

# Allergy and Clinical Immunology

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Choosing Wisely and Italy's "*Doing more does not mean doing better*" project

Hymenoptera venom allergy: what's new?

A cause of pleural effusion caused by *Toxocara* infection

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Official Journal of  
the Italian Society of  
Allergy, Asthma and Clinical Immunology

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## Review

### Hymenoptera venom allergy: what's new?

M. Mauro, E. Boni, M. Russello, C. Incorvaia

*Hymenoptera venom allergy (HVA) can be diagnosed and treated with efficient tools, but the search for improving the performance continues, and recently has led to some development. In particular, the introduction of molecular allergy techniques and of the basophil activation test (BAT) was a real advance in identifying the really causative venom in patients with multiple positive response to common IgE testing due to cross-reactivity and, for BAT, in achieving a correct diagnosis in patients with negative IgE tests. For venom immunotherapy, a major advance was the development of adequate procedures for patients with mast cell disorders, while the issue of safety of VIT with honeybee venom, that is significantly lower compared to vespid venom, remains to be resolved.*

## Case reports

### A cause of pleural effusion caused by Toxocara infection

R. Qualizza, E. Makri, L. Losappio

*Infections from Toxocara species are much more common than believed and cause a number of clinical manifestations due to involvement of various tissues and organs. Here we report the case of a woman long suffering from rheumatoid arthritis, Sjogren syndrome and autoimmune thyroiditis who developed pleural effusion. The disease was considered related to the autoimmune pathology of the patients, but treatment with corticosteroids was unsuccessful. Due to the presence of peripheral eosinophilia, we performed in vitro testing (Western blotting and ELISA) for IgG antibodies to Toxocara, with positive results. Anti-helminthic treatment by mebendazol. for three days repeated after 20, 50 and 80 days achieved the complete recovery of pleural effusion. This suggests to consider also Toxocara infection in patients with persistent pleural effusion with eosinophilia.*

### Fatal multi-organ failure following anaphylactic shock induced by ceftriaxone

E. Ventura Spagnolo, S. Imbesi, V. Cafeo, C. Mannucci, L. Milone, P.L. Minciullo, M. Navarra, S. Gangemi, G. Calapai

*In the latest years, based on the wide use of cephalosporins for antibiotic therapy, a large interest focused on the identification of causal relationship of adverse reactions after their prescription. We report a case of fatal anaphylactic shock following the administration of ceftriaxone in a woman who had tolerated the previous exposure to the drug. This case adds a contribution to the few cases reported in literature to further suggest the possibility of severe anaphylaxis after the administration of ceftriaxone even in patients without any previous reaction to this drug.*

## review

## Choosing Wisely and Italy's "Doing more does not mean doing better" project

S. VERNERO

*Co-founder and Vice President of Slow Medicine*

*Coordinator of the Italian Project "Doing more does not mean doing better"*

Although the Institute of Medicine invited physicians to avoid overuse, underuse and misuse since many years<sup>1</sup>, the main focus has been directed towards the problems of underdiagnosis and undertreatment, while neglecting overtesting, overdiagnosis and overtreatment.

In recent years, however, data about waste and overuse in health-care have been published: according to Brody "waste", defined as "*spending for interventions that do not benefit patients*", actually amounts to at least 30% of the US healthcare budget<sup>2</sup>.

A 2010 WHO report estimates that the amount of services providing no benefit to patients accounts for approximately 20-40% of healthcare spending.

Numerous services appear not to be beneficial for many patients but rather to expose them to additional risks, to over-diagnosis and over-treatments<sup>3</sup>: examples are angioplasties in patients with stable angina<sup>4</sup>, colonoscopies<sup>5</sup> and magnetic resonance imaging (MRIs) at the lumbar spine<sup>6</sup>.

"Medical Professionalism in the New Millennium: A Physician Charter"<sup>7</sup>, published in 2002 and authored by the American Board of Internal Medicine (ABIM) Foundation, the American College of Physicians Foundation, and the European Federation of Internal Medicine, was a first call for physicians to lead the effort against overuse of medical practices. The charter, having as its fundamental principles the primacy of patient welfare, patient autonomy, and social justice, specifically called on physicians to be responsible for the appropriate allocation of resources and to avoid unnecessary tests and procedures.

In April 2012, the ABIM Foundation, together with Consumer Reports, launched the Choosing Wisely<sup>8,9</sup> campaign. According to Brody's proposal<sup>10</sup>, specialty Societies were asked to identify a top-5 list of overused medical tests and procedures that provide little benefits and in some cases harm to many patients, in view

of stimulating physicians/patients conversations about them. Nowadays 62 societies identified the top 5 list in the USA and are actively involved in implementing the recommendations.

