergia, Instituto de Investigación Sanitaria- Hospital Universitario de la Princesa, C/Diego de León 62, 28006, Madrid, Spain
Email: alvarodaschner@gmail.com

²Departamento de Microbiología y Parasitología, Facultad de Farmacia, Universidad Complutense, Madrid, Spain

© Springer Nature Switzerland AG 2020

This article is part of the Topical Collection on *Food Allergy*

Keywords Gastro-allergic Anisakiasis • *Anisakis*, host-parasite-interaction • Healthy diet • Fish-consumption • Zoonosis

Abbreviations GAA Gastro-allergic Anisakiasis • CU Chronic urticaria • CU+ Anisakis sensitization-associated chronic urticaria

Abstract

Purpose of the review *Anisakis* has gained cosmopolitan celebrity mainly through its potential to induce allergic disease. In the last two decades, several regions in the world, including the Mediterranean region, Japan, or Korea have reported high numbers of Anisakiasis-accompanied allergic symptoms: Gastro-allergic Anisakiasis.

Recent findings Recent wide-scale epidemiological studies highlight the global scenario of *Anisakis* for human health, and awareness is the main contributing factor. After two decades of research in the field of *Anisakis* allergy, in the last years, molecular studies of *Anisakis* allergens including omics research abound, fostered by available techniques and the putative necessity to a more precise diagnosis. Knowledge in the form of new massive data should be balanced against the creation of social and scientific alarm.

Summary In gastro-allergic Anisakiasis primary and secondary preventive measures against acute allergic episodes include adequate fish processing before consuming it raw or lightly cooked (deep freezing at –20 °C for at least 24–48 h). Unfortunately, experts working in very different fields do not prioritize basic knowledge of immune biology of parasites and clinical allergy, risking an erroneous interpretation of allergic

features, which could have important deleterious effects on the global implementation of a healthy fish-including diet.

Introduction

Growing awareness of a healthy style of life includes dietary recommendations. Fish and seafood consumption is not only a pillar of the appraised Mediterranean Diet; it has widely been studied for its beneficial effects, which could partly explain the long life expectancy of populations with the worldwide highest per capita fish consumption, such as Japan and Spain. Furthermore, culinary and cultural phenomena bring about a worldwide expansion of traditional raw fish eating. On the other side of the coin are increasing health concerns about the transmission of zoonotic diseases. Parasitic disease produced by cestodes and trematodes are associated with mainly freshwater fish, whereas Anisakidae are cosmopolitan nematodes able to produce human disease by infesting a vast array of saltwater fish [1••]. The unfortunate celebrity of *Anisakis* on the other side is due to its associated allergic phenomena, which have increasingly being reported in the last two decades, and inadequate information not only at the consumer level, but also in the scientific community risks to focus falsely alleged adverse allergic health hazards over the widely recognized health benefits of fish consumption. This could have important deleterious effects on the implementation of a healthy diet [2].

Anisakids are parasites of the genera *Anisakis*, *Pseudoterranova*, *Hysterothylacium*. *Anisakis simplex*, *Anisakis pegreffii*, and *Pseudoterranova decipiens* are species of major public health interest and associated with

marine fish, which are paratenic hosts. International concern on anisakids relates not only to fast transportation systems and import. Several studies have shown that anisakids can be detected in a vast array of fish and cephalopods and have a worldwide distribution, which also explains the cosmopolitan nature of reports on Anisakiasis and allergic phenomena. *A. simplex* commonly occurs in various ecologically and economically important fish species such as herring, mackerel, blue whiting, cod, and monkfish [3].

The last years demonstrated sufficient evidence that allergic food-borne phenomena due to *Anisakis* are associated with active parasitism by this nematode in both clinically visible IgE-mediated reactions, as well as the different forms of digestive Anisakiasis or even subclinical parasitism, which is witnessed by the production of specific IgE [4, 5]. This is due to *Anisakis* being a helminthic parasite able to induce a Th2 immunologic response in all affected individuals irrespective of their atopic status [6]. Therefore, it is necessary to include in the following paragraphs some information also on non-allergic disease elicited by this nematode. The fact that humans are only accidental hosts of *Anisakis* explains that *Anisakis* and humans did not co-evolve, and therefore this larva does not survive more than a few days in humans [7]. This fact is probably responsible for the high prevalence of allergic phenomena associated with this nematode.

History, epidemiology and risk factors of Anisakiasis and allergy

The story begins in 1955 when for the first time in Holland a nematode was detected in a surgical procedure and identified as *Anisakis sp.* in a patient with abdominal pain after eating raw smoked herring. In 1960, van Thiel identified the third stage larva of *Anisakis* in surgical laparotomies and the term Anisakiasis as a clinical entity has been used since then [8]. Lightly salted pickled herring (therefore also called herringworm) was the source of acquisition of this parasite by the patients. In 1968, a decrease of Anisakiasis cases was observed due to Dutch legislation that required freezing of fish before further processing. After the

description of the first case of Anisakiasis in Japan in 1965 [9], the real epidemiological explosion can be attributed to Japanese reports due to a widely use of raw fish-eating habits. Estimates of Anisakiasis are about 2000 cases/year for Japan, South Korea 200 cases/year, or some of the European countries with 500 cases per year [3]. But from all over the world cases are reported, such as from the USA, other countries of Europe, Northern Africa, or even South-America [10–12].

Overall, gastric Anisakiasis is the most prevalent condition, and most cases are reported from Japan, where gastroscopy is able to confirm the diagnosis and treat in situ. Intestinal Anisakiasis is mainly diagnosed by hazard in surgical procedures, whereas ectopic Anisakiasis is very rare.

