

Title page

Drug-Induced Enterocolitis Syndrome: similarities and differences compared with Food Protein-Induced Enterocolitis Syndrome.

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Running Title: Drug-Induced Enterocolitis Syndrome

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Key message: The main aim of this study is to deeply analyses similarities and differences between FPIES and DIES. Three cases are discussed in length to clarify the differences. DIES is a rare condition the study aims to highlight the pathogenesis and management of this disease.

Key words: Drug-Induced Enterocolitis Syndrome; Food Protein-Induced Enterocolitis Syndrome; Children; Beta-lactams; Drug Hypersensitivity Reactions

Abstract

In 2014 Drug-Induced Enterocolitis Syndrome (DIES) was described for the first time. It is still a poorly known disease with symptoms that typically resemble those of Food Protein-Induced Enterocolitis Syndrome (FPIES). To date, six more cases of DIES have been described and new clinical diagnostic criteria have been proposed based on those in the international guidelines for FPIES. In this paper the authors describe three more cases of DIES. In addition, similarities and differences with FPIES have been deeply analysed. To date several unanswered questions, need to be addressed, but clinicians must be instructed how to identify DIES, in order to make an allergy work-up and give definite therapeutic indications to patients, especially in children where DIES seems to be more frequent.

Introduction

Drug-induced enterocolitis syndrome (DIES) is the term used to describe reactions occurring after drug exposure. It is a non-IgE mediated hypersensitivity reaction, characterized by symptoms that typically resemble those of FPIES (food protein-induced enterocolitis syndrome). It is a rare and probably underestimated entity, since very few cases have been reported in literature so far. To date, seven cases of DIES have been described, four in children,¹⁻⁴ one in an eighteen-year-old male⁵ and two in adult patients^{6,7}. In 2014, Novembre et al.¹ described the case of a 6-year-old girl who developed gastrointestinal symptoms of vomiting, diarrhea, pallor and lethargy two hours (hs) after a drug provocation test (DPT) with amoxicillin (AMX). As the clinical and laboratory features, i.e. vomiting, neutrophilia, methemoglobinemia (MethHb), and need for intravenous fluid support resembled those of FPIES, the term DIES was proposed for the first time. Following, five other cases of DIES have been reported, summarized in Table 1.

With this paper, we present our experience with three additional children diagnosed with DIES. Two of them were referred to the Allergy Unit of Meyer Children's Hospital in Florence, Italy for suspected hypersensitivity drug reactions to AMX/CLV in 2018 and one of them was referred to the Division of Pediatric Allergology and Pulmonology of the University Children's Hospital, Inselpital, Bern, Switzerland for suspicion of hypersensitivity reaction to AMX in 2019. At the hospital admission and according to the hospital ethic committee forms, all children's parents signed a written informed consent to the processing of clinical data for future research studies. Patients who did not give the consent were excluded from the present study. In addition, we discuss similarities and differences of DIES with FPIES after comparing clinical, laboratory and therapeutic characteristics of all DIES cases published to date.

Case report

Case 1 (Meyer Children's Hospital, Florence, Italy)

The first patient was a 6-year-old boy with a history of suspected IgE-mediated hypersensitivity reaction (angioedema of hands and feet) to AMX/CLV, cefixime, cefaclor and azithromycin. His clinical history was not conclusive given he had presented with isolated angioedema without any cutaneous rash and to more than one suspected drug belonging to different classes. Thus, he underwent a standard allergy work-up with in vitro tests [specific IgE (sIgE) to Penicilloyl G, Penicilloyl V, Ampicillin, AMX and Cefaclor, ImmunoCAP™ ThermoFischer Scientific, Uppsala, Sweden] and in vivo tests [skin prick test

(SPT) and intradermal test (IDT) with AMX/CLV at 20 mg/ml concentration]. As all tests were negative, a DPT was performed with AMX/CLV, starting at 1/10, followed by 2/10 and lastly 7/10 of the therapeutic dose (50/mg/kg/day in two doses) every 30 minutes. After two hs of observation, the patient was discharged from hospital without any clinical reactions and immediate hypersensitivity to AMX/CLV was excluded. However, thirty minutes later, the parents brought the child back to the Allergy Unit because he had started vomiting. He was in poor general condition, pale and lethargic with protracted vomiting without both skin and respiratory symptoms. Vital signs (blood pressure, oxygen saturation, heart rate) and temperature were in range. Due to the persistence of the severe symptoms and dehydration, the patient was admitted to our Emergency Care Unit where he was started on intravenous saline solution infusion. The blood examination during the acute phase showed leucocytosis [white blood cell (WBC) 15350/mm³] with neutrophilia 13170/mm³ and the blood gas analysis MethHb was slightly above normal at 0.7% (normal range 0.2 – 0.6%). In the next three hs his conditions progressively improved until complete recovery. Diarrhea was not reported. The patient was advised to avoid beta-lactams in general until a DPT with an alternative drug, in particular a cephalosporin, would be conducted to assess cross-reactivity.