Overuse of medical resources is large in Italy too<sup>11</sup>, although Italy ranked below the OECD average in terms of health spending per capita in 2011.

Examples of overuse in Italy include the number of MRI units, only lower of that of Japan and United States and far above the OECD average in 2011, and MRI and CT exams, rates of caesarean delivery as a percentage of all live births, consumption of antibiotics, CRT (cardiac resynchronization therapy) implantations and implantable cardioverter-defibrillators.

Slow Medicine<sup>12</sup>, an Italian movement founded in 2011, opened to health professionals, patients and citizens and aimed at the promotion of a Measured, Respectful and Equitable Medicine, launched a project named "Doing more does not mean doing better"<sup>13</sup> in Italy at the end of 2012, similar to Choosing Wisely in the USA.

Its primary goal is improving the quality and appropriateness of care and ensuring the safety of patients through the reduction of tests and treatments whose necessity should be questioned and discussed. The project also aims to disseminate the culture that "Doing more does not mean doing better" in Italy.

The project involves physicians as well as other health professionals in the responsibility for the appropriate use of medical resources.

Launched by Slow Medicine, it is also promoted by:

- The National Federation of Medical Doctors' and Dentists' Colleges (FNOMCeO);
- The National Federation of Nurses' Colleges (IPASVI);
- The Italian Society for Quality in Healthcare (SIQuAS VRQ);
- Change Institut, a training agency in communication and systemic counseling in Turin;

- Partecipa Salute, a project established by IRCCS-Mario Negri, Italian Cochrane Centre and Zadig srl. aimed at participation of patients and citizens in healthcare;
- Inversa Onlus, the Italian association of patients with hidradenitis suppurativa;
- Altroconsumo, an Italian consumers' association with 345.000 members;
- The Federation for Social Services and Healthcare of Autonomous Province of Bolzano;
- Slow Food Italy, founder of and component of Slow Food International (100.000 members in 150 countries).

A steering group of the project with representatives of these associations was created in March 2013.

Each Italian specialty society engaged in the project must develop a list of the top 5 tests and treatments in its field that are commonly ordered in Italy but whose necessity should be questioned and discussed because:

- they have been shown by the currently available evidence not to provide any meaningful benefit to at least some major categories of patients for whom they are commonly ordered;
- they may cause harm to patients.

Unlike the USA campaign, the cost of tests and treatments was not included among the criteria of choice to avoid the initiative should be interpreted as a way to ration healthcare for cost cutting purposes.

The project aroused the enthusiasm of the physicians and of other healthcare professionals, and many specialty societies joined it. The Italian Society of Allergy, Asthma and Clinical Immunology – SIAAIC was among the first ones.

To date, ten following National specialty societies and associations already created their top 5 lists of overused tests and treatments<sup>14</sup>:

- The Italian Society of Medical Radiology – SIRM;
- The Italian Association of Radiation Oncology – AIRO;
- The Italian Board of Medical Oncology Directors – CIPOMO;
- The Cochrane Neurological Field in Italy – CNF;
- The Italian Association of Dietetics and Clinical Nutrition – ADI;
- The Italian Society of General Practitioners – SIMG;
- The Italian Association of Hospital Cardiologists – ANMCO;
- The Italian Society of Pediatric Allergy and Immunology – SI-AIP;
- **The Italian Society of Allergy, Asthma and Clinical Immunology – SIAAIC;**
- Italian Specialty Societies of Nurses of: Operating Theater, Stomacare, Skin Ulcers, Hospital Medicine – AICO, AIOSS, AIUC, ANIMO.

The top-5 list of the Italian Society of Allergy, Asthma and Clinical Immunology – SIAAIC is:



Fig. 1.

The following National specialty societies and associations also joined the project and are defining their top 5 lists:

- The Italian Association of Neuroradiology – AINR;
- The Italian Association of Medical Diabetologists – AMD;
- The Italian Association of Hospital Dermatologists – ADOI;
- The Italian Federation of Associations of Hospital Internal Medicine – FADOI;
- The Italian Society of Human Genetics – SIGU;
- The Italian Association for the Promotion of appropriate care in Obstetrics, Gynecology and Perinatal Medicine – ANDRIA;
- The Italian Association of Nuclear Medicine – AIMN;
- The Italian College of Chief Vascular Surgeons;
- The Italian Federation of Pediatricians – FIMP;
- The Cultural Association of Pediatricians – ACP;
- The Italian Society of Palliative Care – SICP;
- The International Society of Doctors for the Environment (ISDE);
- The Italian Society for Medical Education (SIPeM);
- The Italian Association of Doctors of Hospital Directions (AN-MDO);
- The Italian Society of Laboratory Medicine – SIMeL;
- The Association of Coroners of Health Authorities – COMLAS;
- The Association of Endocrinologists – AME;
- The Italian Society of Nephrology – SIN;
- Other Italian Specialty Societies of Nurses.