On the other side, from the midst 90's, allergic phenomena, previously mentioned by Japanese authors, have been systematically reported initially from Spain, and then from other Mediterranean countries. Of note, in Europe, allergic episodes are more frequently diagnosed than gastric or intestinal Anisakiasis. Here prevalence data can be interpreted as estimates of allergic cases per year. However, data are widely underestimated. As Anisakiasis with and without allergy is always accompanied by production of specific IgE, the sensitization rate in a given population should give accurate information about this population and previous contact with the live parasite. There are data available from different countries that are given in Fig. 1 and contrasted to the per capita fish consumption in a given country. An idea of the epidemiology of gastro-allergic anisakiasis (GAA) can be

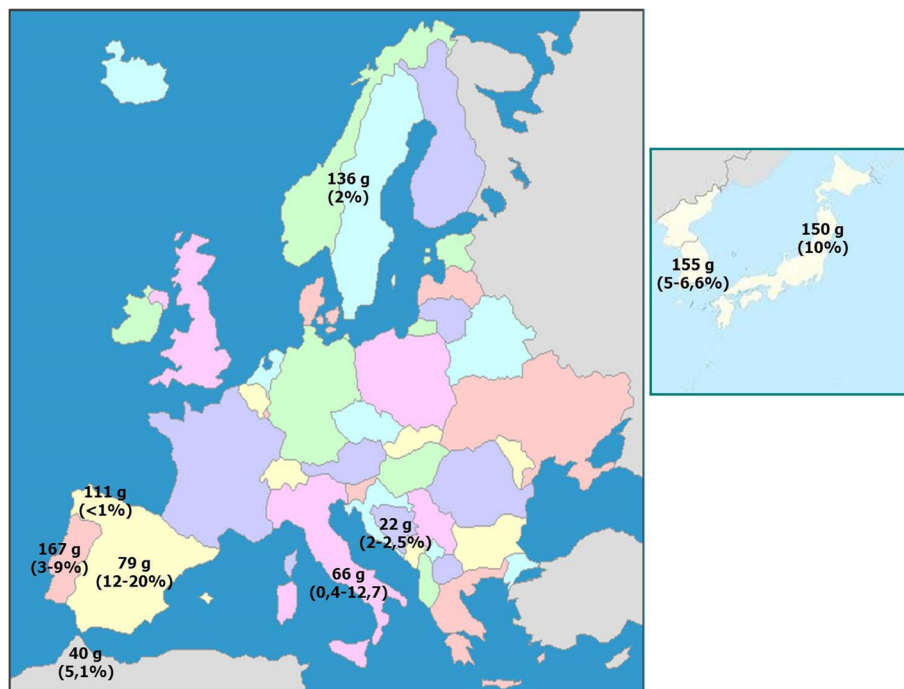


Fig. 1. Fish consumption is shown as per capita per day in gram for those countries, where data are available on prevalence of specific IgE against *Anisakis* in the population. Estimates of IgE sensitization are given in percent as published in the different reports for Spain, Portugal, Morocco, Italy, Norway, Croatia, Korea, and Japan [13, 14, 15–20]. Spain has an overall high fish consumption per capita (113 g). A detailed analysis has shown an even higher consumption in the North-East Galicia compared to Central Spain, whereas here sensitization against *Anisakis* is nearly undetectable due to absence of raw or undercooked fish eating habits, compared to the Central region [20]. Interestingly, epidemiological studies show that fish consumption per se is not the main risk factor for sensitization

derived from one initial study on this entity, where 24 cases were diagnosed of GAA by visual confirmation of the larva in gastroscopic examination, but nearly 100 patients were diagnosed by clinical history and compatible allergic follow-up and serial measurements (see below) [4, 21, 22].

A more recent estimate by a quantitative risk assessment model was developed and suggests that Spain has between 700 and 8320 Anisakiasis cases annually [23••]. Two other epidemiological assessments based on national hospital discharge data have given very interesting data, which highlight the epidemic character of gastro-allergic Anisakiasis and are contrasted to sensitization rates which demonstrate that the vast majority of sensitized subjects have produced specific IgE without any clinical symptoms [24••, 25•]. Importantly, awareness of this disease is crucial to diagnose this entity and that those countries who have proceeded to search for sensitization rates or Anisakiasis cases show considerable underestimation of cases. Another reason for the underestimation of gastric and gastro-allergic cases is the fact that only patients with the most severe cases search for medical advice and mild cases can nurture the high “subclinical” sensitization rate in endemic areas.

Indirect data give also information about the relationship of *Anisakis* and allergic disease. Thus, data on the sensitization rate in patients with chronic urticaria (CU), with other allergic urticaria episodes or from a pool of patients in the allergy clinics are always higher than in the general population and thus should be studied with respect to the encountered association. In patients with CU, several reports show in endemic regions, as are Spain and Italy, positive specific IgE against *Anisakis* in between 49.7 and 55% of patients [26–28].

Epidemiologic studies have shown that several species are implicated in Anisakiasis cases, such as mackerel, herring, anchovies, sardines, blue whiting, or hake, only to name some of the commercially available fish species in Europe or cuttlefish, corvina, sea eel, ling, fatfish, yellowtail, scabbard fish, sea bream and others as published from Korea [27]. This suggests that almost every fish could be affected, but fish preparation is the main risk factor and not so much the species per se. Otherwise, as can be seen from Fig. 1, there is no direct correlation of fish consumption and sensitization or risk of Anisakiasis. There is a very low sensitization rate, but high fish consumption in North West Spain or Norway, due to the fact that in these regions fish is eaten mainly well cooked or if eaten raw, is previously frozen [28, 29]. On the other side, there are some fish species, such as blue whiting and hake, with high infection rate, which are not eaten in raw specialities, but harbor a risk of parasitism when undercooked.

Clinical symptoms

Anisakis infection associated disease has been described from the 60s, initially from raw-fish eating Dutch and then Japanese sushi-eating populations, further from the mid 90s clinically overt allergic reactions have been associated with this parasite and have produced a world-wide concern. Research focus has now extended to several disciplines, not only in the field of fisheries, parasitology, food safety, but also to several specialities in Medicine. Up to 20% of published papers on *Anisakis* are associated with analysis of allergic phenomena in the last years [2]. Thus, classical diseases are digestive diseases and emerging diseases are associated with allergic phenomena.