Case 2 (Meyer Children's Hospital, Florence, Italy)

The second patient was a 14-year-old girl, referred to our Allergy Unit for a suspected drug hypersensitivity reaction. In this specific case, the parents reported more than one episode of persistent vomiting, sometimes with streaks of blood, and lethargy two hs after intake of AMX/CLV syrup some years earlier. Consequently, she had completely avoided penicillins over the previous two years. Her clinical history was not suggestive for an IgE-mediated reaction. Therefore, we decided to perform a standard DPT as described above in Case 1 after a negative result of the delayed reading IDT with AMX/CLV at a 20 mg/ml concentration. To exclude CLV as the causative agent, the patient received increased doses of AMX alone. Two and a half hs after receiving half a cumulative dose of AMX (12.5 mg/kg), she started vomiting (several episodes with dehydration), accompanied by abdominal pain, pallor, lethargy and malaise. No skin neither respiratory symptoms occurred. Temperature was 37 Celsius degree. No diarrhea was reported. Therapy with intravenous ondansetron and saline solution infusion was immediately started. At the beginning of the acute phase, the blood examination showed normal WBC 4400/mm³ and neutrophils 2363/mm³; the blood gas analysis and C-reactive protein (CRP) were in the normal range. After two hs, the patient slowly started to improve, blood tests were repeated and revealed increased WBC

10730/mm³ with neutrophils 9260/mm³; the blood gas and CRP remained normal. Similar to case 1, we recommended to not administer beta-lactams again until a DPT with cefpodoxime reflecting tolerance would be conducted.

Case 3 (University Children's Hospital, Inselspital, Bern, Switzerland)

The third patient was a 9-year-old female who was referred to the Division of Paediatric Allergology and Pulmonology of the University Children's Hospital, Inselspital, Bern, Switzerland for the occurrence of a maculopapular exanthema (MPE) on day 7 of a course of AMX syrup three months before. The antibiotic was prescribed to treat a streptococcus A pharyngitis and had been tolerated in the past. The allergy work-up consisted of patch tests (PTs) with AMX at 20% in petrolatum and IDT with AMX at 20 mg/ml resulting all negative. Then, a DPT with AMX was performed gradually (doses were administered every 30 minutes starting at 1.5% of the regular dose (25 mg/kg two times a day), then 15 % and 150 % of the regular dose (to rule out immediate type reaction). Surveillance lasted for 2 hs, subsequently the girl was discharged with the advice to further intake of standard doses for another 2 days to rule out delayed-type reactions. On the way home however, about 3 hs after the last dose, she started vomiting and she was brought to emergency care, where treatment with intravenous saline solution and ondansetron was provided due to protracted vomiting, reduced status (i.e. lethargy) and pallor. She was discharged after additional 6 hs after complete remission. A subsequent allergological evaluation, in particular, another DPT, was planned as the diagnosis of reaction to AMX was doubtful due to recent history of gastroenteritis in her family. Five months later, a second DPT with AMX was performed according to the previously mentioned protocol. Here, 2.5 hs after the last dose protracted vomiting appeared without skin and respiratory symptoms. The girl appeared dehydrated in poor general condition, pale and lethargic. Temperature was normal and diarrhea did not occur. She was treated with intravenous saline solution and ondansetron, with rapid remission of symptoms. She was stable under close monitoring for about 4 hs and then discharged. DIES to AMX was diagnosed. Three months later, the girl passed a DPT with cefuroxime.

What do we already know about DIES?

Prevalence

While FPIES is well documented in the literature, DIES has only been reported as a definite clinical entity in recent years, probably because its diagnosis is underestimated. The

incidence of DIES in Meyer Children's Hospital Allergy Unit is 0.4% (3/714 total cases of children referred for suspected hypersensitivity reaction from 2014 to 2019), therefore we can consider DIES a rare but not exceptional reaction. With vomiting not being a typical drug hypersensitivity reaction, it is possible that general clinicians therefore often consider it rather an ADR and prefer not to prescribe the putatively causative medication anymore, without the suspicion of a possible allergic reaction. Large multicentric studies are needed to assess the prevalence of this newly described disorder.