As in Choosing Wisely, physicians and patients should have conversations and discuss the use of these tests and treatments, in view of wise and shared choices taking into account patients' values, expectations and desires.

The societies and associations promoting the project or involved in the creation of the lists will play a key role for informing health

professionals about the project and about the tests and the treatments whose necessity should be questioned and discussed in Italy.

They will also promote education and training of physicians and of other health professionals on Evidence Based Medicine, on Medical Humanities and on practices to improve the interaction and the relationship with patients.

Patients and citizens have an active role in the project. They collaborate with health professionals for the development of patient-friendly material about overused tests and treatments as well as in widely disseminating the culture that "Doing more does not mean doing better" and that less healthcare can often result in better health.

Altroconsumo, the Italian consumers' association promoting the project, already created six cards for citizens about overused tests and treatments chosen by Italian specialty societies<sup>15</sup>.

As in Choosing Wisely, there are 5 questions for patients and citizens to ask their doctors, before getting any test, treatment or procedure:

- Are there simpler, safer options?
- What happens if I don't do anything?
- Do I really need this test or procedure?
- What are the risks?
- How much does it cost?

It is very important for everyone to understand that the goal of the project is to protect patients' interests: treatments and diagnostic tests that are inappropriate for patients may be directly harmful;

furthermore inappropriate tests may produce false positive results and overdiagnosis, that in turn lead to more tests, treatments and complications<sup>16</sup>.

"*Primum non nocere*" becomes the strongest argument for eliminating non beneficial medicine, towards the Measured, Respectful and Equitable approach promoted by Slow Medicine.

The project aims at promoting links among the various medical professionals on the one hand, and between medical professionals and "citizen-patients" on the other, with the objective of building up joint or consensual actions and choices for the future: peculiarity of the Italian project "*Doing more does not mean doing better*", as well as of Slow Medicine, is the systemic approach.

Organizational changes will be necessary too, for example the radiologists should become more involved in decisions regarding the appropriate use of their services.

In addition to the Italian specialty societies and associations, some hospitals also started to identify tests and treatments whose necessity should be questioned and discussed. The first were the hospitals in Cuneo (Italy) and in Locarno (Switzerland). Other Italian hospitals and health organizations are expected to plan similar projects in the next future.

The Italian project "Doing more does not mean doing better"<sup>17</sup> was among the worldwide initiatives at the International Roundtable on Choosing Wisely<sup>18</sup> held in Amsterdam in June 2014 and is part of the International campaign on Choosing Wisely.

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## Hymenoptera venom allergy: what's new?

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### Summary

Hymenoptera venom allergy (HVA) can be diagnosed and treated with efficient tools, but the search for improving the performance continues, and recently has led to some development. In particular, the introduction of molecular allergy techniques and of the basophil activation test (BAT) was a real advance in identifying the really causative venom in patients with multiple positive response to common IgE testing due to cross-reactivity and, for BAT, in achieving a correct diagnosis in patients with negative IgE tests. For venom immunotherapy, a major advance was the development of adequate procedures for patients with mast cell disorders, while the issue of safety of VIT with honeybee venom, that is significantly lower compared to vespid venom, remains to be resolved.

### Key words

Hymenoptera venom allergy • Diagnosis • Treatment • Component resolved diagnosis • Basophil activation test • Venom immunotherapy • Mast cell disorders

## Introduction

Hymenoptera venom allergy (HVA) was the first kind of allergy to be reported, if we credit the description in hieroglyphics of the death of the pharaoh Menes after a hornet sting in a time between 2000 and 2500 B.C. <sup>1</sup>.

However, the approach to HVA became scientific only in the late 1970<sup>1</sup>, when was finally recognized that the use of venom from the various Hymenoptera, such as *Apis mellifera*, *Vespula species*, *Dolichovespula species*, *Polistes species*, and *Vespa crabro* allowed to achieve a sound diagnosis <sup>2</sup> and a very effective treatment <sup>3</sup>. Since then, patients with allergic reactions to Hymenoptera sting can be properly diagnosed and excellently managed by venom immunotherapy (VIT), but it is obvious that the different aspect of HVA continue to be investigated for possible further improvement. Here we review the recent advances in epidemiology, pathogenesis, diagnosis and treatment of HVA.

### Epidemiology

The prevalence of systemic reactions to Hymenoptera stings has been evaluated in numerous studies worldwide, being possible to estimate an overall value of approximately 3% in the general

population but much higher values, up to 26%, in subjects at risk of multiple stings such as beekeepers <sup>4</sup>. The surveys conducted in Italy, including recent data, are in line with such figures <sup>5,6</sup>. Of interest, a recent study performed in Istanbul reported a lower prevalence of systemic reactions to insect stings, as confirmed by results of diagnostics test, corresponding to less than 1% <sup>7</sup>. This suggests that the environment of a metropolis (Istanbul has around 13 million inhabitants) is less risky concerning HVA, probably because Hymenoptera avoid places with highly polluted atmosphere.