Classical and digestive diseases

Clinical forms are classified as gastric, intestinal, or extra-intestinal Anisakiasis depending on the location [30]. The most commonly reported form is acute gastric Anisakiasis, followed by acute intestinal Anisakiasis. However, most human cases of Anisakiasis are expected to go unreported, without causing any symptoms or clinical signs, but leaving IgE as witness of previous parasitic episode. In acute cases of gastric Anisakiasis, patients complain typically of epigastric pain, nausea, and vomiting. These symptoms occur mainly within hours of the intake of the suspected meal and are produced by the local inflammatory reaction when the worm penetrates the gastric mucosa. Emergency diagnosis and treatment includes gastroscopic visualization and extraction of the live penetrating larva.

Emerging and allergic diseases

After the first descriptions of *Anisakis*-associated anaphylaxis [31, 32], as soon as by 2000, it has been well established that acute allergic symptoms, such as urticaria, angioedema, or anaphylaxis, are elicited by the live third stage larva of *Anisakis*. This emerging entity is called gastro-allergic Anisakiasis (GAA) [4, 21, 33]. GAA was initially described for *Anisakis simplex*, but a further study showed this entity also to be produced by *A. pegreffii* [34]. The acute IgE-mediated generalized reaction with cutaneous (urticaria-angioedema), and/or respiratory (rhinitis and asthma) symptoms can be accompanied typically by abdominal symptoms like nausea, vomiting, or epigastric pain, but remain often mild or even absent in this clinical picture. Symptoms appear similarly to gastric Anisakiasis mainly after some hours of the intake of raw or undercooked fish, but sometimes the time interval can be as long as 24 or even 36 h, a fact which renders difficult diagnosis. Frequently, suspected agents to be responsible for the acute allergic reaction include drugs and several other food items, taken within the long time interval, even other well-cooked fish in patients with a high weekly fish intake. Of note, Japanese authors already described urticaria in about 8.4% of cases as one of the possible symptoms accompanying gastric Anisakiasis [5, 35]. Comparison of gastric Anisakiasis cases from Japan and Spain highlights that Japanese suffer more from gastric complaints without allergic symptoms, which rapidly lead to gastroscopic examination, whereas in Spain, the predominating entity is gastro-allergic Anisakiasis. Whether this is due to genetic factors, different sibling species of *Anisakis* or other undetermined factors is unknown. In fact, abdominal symptoms had already been attributed to be an “allergic” response, because of specific IgE production in these patients [5].

Anisakis sensitization-associated chronic urticaria (CU+) has also been linked with this nematode. The detection of specific IgE in these patients has to be interpreted as a sign of a previous acute parasitism. In this scenario, the parasitic episode often goes clinically unidentified. The high percentage of sensitization of CU patients in endemic regions described above show that due to still unknown causes sensitized patients have a higher risk of suffering chronic urticaria [26, 27, 36, 37]. In order to study the role of anti-*Anisakis* IgE antibodies in frequent fish-eaters and its association with the chronic reaction, a prospective clinical study was conducted which showed unexpectedly, that patients who followed a diet without fish had a worse prognosis [37]. Several

studies have shown that CU+ behaves differentially when compared to non-sensitized CU patients [27, 37, 38]. Prognosis has been shown to be better in sensitized patients, and immunologic studies have shown that much can be learned in the Pandora box of CU. If *Anisakis* is not interpreted as a mono-causative agent but as one of the possible modulating factors in a multifactorial etiology of CU, it leaves possible range for therapeutic advice.

The fallacy of allergic risk

Hypothetical considerations, but without clinical correlation, have prompted some authors in the laboratory setting to postulate acute allergic reactions to be also possible when sensitized patients enter in contact with allergen alone from killed parasite. Early studies have however shown that gastro-allergic patients with even anaphylaxis challenged with a high number of inactivated larvae or even high doses of excretory-secretory proteins did not show positive reactions [39, 40]. As this concern prompted European authorities to revise the evidence of these statements, it was prudently summarized that “the relative epidemiological impact of the described clinical descriptions is unknown” [3]. Notwithstanding, the number of laboratory studies assessing putative new allergens and experimental studies with artificial sensitization procedures outnumber by far clinical and epidemiological studies. As a recent example, another *Anisakis* *Pseudoterranova decipiens* has been shown to sensitize mice after intraperitoneal inoculation with anisakid proteins [41], but clinical relevance in humans cannot be inferred. This risks a publication bias by repetitive statements on the allergenicity of *Anisakis* molecules, which is based on hypothetical considerations in the food-allergy setting without taking into account most important host-parasite immunology and different immune regulatory features.

Progress in allergens identification and their significance

It should be highlighted that *Anisakis* allergens are not food allergens. Even if not broadly accepted, a proper definition of allergen should include necessity of the allergen to be a non-parasitic antigen [42]. This is logical, as the IgE response against helminths is universal in mammals [7, 43]. Notwithstanding, IgE-producing parasite-derived antigens have been isolated and characterized, and the international nomenclature consensus has been applied to these proteins of *A. simplex* as Ani s 1 through Ani s 14 [44•]. Most of the allergens are excretory-secretory proteins (ESP), putatively implicated in the acute allergic reactions, whereas Ani s 2 and Ani s 3 (paramyosin and tropomyosin respectively) are somatic allergens. Further potential novel allergens have recently been proposed by proteome or transcriptome data analysis [45, 46]. Similarly, *A. pegreffii* has been shown to have similar allergens [47•].