Diagnosis and differential diagnosis of DIES

Antibiotics, and in particular, AMX or AMX/CLV, are known to be able to cause gastrointestinal symptoms including nausea, vomiting or diarrhea, which are relatively frequent (up to 19% of the patients) and well-known adverse drug reactions (ADRs)⁸. These side effects typically occur within one hour after drug administration and are usually mild, not persistent and isolated. As mentioned above, occurrence of "FPIES-like" symptoms, such as delayed profuse vomiting associated with pallor and lethargy lead to the first description of DIES¹. The differential diagnosis of vomiting occurring after drug administration include also IgE-mediated hypersensitivity. To better differentiate these 2 types of idiosyncratic reactions, both latency between drug intake and resulting reaction and clinical presentation of adverse events come into play. Indeed, the latency between drug intake and vomiting is longer > 1.5 - 2 hs in DIES, while in IgE-mediated drug hypersensitivity reactions, gastrointestinal symptoms (including vomiting) typically appear immediately, i.e. within minutes or by no later than 1 hour. Moreover, in case of DIES - similarly to FPIES - vomiting is typically protracted and accompanied by poor general condition, while vomiting secondary to IgE-mediated drug hypersensitivity reactions is commonly associated with involvement of another organ system due to histamine liberation, such as e.g. skin rash or swelling.

In some cases of DIES a skin involvement has been described during the first reaction speculating a possible shift from an IgE to a non-IgE mediated reaction as described for only three cases of FPIES⁹. This hypothesis is difficult to demonstrate and on an immunological point of view also the coexistence of both immediate and delayed mechanisms of reaction in the same patient is difficult to understand. Moreover, skin involvement during an antibiotic course therapy in children is often a "benign" rash due to a viral/bacterial infection and it is not explained with a true state of hypersensitivity.

As for FPIES, the diagnosis of DIES is currently mainly based on clinical diagnostic criteria, and sometimes confirmed by a DPT. Van Thuijl et al.³ proposed diagnostic criteria for DIES,

based on the new diagnostic criteria proposed in the international guidelines for FPIES.¹⁰ Although not mandatory, a DPT is strongly recommended if only a single episode has occurred to confirm or exclude formally the diagnosis. Thus, in a number of cases described in literature^{1,3-6} (Table 1), and in case 2 of this study, the patients reported a previous history of persistent vomiting after taking AMX. To assess the diagnosis, they were referred to an allergist by their paediatricians, which led to a DPT with positive results in the course of diagnostic work-up, thus confirming a diagnosis of DIES. We strongly advise to perform a DPT when possible in order to decrease potential overdiagnosis of DIES. As suggested by Van Thuijl et al.³ and according to this paper the diagnosis of DIES is highly probable when protracted vomiting occurring 1-4 hours after drug intake in the absence of classic IgE-mediated skin and respiratory symptoms plus at least three minor criteria as described for FPIES¹⁰ (i.e. pallor, lethargy, need for emergency department, diarrhea, hypotension, need for intravenous fluid support) are observed.

After a DPT, it may be advisable to monitor patients for at least 3-4 hs. This suggestion comes from the reported cases where the time latency between drug intake and onset of symptoms ranges between 90 minutes to 4 hs (mean latency of 2 hs and 15 minutes).

Potential cross reactivity

Among the diagnostic criteria proposed by Van Thuijl et al.³, one of the minor criteria mentioned “repetitive vomiting episodes 1-4 hs after ingestion of a different drug” suggesting a possible cross-reactivity of AMX with other drugs, similarly to some IgE-mediated drug hypersensitivity reactions. However, there is currently no studies evaluating cross-reactivity among drugs, in particular between penicillins and cephalosporins, which differ by side chains. There is only few case reports published in the literature. Thus, Infante et al.² confirmed tolerance with phenoxymethylpenicillin (also known as penicillin V), suggesting that the side chain was responsible for the reaction in that case. Worcel J et al.⁴ showed tolerance with both phenoxymethylpenicillin and cefpodoxime. At last, Freundt Serpa F et al.⁵ confirmed tolerance with penicillin G and V. It would be interesting to perform a DPT with other beta-lactams in order to assess cross-reactivity in further studies based on patients with confirm DIES. DPT seems to be only useful test to confirm or exclude DIES and to test tolerance towards related or unrelated compounds. So far, skin testing has been reported to be negative in DIES. Anyway, the low number of cases in literature warrants further evaluation, in particular regarding the potential utility of late reading IDT.