## Pathogenesis

HVA is generally considered a perfect model of type 1 hypersensitivity with no inflammatory background, however recent studies showed that this may not be necessarily true. In fact, it was recently reported that Th1, Th2, lymphocyte trafficking and activation markers on CD4+ T-cells in venom-allergic patients were comparable to other kind of allergies, and that comparing venom allergic subjects with non-allergic healthy controls, an up-regulation of CD26, CXCR4, CXCR3, CD154 and a down-regulation of CD30,



CD154 and CD152 was induced by VIT<sup>8</sup>. Another observation on the issue concerns the detection in patients with HVA of an over-expression of the adhesion molecule ICAM-1, that is an important factor in allergic inflammation, and its significant decrease after VIT<sup>9</sup>. An important pathogenetical factor in developing systemic reactions to Hymenoptera stings is mastocytosis as well as other mast cell disorders, that in the latest decade were thoroughly investigated, being possible to accurately define the diagnostic and therapeutical aspects<sup>10</sup>. It is also of interest that the concomitant assumption of nonsteroidal antiinflammatory drugs (NSAIDs) in the same day of a honeybee sting apparently favour the occurrence of systemic reactions. In fact, three cases were reported of systemic reactions to bee stings exclusively occurring after taking NSAIDs, in subjects who tolerated, before and after such reactions, both bee stings and NSAIDs if not in concomitance<sup>11</sup>.

## Diagnosis

The overall performance of classic diagnostic tools such as skin tests and *in vitro* measurement of specific IgE-antibodies is satisfactory. However, the issue of frequent multiple positive results to tests, that is often caused by cross-reactions of allergens with high grade of homology, is an impediment in identifying the really causative venom. The first solution to this problem was offered by RAST-inhibition, of which was demonstrated in 1993 the ability to identify the responsible venom and thus to avoid unnecessary VIT with other venoms<sup>12</sup>. Indeed, the introduction of molecular allergy technique, that defined the component resolved diagnosis (CRD) was a real advance, because it allows to detect the specific IgE to single venom allergens. For example, in patients with apparent double sensitization to *Apis mellifera* and *Vespula spp* CRD was able to identify the culprit venom. Actually, using recombinant species-specific major allergens (rSSMA), namely Api m 1, Ves v 1 and Ves 5, it was possible to demonstrate in 76 patients with double positivity of serum-specific IgE (sIgE) to both *Apis mellifera* and *Vespula spp* venoms that only 47% of patients reacted to rSSMA of both species<sup>13</sup>. However, in interpreting the results of CRD, especially when concerning vespid venom, we must bear in mind the whole knowledge of HVA to avoid incorrect conclusions<sup>14</sup>. As far as the use of microarray technique measuring a large number of allergens is concerned, it was recently highlighted that including in such panels Hymenoptera venom is misleading, because testing insect venom sensitivity in individuals with no history of reactions to stings is contrary to current guidelines and presents the physician with the dilemma of how to manage this information, being possible to face legal issues<sup>15</sup>. An *in vitro* test of increasing importance is the basophil activation test (BAT), that is based on the expression on basophil surface of activation marker

as CD63 or CD203c following contact with the suspected allergen, particularly venom allergens<sup>16</sup>. BAT was shown to be useful not only to identify the really causative venom in patients with multiple positive response to common tests, but also to detect a positive reaction in patients with negative tests<sup>17</sup>, being thus possible to diagnose HVA in patients otherwise classified as non-allergic.

## Treatment

VIT, as stated above, is very effective in preventing reactions to Hymenoptera stings, but according to a recent review there is some room for research concerning the definition of risk of adverse reactions to treatment. The issues under discussion are the use of ultra-rush VIT, the concomitant treatment with angiotensin-converting enzyme inhibitors in relation to their potential to increase such reactions, the elevated baseline serum tryptase levels (greater than 20 µg/l) and the use of honeybee venom for VIT. The latest two factors are also apparently associated to VIT failure, that is, incomplete protection from stings<sup>18</sup>. Indeed, the safety of VIT with honeybee venom is much lower compared with vespid venom, with an incidence of systemic reactions globally corresponding to 25.1% for honeybee venom and 5.8% for vespid venom ( $p < 0.0001$ ) in a systematic review<sup>19</sup>. Thus far, the factors underlying such great difference are unknown. Currently, the issue may be faced by pre-medication with antihistamines<sup>20</sup> or, in case of severe reactions, by the anti-IgE omalizumab<sup>21</sup>. Concerning the optimal duration of VIT, five years are still considered the best choice, unless the patient has a mast cell disorder, that requires a life-span treatment. Further studies are needed to identify the factors influencing the re-occurrence of systemic reactions to stings following VIT stopping, that affects about 15% of patients<sup>22</sup>. As regards emergency drug treatment, epinephrine is the recommended first line drug in anaphylaxis, but a bulk of data define an insufficient use of this agent. Limiting to most recent data, a cohort study of 5-year duration showed that epinephrine was used only in 17% of patients with anaphylaxis in emergency medicine<sup>23</sup>. Also, there is evidence of insufficient prescription of epinephrine auto-injectors as well as of correct use by the patients when needed<sup>24</sup>. When available, the preparations of sublingual tablets of epinephrine that are under current development<sup>25</sup> will be likely to improve the flawed use by patients of this drug in anaphylaxis.