Without merging into the individual characteristics of the allergens, general and well-studied concerns are the heat-, gastric digestion-, and freezing-stability of several allergens as assessed in food security evaluations, without again taking into account that GAA is not a food allergy. Major allergens (as defined by the recognition of > 50% of sensitized individuals) are Ani s 1, Ani s 2, Ani s 7, Ani s 12, and Ani s 13. Big data are now emerging also in this field and an ever-increasing amount of possible allergens, but caution is warranted not to

study and interpret them as if they were food allergens, because it has already led to the false assumption of allergenicity of dead or inactivated *Anisakis* material in a “hidden allergen” scenario. However, it has been demonstrated that these allergens are only relevant in the special situation of the live larva actively invading the mucosa of the gastro-intestinal tract. This is not only due to the fact, that some of the recognized allergens are actively produced and secreted (ESP) during the migration of the larva through the gastro-intestinal mucosa, facilitating the penetration of host tissues and the digestion of tissues for nutrients [48, 49•]. It has also been shown that the invading larva induces not only an IgE response, but also a parallel production of other isotypes of immunoglobulins, such as IgG4 and IgA [50]. These are expected, together with other unknown immune-regulatory factors, to hinder minute quantities of allergens to be able to elicit degranulation of mast cells and thus the allergic response to isolated allergens of an inactivated or dead larva. Only massive secretion of allergens by the live larva is able to overcome these protective factors [7]. Zamora et al. showed that *A. simplex* larval antigens gave rise to murine dendritic cells with a “semi-mature” phenotype, characteristic of anthelmintic Th2 responses, with low expression of surface activation markers [51••]. The Th2 response can induce tolerogenic dendritic cells, generating a balance between Th2 and Treg cells [52].

Peculiarities of allergic *Anisakis* disease

The pathogenesis of the acute IgE-mediated reactions induced by *Anisakis* in gastro-allergic Anisakiasis is the same as in food allergy, at least in the final steps, when IgE bound to the mast cells or basophils recognize specific allergens and cell degranulation leads to local and/or systemic symptoms. Like in other helminth infections, but also in allergies, a Th2-skewed immune response is associated with IgE production, eosinophilia, as well as mast cell activation. The difference lays in the early steps, as described above. Live larva is accidentally ingested within a raw or undercooked fishmeal, and it is the live larva, which “decides” when it enters the gastric mucosa (sometimes several hours later), situation necessary to induce clinical symptoms. In gastric Anisakiasis, the same mechanisms have long been postulated to lead to local swelling and epigastric pain, associated with eosinophilic infiltration [5]. Granuloma formation due to a foreign body reaction accounts for the chronic manifestations of Anisakiasis. Interestingly, it has been shown that in these chronic manifestations, no acute allergic IgE-mediated reactions precede granuloma formation and even postulated that the allergic reaction is able to protect the host from further larva migration, expelling the parasite early [7, 53]. Very early gastroscopic examinations in the emergency room have shown in GAA mucosal ulcerations erosions or hemorrhagic points due to a recently expelled larva [22, 32].

With regard to the possible pathomechanisms leading to chronic urticaria in CU+, it cannot be discarded that the by long higher sensitization rate in this entity compared to the general population in the same area is only a non-causal association. On the other side, the fact, that the sensitization phenotype is clinically and immunologically different compared to non-sensitized CU, points at least to regulatory features of previous contact with *Anisakis* in CU. Interestingly, although raw fish-eating habits is a clear risk factor for

sensitization as well as clinical visibility of sensitization (GAA, CU+), these patients consume frequently much fish overall. Especially oily fish intake has not only been associated with anti-inflammatory cytokine production. In addition, those patients with better prognosis of CU, as measured by evolution of Urticaria Activity Score, consumed habitually more oily fish. In fact, a temporary diet without fish led to a worse UAS outcome compared to those who continued to consume fish (but avoiding raw or undercooked fish). These data indicate that dietary factors associated with *Anisakis* sensitization are able to modulate the activity of urticaria, irrespective of probably other multifactorial genesis of CU [37]. *Anisakis* larval antigens potentiate different responses depending on the host base factors through induction of both immature and inflammatory dendritic cells. BALB/c mice generated an acute, inflammatory and susceptible response, with higher expression of IL-12 and lower IL-10 than C57BL/6 J mice, which developed a discrete and resistant response [51••]. This imbalance can determine tissue damage (Th1/Th17), expulsion of parasites (Th2), or asymptomatic infection (Treg/Th2) [54].

Diagnostic approaches

Perhaps even more than in other fields of Allergology, in the case of allergic features associated with *Anisakis*, the clinical history is the most important guide for further assessment. An acute reaction of urticaria/angioedema or anaphylaxis should not only include the description of the ingested foods or drugs in the few hours before the onset of symptoms. It should also directly ask for fish intake and preparation (raw, undercooked? previously frozen?) with a wider range up to 24 or 36 h. In the emergency room and when abdominal symptoms are important and accompanying the allergic reaction, the gastroscopic examination can be diagnostic and therapeutic. In the allergologic laboratory work-up, a first search for sensitization by means of positive skin prick test or specific serum IgE is useful in order to discard previous *Anisakis* contact, but a positive test, irrespective of the IgE titer, does not necessarily be diagnostic, as it only shows a previous parasitic contact at any time in the patient's life. Therefore, serial measurements of specific IgE have been proposed to have a high diagnostic specificity for a recent contact if levels are on the rise for 4 weeks and fall afterwards during the next 6 months. Likewise, polyclonal stimulation after the parasitic episode elicits also elevation of total IgE, whose curve goes parallel to that of specific IgE [55].

Cross-reactivity is one of the possibilities for subjects to display positive IgE against *Anisakis* [56, 57]. Antigens of this nematode may cross-react with homologous antigens of other ascarids, such as *Ascaris suum*, *Ascaris lumbricoides*, *Hysterothylacium aduncum*, or *Toxocara canis*, but also other helminths [58•, 59, 60] or even species from other invertebrate orders [57]. Typically, cockroaches, chironomids, or dust mites from the respiratory allergens or crustaceans and mollusks from the food allergens are able to cross-react with *Anisakis*. Somatic pan-allergens Ani s 2 and Ani s 3 (paramyosin and tropomyosin, respectively) are more likely to cross-react, whereas excretory-secretory proteins are more frequently species specific [58•]. Of these, Ani s 1 and Ani s 7 are considered to have no cross-reactivity with other allergens; furthermore, these proteins have higher allergenic potential and can therefore be used to diagnose previous

Anisakiasis cases with possibly higher sensitivity. In the era of component-resolved diagnosis in Allergology, there is also scientific endeavor to lead *Anisakis* diagnosis to the Allergy field [61]. However, as diagnosis is mainly based on clinical suspicion, together with the fact that current extracts for skin tests and in vitro diagnosis are very sensitive, diagnostic sensitivity is therefore not the current problem in diagnosis. Interestingly, Ani s 13 is hemoglobin and should be suspected to have cross-reactive panallergenic potential. But specificity of this major allergen has been shown, especially absence of IgE reactivity to the phylogenetically closely related *Ascaris* hemoglobin in *Anisakis*-sensitized patients rendering Ani s 13 a potential candidate for developing more specific diagnosis tools [62]. However, native Ani s 13 was superior in sensitivity compared to recombinant Ani s 13, a fact to consider when searching for gold standard in the diagnosis of allergic disease [63].

