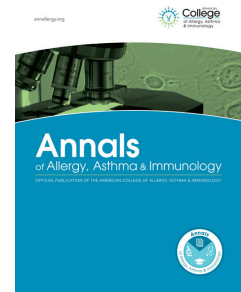


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Drug Induced Enterocolitis Syndrome (DIES): a clinical entity which deserves more awareness

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Title

Drug Induced Enterocolitis Syndrome (DIES): a clinical entity which deserves more awareness

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Drug induced enterocolitis syndrome (DIES) is a rare, non-IgE mediated hypersensitivity reaction provoked by drugs which can be severe and lead to shock. Despite the potential severity of the reactions, awareness of DIES is low. In contrast, enterocolitis syndrome induced by food proteins (FPIES) has been better documented. Previous studies have reported the occurrence of hypovolemic shock in approximately 15% of reactions, which indicates that FPIES is a potentially life threatening disease.⁽¹⁾ To increase clinical awareness on DIES we here report a case of a child who was referred to our pediatric allergy clinic and was diagnosed with DIES by amoxicillin. In addition, we propose diagnostic criteria for DIES in order to improve both clinical and scientific knowledge.

A 4-year-old boy was referred to the pediatric allergy unit of the Erasmus University Medical Center (Rotterdam, The Netherlands) for a suspected drug hypersensitivity. At the age of 2 years, he developed an erythematous skin reaction and a short period of drowsiness after the administration of amoxicillin. The symptoms spontaneously disappeared within 24 hours. At the age of 4 years old, he developed an acute episode of repetitive vomiting and lethargy 1.5 hours after ingestion of a first dose of amoxicillin for treatment of a dental infection. His parents called an ambulance and he was treated with intramuscular adrenaline and intravenous injection of clemastine and dexamethasone. He was admitted to the emergency department and physical examination showed a blood pressure of 100/80 mm/Hg, a heart rate of 125 beats/minute and a normal respiratory rate and oxygen saturation. Further physical examination showed no classic IgE mediated skin or respiratory symptoms. The vomiting and lethargy persisted for approximately 2 hours and was followed by complete clinical recovery. He was referred to our allergy unit for further analysis of the hypersensitivity reactions to amoxicillin.

A skin prick test with amoxicillin was performed and blood levels of specific IgE to amoxicillin were measured; both test results were negative. An intradermal skin test was not performed because of the relative young age of the patient. Consecutively, an open 3-step graded oral challenge with amoxicillin was performed according to the ENDA guidelines.⁽²⁾ 1.5 hours after the last dose intake, he developed severe abdominal pain, started to vomit and became pale and lethargic. Because of persistent vomiting he was given intramuscular adrenaline and an oral antihistaminic about 15 minutes after onset of symptoms. Despite administration of intramuscular adrenaline the vomiting persisted, and about 25 minutes after onset of the reaction an intravenous catheter was inserted. Ondansetron and hydrocortisone were given intravenously, after which the abdominal pain and vomiting diminished. Approximately 90 minutes after onset of the reaction he again started to complain of abdominal pain and vomited again. Intramuscular adrenaline was given a second time after which he showed progressive improvement to a complete recovery 2.5 hours after onset of symptoms. During the reaction he had no skin or respiratory symptoms and he remained hemodynamically stable. A blood test (which was performed two hours after the last dose of amoxicillin) showed an increase in the white blood cell count ($24 \times 10^9/L$; normal range $4.9 - 13.4 \times 10^9/L$) with neutrophilia ($19.8 \times 10^9/L$; normal range $1.6 - 10.5 \times 10^9/L$), thrombocytosis ($433 \times 10^9/L$; normal range $189 - 403 \times 10^9/L$) and normal tryptase levels ($3.4 \mu g/L$; normal range $< 13.4 \mu g/L$).