## Conclusions

For patients with HVA valid diagnostic procedures and effective treatments are available. Most of the recent advances in HVA concern diagnosis, where molecular allergy techniques and the

basophil activation test allow to identify the really responsible venom in patients with multiple positive response to common IgE testing and, for the latter, to achieve a correct diagnosis in patients with negativity of IgE tests. For VIT, a major advance was the

development of adequate procedures for patients with mast cell disorders, while the issue of safety of VIT with honeybee venom, that is significantly lower compared to vespid venom, remains to be resolved.

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## case report

# A cause of pleural effusion caused by *Toxocara* infection

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### Summary

Infections from *Toxocara* species are much more common than believed and cause a number of clinical manifestations due to involvement of various tissues and organs. Here we report the case of a woman long suffering from rheumatoid arthritis, Sjogren syndrome and autoimmune thyroiditis who developed pleural effusion. The disease was considered related to the autoimmune pathology of the patients, but treatment with corticosteroids was unsuccessful. Due to the presence of peripheral eosinophilia, we performed *in vitro* testing (Western blotting and ELISA) for IgG antibodies to *Toxocara*, with positive results. Anti-helminthic treatment by mebendazol, for three days repeated after 20, 50 and 80 days achieved the complete recovery of pleural effusion. This suggests to consider also *Toxocara* infection in patients with persistent pleural effusion with eosinophilia.

### Key words

*Toxocara* species • Pleural effusion • Eosinophilia • Anti-helminthic treatment

## Introduction

Infection from *Toxocara canis* and *Toxocara cati*, due to the migration and prolonged surviving of their larvae in various tissue and organs, may be clinically expressed with a wide range of manifestations, including respiratory, gastrointestinal, cutaneous and neurologic symptoms<sup>1-3</sup>. However, the pathogenic role of *Toxocara* is scarcely known and this often results in missing a correct diagnosis and an effective treatment. Here we describe an unusual case of pleural effusion caused by *T. canis* infection.

## Case report

A 56 years old Caucasian woman was referred to our Allergy Department due to peripheral eosinophilia. However, no allergy background was detected. Since 1985 the patient suffered from joint pain and migrant arthralgia. After a complete work-up for autoimmune diseases a diagnosis of rheumatoid arthritis was

reached, followed in 1995 by development of Sjogren syndrome and autoimmune thyroiditis. Antiinflammatory treatment including corticosteroids courses had been prescribed with no significant improvement. Subsequently, immunomodulatory medication was introduced, with methotrexate and hydroxychloroquine, and levotiroxine 75 mcg/day was added because of hypothyroidism. On July 2009, the patient had facial erythema, unrelated to drugs or foods, that disappeared after corticosteroid treatment. One month later, she developed severe dyspnea and intercostals retractions, a spirometry detected a mild restrictive deficit, while a standard chest X ray showed right basal pneumonia with mild pleural effusion. A computed tomography confirmed the pleural effusion and excluded pulmonary embolism and mesothelioma. Subsequently, the presence of low-grade fever prompted antibiotic therapy by clarithromycin for 10 days associated with tapered dose prednisone. However, a chest X ray control after 20 days showed the appearance of slight elevation of the right hemi diaphragm, and an ecography demonstrated the presence of a minimal free pleural layer on the right field along with subsegmentaria lobe atelectasis on the basal right lung.

On February 2010, a new chest X ray control showed a moderate improvement but not a recovery of the pleural effusion.

When the patient was referred to us because of persistent eosinophilia, we performed allergy testing and parasitologic examination, with negative results. Instead, *in vitro* tests for IgG antibodies to *T. canis*, namely Western blotting and ELISA were both positive. Anti-helminthic treatment was started using mebendazole one 100 mg tablet b.i.d. for three days, that was repeated after 20, 50 and 80 days. The figures 1 to 4 show the changes induced by treatment as assessed by imaging.