Many of the mentioned studies justify on searching for new diagnostic tools. Like in other medical conditions, delegating diagnostics to sophisticated molecular tools compromises basic diagnostic work-up as described above. Furthermore, it encourages indirectly assessing *Anisakis* allergy like in food allergy.

Treatment and prevention

Symptomatic treatment of acute allergic reactions in the emergency room does not differ from that in food allergies. Gastroscopic examination and larva extraction will rarely be necessary due to the expulsion potential of the allergic reaction [7, 21]. Pharmacological treatment of CU+ begins with stepwise use of antihistamines and can include in severe cases use of immunomodulatory drugs.

Patients should be motivated not to reduce their habitual fish consumption, but should be advised to avoid intake of raw or undercooked fish if not adequately frozen previously [3]. Proper food preparation is sufficient for inactivation of parasites and also to avoid allergic reactions.

On the epidemiological level, preventive measures for *Anisakiasis* have been implemented in different regions due to the risk of acute parasitism with *Anisakis* [3]. It has been documented that traditional processing methods are not sufficient to kill *Anisakis*. Importantly, freezing at -20°C for not less than 24, preferably 48 h, or heat treatment at $>60^{\circ}\text{C}$ at the core of the fishery products for at least 1 min are recommendations of the European Food Safety agency, which takes into account also the emerging allergic phenomena [3]. These basic fish-eating preparations and habits should avoid on a grand scale new allergic episodes also in already sensitized individuals. In fact, recent studies about the effectiveness of freezing or the gene expression profiles of antigenic proteins have translational character and underpin the usefulness of proper fish treatment before consumption for prevention of parasitic disease and accompanying allergic reactions [49•, 64•]. Another study assessed traditional open-air drying of stockfish fillets of Northeast Arctic cod concluding this method as an alternative and efficient treatment for inactivation of anisakids [65•].

Another point is prevention and regulation on fishing practices. Control measures could focus on the post-harvest handling, storage, and preparation of fish in order to avoid post-fishing migration of larvae into the flesh [66], as well

Table 1. Differences between food allergy and *Anisakis*-induced allergy

	Food allergy	<i>Anisakis</i>-induced allergy
Clinical symptoms	Typically IgE-mediate (urticaria-angioedema, anaphylaxis, asthma)	Typically IgE-mediated + digestive symptoms
Latency	Immediate	Immediate up to 36 h
Atopy	Yes	Not necessary
Challenge test	If relevant positive	Always negative
Co-factors	Sometimes NSAID, exercise, alcohol	Live larva as “co-factor” necessary
Matrix of allergy	Food item	Parasite
Immune type	Th2	Th2 + Th1
Immunoglobulins	IgE	IgE + IgG+ IgA + IgM

as control of the practice of waste elimination from fishing vessels, one of the suspected but avoidable factors accounting for the increasing incidence of *Anisakidae* in fish.

Conclusions and future perspective

Anisakis-induced disease follows several features of globalization. On one side, culinary preferences including raw fish dishes are spreading around the world; on the other side, migratory patterns of fish as well as methods in fishing practices are probably behind the ever-increasing infection rates of commercially available fish by anisakids. However, clinical awareness and scientific dissemination are also spreading, and reports of allergic features associated with *Anisakis* are to be expected to still increase in the next decades. Experimental and laboratory research have been able to elucidate some of the responsible mechanisms of disease in GAA and CU+, whereas clinical studies have underpinned the necessity of a live larva to induce acute allergic IgE-mediated symptoms, a fact that makes this entity highly preventable.

It has been shown that in CU not only sensitization to *Anisakis* is associated with a different phenotype; also, fish intake per se seems to modulate its prognosis. As with other parasites, research is also focused on the possible immuno-regulatory features of some compounds of *Anisakis* [67, 68]. The future will show if *Anisakis*-derived factors could account for influencing urticaria severity and even be used therapeutically.

Healthy fish-eating habits, such as in the Mediterranean Diet are at risk because of fears about mercury or chemical contaminants, but also increased awareness of parasite infection and allergies, especially by *Anisakis* spp., and may result in reduced fish consumption, even when it has been demonstrated that only live parasites are able to elicit disease [2].

According to FAO, it is necessary to assess the health benefits and risks associated with the consumption of fish and balance them in order to enjoy the benefits while minimizing the risks [69]. Although high compliance with recommended fish consumption patterns can improve public health, unintended shifts in consumption can lead to public health losses [70]. The world-wide

expansion of raw fish-eating habits and restaurants which offer raw fish specialties should therefore not only be seen through the prism of *Anisakis*-induced health hazards, but one should be aware of the opportunity not only from the culinary viewpoint, but also as a means of partially satisfying essential nutritional necessities. Proper handling of raw fish prior to its intake has been shown to be sufficient to inactivate possible parasite hazards (Table 1).