Because of the delayed type reaction, the excessive and repetitive vomiting accompanied by extreme pallor and lethargy together with the poor clinical recovery after administration of intramuscular adrenaline, we recognized the reaction as a “FPIES-like” reaction and considered the diagnosis enterocolitis syndrome induced

by amoxicillin. According to recently published diagnostic criteria for FPIES, patients can be diagnosed with FPIES by fulfilling a combination of clinical and/or laboratory parameters.(3) Based on the results of the oral challenge test and the laboratory results (including neutrophilia), we suggest that our patient meets the criteria for DIES by amoxicillin. We advised our patient to perform an additional oral challenge with penicillin in order to find out if he is intolerant to the nucleus of beta-lactam antibiotics or to a side chain of the amoxicillin. However, the parents of the patient refused to perform an additional drug challenge test because of anxiety to experience another hypersensitivity reaction. Subsequently, we advised him to avoid beta-lactam antibiotics.

DIES is an uncommon drug hypersensitivity reaction. We performed a comprehensive literature search and found a limited number of two case reports in which DIES has been described previously.(4, 5) The clinical findings and laboratory results described in these case reports are similar to our patient. Interestingly, an increased white blood cell count and neutrophilia is reported in all three cases, which could have been caused by exposure to systemic steroids. However, previous studies on FPIES showed an increased in absolute neutrophil count after positive oral food challenge in children who did not receive steroids (6), which implicates that the leukocytosis and neutrophilia could also been part of an immunological reaction.

In contrast to the limited number of publications on DIES so far, the amount of publications on FPIES has been increased significantly since Geraldine Powell proposed the first diagnostic criteria for FPIES in 1978. (7) As a result, FPIES is much better recognized by clinicians and recently new consensus guidelines for the

diagnosis and management of FPIES were published by an international workgroup.

(3) In our opinion, the clinical awareness on DIES should also be improved and clear diagnostic criteria are needed which can help the clinician to recognize and diagnose DIES. Moreover, well defined diagnostic criteria could also be used for investigative purpose and lead to more scientific knowledge on DIES. Therefore, we decided to propose diagnostic criteria for the diagnosis of DIES. Because of the clinical resemblance with FPIES and the limited number of publications on DIES so far, we decided to define diagnostic criteria for the diagnosis DIES which are based on the latest published diagnostic criteria for FPIES (table 1). (3)

In conclusion, we report on a case of DIES by amoxicillin, which was confirmed by an oral challenge test. DIES is a rare, non-IgE mediated drug hypersensitivity reaction that can be severe and lead to shock. In order to improve both clinical and scientific knowledge, we hereby propose the first diagnostic criteria for DIES.

References

1. Michelet M, Schluckebier D, Petit LM, Caubet JC. Food protein-induced enterocolitis syndrome - a review of the literature with focus on clinical management. *J Asthma Allergy* 2017;**10**:197-207.
2. Gomes ER, Brockow K, Kuyucu S, et al. Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group. *Allergy* 2016;**71**(2):149-161.
3. Nowak-Wegrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2017;**139**(4):1111-1126 e1114.
4. Infante S, Zapatero L. Drug-induced enterocolitis syndrome by amoxicillin. *Pediatr Allergy Immunol* 2016;**28**(1):105-106.
5. Novembre E, Mori F, Barni S, Pucci N. Drug-induced enterocolitis syndrome (DIES). *Pediatr Allergy Immunol* 2014;**25**(4):415-416.
6. Shimomura M, Ito Y, Tanaka H, Meguro T, Kimura M. Increased serum cortisol on oral food challenge in infants with food-protein induced enterocolitis syndrome. *Pediatr Int* 2018; **60**(1): 13-18.
7. Powell GK. Milk- and soy-induced enterocolitis of infancy. Clinical features and standardization of challenge. *J Pediatr* 1978;**93**(4):553-560.

Diagnostic criteria for patients presenting with possible DIES

Major criteria:	Minor criteria:
Vomiting in the 1- to 4-h period after ingestion of the suspected drug and absence of classic IgE-mediated allergic skin or respiratory symptoms	1. A second episode of repetitive vomiting after ingestion of the same drug 2. Repetitive vomiting episode 1-4 h after ingestion of a different drug 3. Extreme lethargy 4. Marked pallor 5. Need for emergency department visit 6. Need for intravenous fluid support 7. Diarrhea in 24 h (usually 5-10 h) after ingested drug 8. Hypotension 9. Hypothermia

The diagnosis of DIES requires that a patient meets the major criterion and >3 minor criteria. If only a single episode has occurred, a diagnostic OFC should be strongly considered to confirm the diagnosis

Table 1. Adapted from reference (3)