## Conclusions

*Toxocara* infection, despite its epidemiological importance defined by substantial prevalences worldwide <sup>4-6</sup>, is still overlooked as a



Fig. 1. Pleural effusion as shown by standard chest X-ray.



Fig. 2. Pleural effusion as shown by computed tomography.



Fig. 3. Pleural effusion as shown by echography.



Fig. 4. Recovery of pleural effusion as shown echography.

cause of disease in a large spectrum of clinical manifestations. We describe a further case of pleural effusion caused by *Toxocara* that, even though its first description dates back to 1987 <sup>7</sup> and the number of reports, mostly associated with eosinophilic infiltration, is not negligible <sup>8-12</sup>, was not taken into account in the diagnostic work-up. The detection of *T. canis* specific IgG antibodies finally allowed to recognize the cause of pleural effusion and to achieve by appropriate treatment the recovery of the illness.

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## case report

# Fatal multi-organ failure following anaphylactic shock induced by ceftriaxone

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### Summary

In the latest years, based on the wide use of cephalosporins for antibiotic therapy, a large interest focused on the identification of causal relationship of adverse reactions after their prescription. We report a case of fatal anaphylactic shock following the administration of ceftriaxone in a woman who had tolerated the previous exposure to the drug. This case adds a contribution to the few cases reported in literature to further suggest the possibility of severe anaphylaxis after the administration of ceftriaxone even in patients without any previous reaction to this drug.

### Key words

Adverse drug reaction • Anaphylaxis • Ceftriaxone • Cephalosporins • Multi-organ failure • Shock

## Introduction

Until about 10 years ago, the frequency of immediate allergic reactions in subjects primarily sensitized to cephalosporins has been considered a rare adverse event <sup>1</sup>. In the latest years, based on the wide use of cephalosporins for the treatment of common infections, a greater interest focused on reporting of adverse reactions following their prescription <sup>2,3</sup>.

Cephalosporins are responsible for severe allergic reactions approximately in 15% of cases of adverse reactions reported as induced by antibiotics and in 27 % of cases of those reported as induced by betalactams class drugs <sup>4</sup>. Most common reactions caused by cephalosporins are maculopapular rashes and fever; with a lower number of reactions being characterized by urticaria, while anaphylaxis is rarely reported <sup>1,5</sup>.

Hypersensitivity reactions to cephalosporins may occur because of sensitization to determinants shared with penicillins or to unique

cephalosporin determinants, although the different epitopes have not been yet defined <sup>6</sup>. Sometimes, following an anaphylactic reaction, cardiovascular complications may occur, especially in subjects with underlying ischaemic heart disease. Two cases of stress-induced cardiomyopathy following anaphylaxis from cephalosporin have been described <sup>7,8</sup>.

Ceftriaxone is one of the most used cephalosporins in clinical practice, however, ceftriaxone-induced anaphylaxis is still considered a rare event <sup>1</sup>. Knowledge on allergic reactions to this antibiotic is fundamentally derived from publication of case reports describing adverse reactions involving ceftriaxone <sup>9-13</sup>. Among these, only two cases of anaphylaxis have been reported after single-dose ceftriaxone without previous exposure to ceftriaxone <sup>10,12</sup>. Another case was reported in a man with allergy to amoxicillin/clavulanate who developed a cross-reaction to cephalosporins <sup>14</sup>.

Here we report a case of fatal anaphylactic shock following the administration of ceftriaxone in a subject who had tolerated the previous exposure to the drug.

## Case report

Through a retrospective analysis of deaths occurred over the past 10 years and subjected to legal investigations in the city of Palermo (Italy), we detected a case of anaphylactic shock related to intramuscular (i.m.) administration of ceftriaxone. A 44-year-old heavy-smoker nurse with no history of chronic or severe diseases, being affected by cough, sneezing and sore throat prepared a vial of ceftriaxone and asked a colleague to administer it to her during their work shift. She had already used the same drug in the past, confirming this to the colleague. A few seconds after the i.m. administration, the woman developed severe dyspnea and wheezing. For this reason, she was promptly accompanied, on a stretcher, to the local Emergency Room, where she arrived yellow-crowned in a pre-agonic state with frothing at the mouth and warm skin. Despite the emergency treatment, the woman died in about 30 minutes.

### POST-MORTEM EXAMINATION

The external examination of the corpse showed cervico-cephalic congestion, petechiae at the medial face of the arms and at the level of the shoulder, subungual cyanosis in the fingers and the sign of acupuncture to the right side above the buttock. Moreover, it was observed: bilateral tonsillar hypertrophy, mainly on the right; hyperemic pharyngeal and epiglottic mucosa; slightly narrowed laryngeal aditus; congestion of tracheal mucosa with hypertrophic paratracheal and hilar lymph nodes, bilaterally; intense bronchial and polivisceral congestion.