Compliance with Ethical Standards

Conflict of Interest

Alvaro Daschner and Carmen Cuéllar declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. •• Levsen A, Svanevika CS, Cipriani P, et al. A survey of zoonotic nematodes of commercial key fish species from major European fishing grounds—introducing the FP7 PARASITE exposure assessment study. *Fish Res.* 2017. <https://doi.org/10.1016/j.fishres.2017.09.009>
- This European study represents a large and comprehensive epidemiological data compilation of anisakids ever generated in terms of geographical range as well as number of many fish host species and represents a basic tool for risk assessments.
2. Daschner A. Risks and possible health effects of raw fish intake. In: Raatz SK, Bibus DM, editors. *Fish and fish oil in health and disease prevention*. Amsterdam: Elsevier/Academic Press; 2016. p. 341–54.
3. EFSA. Scientific Opinion on risk assessment of parasites in fishery products. *EFSA J.* 2010;1543–634.
4. Daschner A, Alonso-Gómez A, Cabañas R, Suarez-de-Parga J, López-Serrano M. Gastroallergic anisakiasis: borderline between food allergy and parasitic disease-clinical and allergologic evaluation of 20 patients with confirmed acute parasitism by *Anisakis simplex*. *J Allergy Clin Immunol.* 2000;105:176–81.
5. Asaishi K, Nishino C, Ebata T, Totsuka M, Hayasaka H, Suzuki T. Studies on the etiologic mechanism of anisakiasis. –1. Immunological reactions of digestive tract induced by *Anisakis* larva. *Gastroenterol Jpn.* 1980;15:120–7.
6. Nieuwenhuizen NE, Lopata AL. *Anisakis*—a food-borne parasite that triggers allergic host defences. *Int J Parasitol.* 2013;43:1047–57.
7. Daschner A, Cuéllar C, Rodero M. The *Anisakis* allergy debate: does an evolutionary approach help? *Trends Parasitol.* 2012;28:9–15.
8. van Thiel P, Kuipers FC, Roskam RT. A nematode parasitic to herring, causing acute abdominal syndromes in man. *Trop Geogr Med.* 1960;12:97–113.
9. Asami K, Watanuki T, Sakai H, Imano H, Okamoto R. Two cases of stomach granuloma caused by *Anisakis*-like larval nematodes in Japan. *Am J Trop Med Hyg.* 1965;14:119–23.
10. Kliks M. *Anisakiasis* in the western United States: four new case reports from California. *Am J Trop Med Hyg.* 1983;32:526–32.
11. Oshima T. *Anisakiasis* - is the sushi bar guilty? *Parasitol Today.* 1987;3:44–8.
12. Patiño JA, Olivera MJ. Gastro-allergic anisakiasis: the first case reported in Colombia and literature review. *Biomedica.* 2019;39:241–6.
13. Daschner A, Vega de la Osada F, Pascual C. Allergy and parasites reevaluated: wide-scale induction of chronic urticaria by the ubiquitous fish-nematode *Anisakis simplex* in an endemic region. *Allergol Immunopathol (Madr).* 2005;33:31–7.