Moreover, when comparing DIES with FPIES, it should be taken into account that a wide range of foods can trigger FPIES, and there is no clear similarity between the trigger foods to explain the molecular basis of FPIES, thus also the role of cross reactivity due to similarities of drugs molecular structures needs more studies.

Underlying mechanisms

In order to be classified as an allergy, an underlying immunological mechanism should be demonstrated. However, to date, it remains still unclear which molecular structure of food/drug allergens serve responsible for this reaction and which immunological mechanism are involved¹⁰. Most drug are rather simple hapten (in case of AMX, a beta-lactam ring and the above-mentioned side chains¹¹), which according to Infante et al.² could be responsible for the reaction. However, studies evaluating other type of drug hypersensitivity suggest that the immune response to AMX is determined not only by its chemical structure but also by the nature of carrier molecules¹² and therefore other mechanisms are possible.

For FPIES, the role of T cells has been strongly questioned recently, and other cells type such as innate immune cells have been incriminated^{13,14}. In two out of the three new cases described, in line with the literature and with FPIES diagnostic results, blood exams showed increased WBC with neutrophilia (in case 2, we demonstrated how the values rose between 2 and 6 hs after administration of AMX). More properly, neutrophils could peak 6 hs after drug intake. In fact, in the case from Freundt Serpa F et al.⁵ three hs after taking the drug neutrophils were still within normal range. In case 1, there was also a slight increase of MethHb. To date, apart from neutrophilia and in some cases MethHb, there are no specific markers for DIES or for FPIES, since there has not been any increase in tryptase during the acute phase⁵. Neutrophilia during acute FPIES reaction might suggest an underlying role of neutrophils in the pathomechanism which has been suggested in some studies¹⁵. Alternatively, neutrophilia might rather be linked to vomiting, stress of the reaction or administration of corticosteroids, factors all known to increase neutrophils in peripheral blood. At this time point, in our opinion, any investigation that can help to better define the diagnosis and/or pathogenesis of DIES such as neutrophils count and MethHb levels should be recommended.

The only study that identified a new biomarker is the one published by Freundt Serpa F et al⁵, reporting an increase in eosinophil cationic protein (ECP) in stool samples from 24 and 48 h after DPT with AMX/CLV. More studies confirming these data are required.

In general, drug-induced intestinal damage is caused by more than one mechanism¹⁶, the most likely of which in the case of antibiotics, is the increased delivery of toxic or immunogenic drug metabolites following first-pass hepatic and intestinal processing. It would be worthwhile to study the influence of gastrointestinal microbiota in drug mucosal damage, and whether a probiotic supplementation could play a role in modifying the natural history of DIES.

Further studies are needed to determine which immunological mechanisms are involved in DIES.

Treatment of DIES and natural history

DIES cases showed good response to antiemetics (ondansetron) and intravenous fluid and corticosteroids; conversely, epinephrine was found to be ineffective^{3,6}. It is interesting that the culprit drug in the cases described has been always AMX or AMX/CLV⁵, probably related to a higher frequency of prescription of these antibiotics. Thus, it is likely that other antibiotics could also be responsible for DIES. For that reason, we may suggest that patients with DIES could benefit of oral ondansetron in order to treat quickly potential recurrences with other related or unrelated drugs. In six FPIES cases Le and al¹⁷ reported that oral ondansetron may be useful for children, at least before they reach emergency room departments. So far, the patients with DIES recovered completely after the acute phase and no fatal cases have been described.

Because of the few cases identified, it is difficult to determine whether DIES is a transient or persistent condition. The mean age of children reported in literature (including the three cases in this study and excluding the 18-year-old male) is 7.4 years at the time of the DPT, but the history of suspected reactions refers to an earlier period. In particular in the study by Freundt Serpa F et al.⁵, the patient had a 9-year interval between the first reaction and the positive DPT. So far there is a lack of information to recommend the right latency time period to perform another DPT later. One of the two adult patients had instead tolerated AMX many times before the onset of symptoms at the age of 60. For this reason, medical doctors dealing with adults should also be aware of the possibility of developing DIES later on in life.

Are DIES and FPIES the same disease?

FPIES and DIES are non-immediate hypersensitivity reactions, poorly understood, but similar in term of clinical presentation. Also, treatment of both FPIES and DIES is based on intravenous fluid administration and use of antiemetic drug (ondansetron). The triggers of FPIES and DIES are different, and cross-reactivity is described between foods, apart from drugs of the same class so far.