### Hystological exam

The hystological exam of small fragments extracted from the organs during autopsy and embedded in paraffin confirmed the polivisceral involvement with intense tissue eosinophilia.

### Chemical and toxicological analysis

The chemical examination of the residual liquid in the syringe used for i.m. administration of the drug detected the presence of the drug in question and the absence of other substances.

### Conclusion

The autopsy findings (both macro-and microscopic), the absence of previous significant diseases, the symptoms and the rapid progression of the events leading to a diagnosis of acute cardio-

respiratory failure and rapid outcome of death come out in favor of an anaphylactic shock due to a hypersensitivity reaction to ceftriaxone.

## Discussion

Cephalosporins are one of the most commonly prescribed classes of antibiotics. Immediate hypersensitivity reactions have been reported following the administration of specific cephalosporins, usually after a first exposure which has induced the sensitization or for the first time because of cross-reactions with other cephalosporins or beta-lactams<sup>15</sup>.

Different types of adverse reactions are reported to be induced by ceftriaxone. The most frequently reported serious events with ceftriaxone were cardiac arrest, and anaphylactic reactions. An Iranian study reporting death due to adverse drug reactions established that ceftriaxone is a drug frequently linked to a fatal outcome and that the leading cause of death was cardiac arrest<sup>16</sup>. The real number of probable ceftriaxone-related deaths and other serious adverse events could be probably higher than reported, because under-reporting is a common problem in spontaneous reporting systems<sup>17</sup>.

Recently, possible explanation of death induced by ceftriaxone anaphylaxis has been suggested with publication of a case in which multi-organ failure was observed, associated with stress-induced cardiomyopathy mimicking ST-elevation acute myocardial infarction. This last event has been considered as responsible of death induced by ceftriaxone<sup>7</sup>. According to the Naranjo algorithm<sup>18</sup> (score 6) for this case the causality relationship between the adverse reaction and the administration of the suspected drug has to be considered as probable. The case we described suggests that systemic quick injection of the medicine, unnecessary administration of the drug and administration of the drug to patients with a previous history of allergic reactions to cephalosporins or penicillins should be avoided to reduce the frequency of such serious, life-threatening adverse reactions<sup>16</sup>.

In conclusion, this case report adds a contribution to the few cases described in literature to make the clinicians aware of the possibility of anaphylaxis occurring with administration of ceftriaxone, even in patients without any previous reaction to this drug or to drugs belonging to the same class.

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## letter to the Editor-in-Chief

# Non-atopic asthma in childhood is a clinical problem into adulthood?

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Asthma is a complex syndrome characterized by multiple features and particularly associated to spasm of the smooth bronchial muscles, swelling of the bronchial mucous membrane and by a specific form of inflammation of the smaller bronchioles. Asthma is atopic when triggered by antibodies of the IgE isotype, synthesized against specific environmental antigens, called allergens. The binding of specific IgE (sIgE) to the cutaneous mast cells also sensitize the skin, allowing the identification of the responsible allergen through a skin tests. The IgE-mediated immunological reaction into the sensitized bronchus causes an inflammation that causes bronchoconstriction, which is also influenced by the phenomenon of bronchial hyperresponsiveness (BHR). This inflammation can be studied with invasive techniques, such as biopsies and/or bronchial washing, or with the recently introduced test measuring nitric oxide (NO), that is non-invasive and easy to perform in children, and whose positivity reveals an eosinophilic inflammation of the bronchioles <sup>1</sup>.

However, atopy is not always involved in asthma <sup>2</sup>. Therefore, other non-atopic factors such as passive smoking <sup>3</sup> or obesity <sup>4</sup>, may be significantly related to asthma through a different kind of inflammation. Regarding the relationship between obesity and asthma, in 1990 a prevalence of obesity, defined as weight/height ratio higher than the 95th percentile, of 14.4% was reported among 584 asthmatic children (range 1-17 years) admitted to the Allergy Unit of the University Department of Pediatrics in Naples. A stratified analysis of the 584 patients identified 486 atopic (SPTs+) and 98 non atopic (SPTs-) patients. The prevalence of obesity showed a statistically significant difference between the two groups (23.5% (23/98) in asthmatic SPTs- vs 12.6% (61/486) in asthmatic SPTs+ patients; OR 2.14; 95% CI 1.2-3.8;

$p = 0.008$ ) <sup>5</sup>. If atopy is not detected, the diagnosis of non-atopic asthma is based on a history of recurrent wheezing with a bronchospasm that is sensitive to beta2-agonist bronchodilators drugs, and that is triggered by non-atopic environmental factors. Such non-atopic asthma in children can recede spontaneously, or, triggered by the same non-atopic environmental factors, in some cases could evolve into a chronic obstructive pulmonary disease (COPD), which shares the same environmental risk factors and is characterized by a non-eosinophilic airway inflammation <sup>6</sup>. The genetic variability of people with asthma, also in the genesis of the remodeling of the airway wall <sup>7</sup>, creates a great variety of asthma phenotypes, that are clinically distinguishable, mainly because of their variable capacity of interaction with the environment. The possible coexistence in the same individual of sensitivity to allergic and non-allergic environmental factors, and of a atopic and non-atopic inflammatory process and genetic characteristics related to the remodeling of the bronchial wall may explain some treatment failures.