14. López-Sáez M, Zubeldia J, Caloto M, Olalde S, Pelta R, Rubio M, et al. Is *Anisakis simplex* responsible for chronic urticaria? *Allergy Asthma Proc.* 2003;24:339–45.
 15. Falcão H, Lunet N, Neves E, Iglésias I, Barros H. *Anisakis simplex* as a risk factor for relapsing acute urticaria: a case-control study. *J Epidemiol Community Health.* 2008;62:634–7.
 16. Abattouy N, Valero A, Martín-Sánchez J, Peñalver MC, Lozano J. Sensitization to *Anisakis simplex* species in the population of northern Morocco. *J Investig Allergol Clin Immunol.* 2012;22:514–9.
 17. Mladineo I, Poljak V, Martínez-Sernández V, Ubeira FM. Anti-*Anisakis* IgE seroprevalence in the healthy Croatian coastal population and associated risk factors. *PLoS Negl Trop Dis.* 2014;8:e2673.
 18. Kim J, Jo JO, Choi SH, Cho MK, Yu HS, Cha HJ, et al. Seroprevalence of antibodies against *Anisakis simplex* larvae among health-examined residents in three hospitals of southern parts of Korea. *Korean J Parasitol.* 2011;49:139–44.
 19. Kasuya S, Koga K. Significance of detection of specific IgE in *Anisakis*-related diseases. *Arerugi.* 1992;41:106–10.
 20. Puente P, Anadón A, Rodero M, Romarís F, Ubeira F, Cuéllar C. *Anisakis simplex*: the high prevalence in Madrid (Spain) and its relation with fish consumption. *Exp Parasitol.* 2008;118:271–4.
 21. Daschner A, Alonso-Gómez A, Caballero T, Barranco P, Suarez-De-Parga JM, López-Serrano MC. Gastric anisakiasis: an underestimated cause of acute urticaria and angio-oedema? *Br J Dermatol.* 1998;139:822–8.
 22. Alonso-Gómez A, Moreno-Ancillo A, López-Serrano M, Suarez-de-Parga J, Daschner A, Caballero M, et al. *Anisakis simplex* only provokes allergic symptoms when the worm parasitises the gastrointestinal tract. *Parasitol Res.* 2004;93:378–84.
 - 23.●● Bao M, Pierce GJ, Pascual S, González-Muñoz M, Mattiucci S, Mladineo I, et al. Assessing the risk of an emerging zoonosis of worldwide concern: anisakiasis. *Sci Rep.* 2017;7:43699
- This study uses data on fishery landings, fish infection rates and consumption habits of the Spanish population from questionnaires and develops a quantitative risk assessment (QRA) model for the anchovy value chain and thus show the large underestimation of *Anisakis* cases to be suspected in Europe.
- 24.●● Herrador Z, Daschner A, Perteguer MJ, Benito A. Epidemiological scenario of *Anisakidosis* in Spain based on associated hospitalizations: the tip of the iceberg. *Clin Infect Dis.* 2019;69:69–76
- This is the first European epidemiological study, based on hospital discharge data over nearly 20 years and extrapolates these data to interpret the estimated annual numbers of gastro-allergic *Anisakis* and subclinical parasitic episodes in Spain.
- 25.● Cavallero S, Martini A, Migliara G, De Vito C, Iavicoli S, D'Amelio S. *Anisakis* in Italy: analysis of hospital discharge records in the years 2005–2015. *PLoS One.* 2018;13:e0208772
- This Italian epidemiological study is similar in methodology to the previous recorded in Spain and offers also interesting numbers.
26. Ventura MT, Napolitano S, Menga R, Cecere R, Asero R. *Anisakis simplex* hypersensitivity is associated with chronic urticaria in endemic areas. *Int Arch Allergy Immunol.* 2013;160:297–300.
 27. Im KI, Shin HJ, Kim BH, Moon SI. Gastric anisakiasis cases in Cheju-do, Korea. *Korean J Parasitol.* 1995;33:179–86.
 28. Lin AH, Nepstad I, Florvaag E, Egaas E, Van Do T. An extended study of seroprevalence of anti-*Anisakis simplex* IgE antibodies in Norwegian blood donors. *Scand J Immunol.* 2014;79:61–7.
 29. Valiñas B, Lorenzo S, Eiras A, Figueiras A, Sanmartín M, Ubeira F. Prevalence of and risk factors for IgE sensitization to *Anisakis simplex* in a Spanish population. *Allergy.* 2001;56:667–71.
 30. Smith J, Wootten R. *Anisakis* and anisakiasis. *Adv Parasitol.* 1978;16:93–163.
 31. Audicana M, Fernández de Corres L, Muñoz D, Fernández E, Navarro J, del Pozo M. Recurrent anaphylaxis caused by *Anisakis simplex* parasitizing fish. *J Allergy Clin Immunol.* 1995;96:558–60.
 32. Alonso A, Daschner A, Moreno-Ancillo A. Anaphylaxis with *Anisakis simplex* in the gastric mucosa. *N Engl J Med.* 1997;337:350–1.
 33. López-Serrano M, Gomez A, Daschner A, Moreno-Ancillo A, de Parga J, Caballero M, et al. Gastroallergic anisakiasis: findings in 22 patients. *J Gastroenterol Hepatol.* 2000;15:503–6.
 34. Mattiucci S, Fazii P, De Rosa A, Paoletti M, Megna AS, Glielmo A, et al. *Anisakis* and gastroallergic reactions associated with *Anisakis pegreffii* infection, Italy. *Emerg Infect Dis.* 2013;19:496–9.
 35. Kasuya S, Hamano H, Izumi S. Mackerel-induced urticaria and *Anisakis*. *Lancet.* 1990;335:665.
 36. Daschner A, Pascual C. *Anisakis simplex*: sensitization and clinical allergy. *Curr Opin Allergy Clin Immunol.* 2005;5:281–5.
 37. Daschner A, Fernández-Figares V, Valls A, de Frutos C, Rodero M, Ubeira FM, et al. Different fish-eating habits and cytokine production in chronic urticaria with and without sensitization against the fish-parasite *Anisakis simplex*. *Allergol Int.* 2013.
 38. Daschner A, De Frutos C, Valls A, Vega F. *Anisakis simplex* sensitization-associated urticaria: short-lived immediate type or prolonged acute urticaria. *Arch Dermatol Res.* 2010;302:625–9.
 39. Alonso A, Moreno-Ancillo A, Daschner A, López-Serrano M. Dietary assessment in five cases of allergic reactions due to gastroallergic anisakiasis. *Allergy.* 1999;54:517–20.
 40. Baeza M, Rodríguez A, Matheu V, Rubio M, Tornero P, de Barrio M, et al. Characterization of allergens secreted by *Anisakis simplex* parasite: clinical relevance in comparison with somatic allergens. *Clin Exp Allergy.* 2004;34:296–302.
 41. Ludovisi A, Di Felice G, Carballeda-Sangiao N, Barletta B, Butteroni C, Corinti S, et al. Allergenic activity of