Table 2 contains the summarised similarities and differences between FPIES and DIES¹⁸⁻²⁶, plus several still unanswered questions. In particular, phenotypes of the diseases (i.e acute vs chronic forms), the natural history of the disease, triggers and outcome are still under investigation. Moreover, as the pathophysiology of FPIES is unknown, this unfortunately does not enlighten us on the mechanisms responsible for DIES, even both DIES and FPIES could be considered as potentially related syndromes. In conclusion, clinicians must be instructed how to identify DIES, in order to make an allergy work-up and give definite therapeutic indications to patients, especially in children where this kind of reaction seems to be more frequent.

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Author, year	Age (years)	Culprit drug	Drug tolerated in the past	History of drug reaction	Symptoms during DPT	Latency between drug administration and onset of symptoms during DPT (hours)	Therapy	Blood examination performed	DPT with alternative/cross reactivity
Novembre et al, 2014 ¹	6	AMX	yes	At 1 year of life prolonged vomiting 1-2 hours after ingestion of AMX; the next day a morbilliform rash appeared	Vomiting, diarrhea, pallor, lethargy	2	Intravenous hydrocortisone and normal saline solution infusion	WBC 20480/mm ³ with neutrophils 16834/mm ³ PH 7.33, MethHb 1.1%	n.p.
Infante et al, 2017 ²	3	AMX	yes	At 2 years of life acute urticaria	Abdominal pain, vomiting, mild malaise	2	Methylprednisolone, dexchlorpheniramine	n.p.	Phenoxymethylpenicillin tolerated at DPT
					Same symptoms of the previous DPT	4	Antiemetics, hydrocortisone and saline solution infusion	WBC 17800/mm ³ with neutrophilia 13100/mm ³	

Rodriguez et al, 2017⁶	60	AMC/CLV	yes	Nine months before vomiting, diarrhea, malaise. A similar prior reaction with the same drug a few months earlier	Abdominal pain, vomiting, low oxygen saturation, low blood pressure, drowsiness	2	Intramuscular epinephrine, intravenous hydrocortisone and ondansetron, oxygen therapy.	Neutrophils 11600/mm ³ . PH 7.25	n.p.
Van Thuijl et al, 2019³	4	AMX	unknown	At 2 years of age erythematous skin reaction. At 4 years, repetitive vomiting and lethargy	Severe abdominal pain, persistent vomiting, lethargy	1,5	Intramuscular epinephrine (administered again after 90 minutes), intravenous hydrocortisone and ondansetron	WBC 24000/mm ³ with neutrophilia 19800/mm ³	n.p.
Freundt Serpa et al, 2020⁵	18	AMC/CLV	no	At 9 years of age vomit after intravenous infusion of AMC/CLV	1 st DPT: Epigastric pain, dizziness, nausea and one vomit	2,5	Physiological saline solution, ranitidine and ondansetron		Penicillin G and V tolerated at DPT
					2 nd DPT (three weeks later): abdominal pain, profuse diarrhea, nausea and repetitive vomits, marked pallor and dizziness	1,5	Physiological saline, ranitidine, ondansetron, methylprednisolone, loperamide	Two days later: hemoglobin 15.4 g/dL, tryptase 3.2 mcg/dL. Eosinophil	

								cationic protein (ECP) 77.4 mcg ECP/g feces 24 hours after DPT	
Worcel et al, 2020⁴	10	AMX	yes	Nine months before repetitive vomiting, pallor and diarrhea	repetitive and protracted vomiting with pallor, lethargy, and abdominal pain. Watery diarrhea 8 h later	3	Desloratadine and prednisolone	n.p.	Phenoxymethylpenicillin and cefpodoxime tolerated at DPT
Present study	6	AMC/CLV	yes	Two years before angioedema of hands and feet	Protracted vomiting, pallor, lethargy, dehydration	2,5	Saline solution infusion	WBC 15350/mm ³ with neutrophilia 13170/mm ³ . MethHb 0.7%	n.p.
	14	AMC/CLV (DPT with AMX)	yes	Some years earlier some episodes of persistent vomiting with streaks of blood, lethargy	Protracted vomiting, pallor, lethargy, abdominal pain, malaise, dehydration	2,5	Intravenous ondansetron and saline solution infusion	WBC 10730/mm ³ with neutrophilia 9260/mm ³	Cefpodoxime tolerated at DPT
	9	AMX	yes	Three months before	1 st DPT: vomiting	3	Intravenous	n.p.	Cefuroxime tolerated at