In conclusion, subjects in pediatric age with non-atopic asthma, because of its unlikely disappearance over time, must be carefully diagnosed and monitored. This is needed because this condition may evolve into atopic asthma, or, in some cases into COPD, the two diseases requiring a different approach and management, with a special role for allergen immunotherapy in atopic asthma <sup>8</sup>. Instead, non-atopic asthma and COPD share an non-eosinophilic inflammation of the bronchioles and probably also a particular type of remodeling of the bronchial wall <sup>9</sup>.

We believe that non-atopic asthma in children should be carefully diagnosed and followed over time, to prevent a detrimental evolution in adulthood.

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## Per la scomparsa del Prof. Alberto Marmont

Alle prime luci dell'alba del 3 aprile 2014 Alberto Marmont du Haut Champ muore a 95 anni ospite del "suo" reparto nell'Ospedale San Martino di Genova, brillante e attivo scienziato fino alla fine: l'ultimo Suo lavoro "*Lupus sistemico complicato da timoma ed eritroblastopenia*" è stato accettato dalla rivista *Bone Marrow Transplantation* qualche settimana prima e verrà pubblicato postumo. Alberto Marmont si laurea a Genova nel 1942, frequenta quindi la Clinica Medica dell'Università di Genova con la carica di Aiuto e successivamente consegue la Libera Docenza in Patologia Speciale Medica (1951), quella in Ematologia (1956) e quella in Clinica Medica Generale (1959). Negli anni '60 deve lasciare questo incarico per diventare Primario Medico presso l'Ospedale Civile di Sampierdarena, laboriosa ed attiva delegazione del capoluogo ligure.

Nel 1974 viene chiamato quale Primario Ematologo dell'Ospedale Regionale San Martino ove resterà fino all'età del pensionamento, indi ancora ospite nel Suo reparto per continuare studi, ricerche, insegnamenti. La Sua grande passione era l'autoimmunità, indirizzata negli anni '50-'60 prevalentemente verso quelle allora definite "collagenopatie o mesenchimopatie" (fondamentali i Suoi contributi sul Lupus Eritematoso Sistemico, sul fenomeno LE), e poi sempre più specificamente verso l'immunoematologia: nel 1976 esegue con successo e primo in Italia un trapianto di midollo in soggetto affetto da anemia aplastica autoimmune: essenziale intervento che aprirà la strada all'approccio verso la guarigione di svariate patologie neoplastico-ematologiche.

Dall'originario reparto si sono poi sviluppate per Sua iniziativa due divisioni indipendenti pur strettamente collegate, una dedicata al trapianto di cellule staminali midollari, l'altra di oncoematologia dirette dai Suoi fedeli allievi. Innumerevoli i Suoi contributi scientifici originali e di ricerche personali apparsi in articoli, riviste, monografie, trattati tutti prestigiosi che lo hanno reso noto ed ammirato in Italia, Europa, ed al di là dell'Atlantico.

È stato insignito della Laurea Honoris Causa alla Sorbona, della Medaglia d'Oro al merito della Sanità Pubblica, del Grifo d'Oro della città di Genova (massima onorificenza della città), del Cavalierato di Gran Croce della Repubblica Italiana. È stato Presidente del gruppo Europeo EBMT e della Società Italiana di Ematologia, Vice Presidente della Società Italiana di Allergologia ed Immunologia Clinica dal 1977 al 1985, Membro del Direttivo della stessa dal 1968 al 1977. Scienziato gentiluomo, gran conversatore poliglotta, nelle Sue esposizioni scientifiche mai aride o strettamente tecnologiche, era sempre presente il paziente e la correlata casistica illustrata con quella passione di sempre. Colto nello scibile umano citava con semplicità e perfezione Dante o Virgilio, Shakespeare o Cicerone, Goethe o Foscolo, e poi di storia, letteratura sovente intramezzate da frecciate di umorismo, corteggiato e ricercato ospite nei salotti della "Genova bene".

È stato un privilegio averlo conosciuto, aver con Lui lavorato e studiato, avere da Lui appreso.

Arsenio Corrado Negrini