- Pseudoterranova decipiens (Nematoda: Anisakidae) in BALB/c mice. *Parasit Vectors*. 2017;10:290.
42. Goldsby RA. *Immunology*. 5th ed. New York: W.H. Freeman; 2003.
 43. Hopkin J. Immune and genetic aspects of asthma, allergy and parasitic worm infections: evolutionary links. *Parasite Immunol*. 2009;31:267–73.
 - 44.● Moneo I, Carballeda-Sangiao N, González-Muñoz M. New perspectives on the diagnosis of allergy to *Anisakis* spp. *Curr Allergy Asthma Rep*. 2017;17:27
- This paper summarises diagnostic tools in *Anisakis* Allergy, highlighting the putative advantage of use of purified allergens (discussed above) and gives also emphasis to subclinical sensitization.
45. Arcos SC, Ciordia S, Roberston L, Zapico I, Jiménez-Ruiz Y, Gonzalez-Muñoz M, et al. Proteomic profiling and characterization of differential allergens in the nematodes *Anisakis simplex sensu stricto* and *A. pegreffii*. *Proteomics*. 2014;14:1547–68.
 46. Faeste CK, Jonscher KR, Dooper MM, Egge-Jacobsen W, Moen A, Daschner A, et al. Characterisation of potential novel allergens in the fish parasite *Anisakis simplex*. *EuPA Open Proteom*. 2014;4:140–55.
 - 47.● Mattiucci S, Colantoni A, Crisafi B, Mori-Ubaldini F, Caponi L, Fazio P, et al. IgE sensitization to *Anisakis Pegreffii* in Italy: comparison of two methods for the diagnosis of Allergic Anisakiasis. *Parasite Immunol*. 2017;39
- This study analyses IgE sensitization to *Anisakis pegreffii* in Italian subjects suffering from gastro-allergic anisakiasis or showing chronic urticaria and describe *Ani s 1*-like, *Ani s 7*-like, *Ani s 13*-like allergens in this *Anisakis* sibling species.
48. Donnelly S, Dalton JP, Loukas A. Proteases in helminth- and allergen- induced inflammatory responses. *Chem Immunol Allergy*. 2006;90:45–64.
 - 49.● Palomba M, Paoletti M, Colantoni A, Rugghetti A, Nascetti G, Mattiucci S. Gene expresión profiles of antigenic proteins of third stage larvae of the zoonotic nematode *Anisakis pegreffii* in response to temperature conditions. *Parasite* 2019;26:52.
- Interesting study which explores the temperature associated expression of possible allergenic proteins and could thus help to minimise allergen production depending on temperature conditions.
50. Daschner A, Cuéllar C, Sánchez-Pastor S, Pascual C, Martín-Esteban M. Gastro-allergic anisakiasis as a consequence of simultaneous primary and secondary immune response. *Parasite Immunol*. 2002;24:243–51.
 - 51.● Zamora V, Rodero M, Andreu-Ballester JC, Mendez S, Cuéllar C. Induction of tolerogenic properties by *Anisakis* larval antigens on murine dendritic cells. *Parasite Immunol*. 2019;4:e12616
- In this work *Anisakis simplex* larval antigens are studied for their possible immunomodulatory properties by the induction of tolerogenic dendritic cells in a murine model. It concludes the larval production of anti-inflammatory molecules, which could be of interest not only for the direct application on the development of anthelmintic strategies, but also for the development of new anti-inflammatory products.
52. Everts B, Smits HH, Hokke CH, Yazdanbakhsh M. Helminths and dendritic cells: sensing and regulating via pattern recognition receptors, Th2 and Treg responses. *Eur J Immunol*. 2010;40:1525–37.
 53. Daschner A, Cuéllar C. The hidden sense of symptoms: urticaria can be beneficial. *Med Hypotheses*. 2010;75:623–6.
 54. Nutman TB. Looking beyond the induction of Th2 responses to explain immunomodulation by Helminths. *Parasite Immunol*. 2015;37:304–13.
 55. Daschner A, Alonso-Gómez A, Caballero T, Suarez-De-Parga J, López-Serrano M. Usefulness of early serial measurement of specific and total immunoglobulin E in the diagnosis of gastro-allergic anisakiasis. *Clin Exp Allergy*. 1999;29:1260–4.
 56. Lorenzo S, Romarís F, Iglesias R, Audicana M, Alonso J, Leiro J, et al. O-glycans as a source of cross-reactivity in determinations of human serum antibodies to *Anisakis simplex* antigens. *Clin Exp Allergy*. 2000;30:551–9.
 57. Pascual C, Crespo J, San Martín S, Orma N, Ortega N, Caballero T, et al. Cross-reactivity between IgE-binding proteins from *Anisakis*, German cockroach, and chironomids. *Allergy*. 1997;52:514–20.
 - 58.● Mehrdana F, Buchmann K. Excretory/secretory products of anisakid nematodes: biological and pathological roles. *Acta Vet Scand*. 2017;59:42
- Here excretory secretory compounds produced by the parasites are explored, which are assumed to be key players in clinical manifestation humans disease, such as in *Anisakis*, but interesting is the knowledge about their general biological role in invertebrates and lower vertebrates as well.
59. Perteguer MJ, Aguila C, Fenoy S, Guillén JL, Cuéllar C. Cross-reactivity induced by *Anisakis Simplex* and *Toxocara Canis* in mice. *J Helminthol*. 2003;77:331–4.
 60. Perteguer MJ, Cuéllar C, Guillén JL, Aguila C, Fenoy S, Chivato T, et al. Cross-reactivity between *Anisakis Simplex* sensitization and visceral larva migrans by *Toxocara Canis*. *Acta Trop*. 2003;89:85–9.
 61. Cardona V, Ansotegui IJ. Component-resolved diagnosis in anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2016;16:244–9.
 62. González-Fernández J, Daschner A, Nieuwenhuizen NE, Lopata AL, Frutos CD, Valls A, et al. Haemoglobin, a new major allergen of *Anisakis simplex*. *Int J Parasitol*. 2015;45:399–407.
 63. González-Fernández J, Rivas L, Luque-Ortega JR, Núñez-Ramírez R, Campioli P, Gárate T, et al. Recombinant vs native *Anisakis* haemoglobin (*Ani s 13*): its appraisal as a new gold standard for the diagnosis of allergy. *Exp Parasitol*. 2017;181:119–29.
 - 64.● Podolska M, Pawlikowski B, Nadolna-Altyn K, Pawlak J, Komar-Szymczak K, Szostakowska B. How effective is freezing at killing *Anisakis simplex*, *Pseudoterranova* *krabbei*, and *P. decipiens* larvae? An experimental evaluation of time-temperature conditions. *Parasitol Res*. 2019;118:2139–47

This study adds to practical issues to reduce zoonosis by Anisakids. Viability of larvae are assessed by different freezing procedures.

65. • Bao B, Cipriani P, Giulietti L, Sunde Roiha S, Paoletti M, Palomba M, et al. Air-dried stockfish of Northeast Arctic cod do not carry viable anisakid nematodes. *Food Control*. 2020;116:107322

This study also adds to practical issues, very useful not only for food security agencies, but also for the clinician, when recommending prevention to patients. It is to be expected, that different fish preparation procedures will in the future be studied in this respect.

66. Abollo E, Gestal C, Pascual S. Anisakis infestation in marine fish and cephalopods from Galician waters: an updated perspective. *Parasitol Res*. 2001;87:492–9.
67. Park SK, Cho MK, Park HK, Lee KH, Lee SJ, Choi SH, et al. Macrophage migration inhibitory factor homologs of anisakis simplex suppress Th2 response in allergic airway inflammation model via CD4+CD25+Foxp3+ T cell recruitment. *J Immunol*. 2009;182:6907–14.

68. Haarder S, Kania PW, Holm TL, von Gersdorff JL, Buchmann K. Effect of ES products from Anisakis (Nematoda: Anisakidae) on experimentally induced colitis in adult zebrafish. *Parasite Immunol*. 2017;39.
69. FAO, The state of world fisheries and aquaculture, 2014.
70. Cohen JT, Bellinger DC, Connor WE, Kris-Etherton PM, Lawrence RS, Savitz DA, et al. A quantitative risk-benefit analysis of changes in population fish consumption. *Am J Prev Med*. 2005;29:325–34.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.