



## A Challenging Case of Multiple-Drug Intolerance Syndrome in a Child

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Multiple drug intolerance or multiple drug allergy syndrome was defined as intolerance to two or more structurally or pharmacologically unrelated drugs taken on 3 different occasions [1]. This definition excludes patients who react to chemically related drugs or to pharmacologically related drugs. In adults, multiple drug intolerance syndrome is reported in few studies. Management of these patients is very difficult as they believe themselves to be allergic to all drugs; and frequently, their practitioners share the same opinion, avoiding prescribing any drug therapy, even when required [1].

In children, multiple drug intolerance syndrome is still unknown. The management of this syndrome in infants is much more challenging and prescribing indispensable drugs may be life threatening and may expose infants to severe complications [2].

Herein, we report a case of a 4-year-old girl who was diagnosed with cystic fibrosis at the age of 4 months and who presented a generalized urticaria occurring after treatment with voriconazole. Urticaria reappeared after imipenem infusion associated with amikacin, the treatment was withdrawn and the patient received corticosteroids with a favorable evolution. The eruption recurred after receiving ceftazidime. Few months later, she received ciprofloxacin and she developed again a generalized urticaria. In our patient, multiple drug intolerance syndrome was suspected. Although symptomatic supportive therapies were initiated, urticaria recurred few minutes after each drug intake.

Although the exact mechanism of multiple drug-intolerance syndrome is still unknown, suggested mechanisms include non-specific mast cell activation, a non-immunological response or alternate complement pathway activation. This suggests the presence of autoreactive antibodies in the serum of patients with multiple drug-intolerance syndrome. It is thought that these antibodies, when triggered by culprit drugs, may target the high affinity IgE receptor to induce histamine release [3,4]. Adverse drug reactions not caused by an immunological mechanism may be pseudo-allergic, idiosyncratic, or defined as an intolerance. Although some medications non-specifically increase histamine release from basophils and are known to aggravate or cause urticaria by decreasing prostaglandin E 2 (PGE 2) levels, the above mentioned medications are not known to cause the same mechanisms except for ciprofloxacin.

In adults, multiple-drug intolerance syndrome is more frequently reported in anxious patients with specific wary of medications. In a study conducting oral drug provocation testing on self-reported multiple drug reactors; no patient was objectively qualified as a multiple drug reactor. Authors reported that such patients possibly suffer from drug phobia rather than true allergies [5]. Such a wrong conviction can lead to undesirable consequences: less effective and/or more expensive alternatives may be prescribed in order to avoid allergy due to the incriminated drug.

In this context, challenge testing has been recommended to clarify the situation [6]. Elective oral challenges were able to identify at least one tolerated antibiotic class in most patients with multiple drug allergy syndrome [5]. However, in children, multiple-drug intolerance syndrome is quite different of that reported in adults. In fact, the symptomatology seems to be more sensible with objective criteria. In children, especially those with susceptible chronic diseases requiring more frequently the use of drugs to treat complications, identifying the culprit drug in the current era of polypharmacy may be difficult. Although drug provocation testing may be the only way to resolve the issue of suspected multiple drug allergy syndrome, it is not usually riskless in children and it requires introducing the drugs under medical supervision [5]. Nevertheless, in children, the development of urticaria associated with an infection for which drugs are taken may be triggering with an impression of drug hypersensitivity, leading to more complicated diagnosis and management.

Multiple drug hypersensitivity is a valid diagnosis but true multiple drug reactors appear to be rare. Oral challenge is a reliable way of demonstrating this to patients and providing them with a list of safe drugs. In children, investigations may be more challenging and precautions should be taken.

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