				maculopapular exanthema			ondansetron and saline solution infusion		DPT
					2 nd DPT (five months later): protracted vomiting, pallor, lethargy, dehydration	2,5	Intravenous ondansetron and saline solution infusion		
Bouvette et al 2020⁷	69	Panto prazole	unknown	Vomiting, profuse bloody diarrhea, abdominal pain, emergency department. Three months before same symptoms plus hypotension	nausea, vomiting, diarrhea, abdominal pain, high blood pressure, rapid heart rate, low blood oxygen saturation, hypovolemia	1	intramuscular epinephrine intravenous diphenhydramine, intravenous methylprednisolone. Intravenous antiemetic, Aggressive intravenous fluid resuscitation	WBC 14000/mm ³ with neutrophilia 10500/mcl Elevated serum creatinine 2.1 mg/dl, metabolic acidosis	n.p

Table 1 Cases of drug-induced enterocolitis syndrome described in literature and their characteristics. AMX: amoxicillin; AMC/CLV: amoxicillin-clavulanic acid; DPT: drug provocation test; MethHb: methemoglobinemia; n.p.: not performed; WBC: white blood cell count.

Similarities and differences between FPIES and DIES		
	<i>Similarities</i>	<i>Differences</i>
Tolerance towards the offending allergen	About 60% of FPIES occurred at the first intake of the culprit food Seven out of 8 (87%) DIES cases had previously tolerated the culprit drug (unknown in 2 cases)	
Clinical pattern of previous reaction with the suspected allergen	- Five out of 10 cases with the skin involved in the previous reaction - Three FPIES cases previously reported a skin reaction	
Mean age at the onset of symptoms	- In case of FPIES with the most common allergens (i.e. milk, soy, rice, fish) within the first year of life - All cases of DIES from AMX or AMX/CLV in children at a mean age of 7,4 years	
Time of recovery from the disease	- In case of FPIES with milk: 75% by 1 year, 63-89% by 2 years, 20-94% by 3 years; with soy: 25-83% by 3 years; with rice: 50% by 50 months, 80-87% by 3 years; with fish: 63% by 53 months, 75% by 60 months. - Not known in case of DIES	
Time latency	1,5-4 hours for FPIES and DIES cases	
Clinical symptoms	Vomiting, pallor, lethargy in cases of FPIES and DIES	
	No skin involvement in cases of FPIES and DIES Two out of 10 cases of DIES reported low blood oxygen saturation and both were adults' patients.	

Laboratory findings	Increase in WBC and neutrophilia, methemoglobinemia in cases of FPIES and DIES. High level of ECP in the stool.
Allergy tests	No specific IgE detected in either FPIES or DIES. In FPIES cases a T cell mechanism has been proposed. In DIES cases a T cell mediated mechanism could be suspected but it has not been confirmed by delayed reading of intradermal test until now.
Eliciting dose	No consensus has been reached regarding the starting dose for the oral provocation test in either FPIES or DIES.
Treatment in the acute phase	FPIES ondansetron, systemic corticosteroids, fluids DIES ondansetron, systemic corticosteroids, fluids, except for three cases treated with epinephrine (for hypovolemic shock due to misdiagnosis?)
Cross reactivity	Not reported in cases of DIES-Not investigated In cases of FPIES with fish: 35-45% to other fish and 6% to shellfish; cross reactivity of another trigger food: • CM with soy: 30-40% and vice-versa • CM/soy with solid food: <16% • solid food to CM/soy: <25% • solid food to another solid food:<44% • legumes to soy: <80% • grains to other grains: 50% • poultry to other poultry: <40%
Molecular structure	DIES: most cases due to AMX or AMX/CLV, simple molecules consisting of a beta lactam ring and side chains. Only one adult had DIES to pantoprazole. FPIES: i.e. a wide range of foods can trigger FPIES, and there is no clear

	similarity between the trigger foods.
Unanswered questions	
• What is the natural history of the disease? • What is the level of cross-reactivity among drugs of the same class? • Can drugs other than beta lactams cause this kind of reaction? • Does atypical DIES exist? • Does chronic DIES exist?	

Table 2 Similarities and differences between Food Protein-Induced Enterocolitis Syndrome (FPIES) and Drug-Induced Enterocolitis syndrome (DIES) and unanswered questions. AMX: amoxicillin; AMC/CLV: amoxicillin-clavulanic acid.