The adult-onset mammalian meat-induced delayed anaphylaxis is a newly recognised allergic disease associated with the ingestion of meat. Since the onset of signs and symptoms of this allergy occurs 3 to 6 hours after the ingestion of meat, these cases were previously labelled as idiopathic. Many individuals with this allergy also showed negative allergy skin prick tests to meat, which made the diagnosis of this allergy difficult. The article describes this new syndrome in the light of three clinical cases. The article also discusses the discovery of immunoglobulin E (IgE) specific to glycoprotein galactose-α-1,3-galactose (alpha-gal), a carbohydrate moiety found in non-primate mammalian meat and tick, and its impact on the current approach to anaphylaxis.

In the three case studies, the patients presented with symptoms of anaphylaxis after ingestion of mammalian meat (pork/beef) and with a history of tick bite. Immunological analysis of patients’ sera revealed high levels of IgE, specific to alpha-gal, beef and pork. The result of the skin prick test to meat, performed in one of the patients, was negative. The symptoms resolved upon specific treatment and the patients remained symptom-free with abstinence from beef and pork. In contrast, chicken, turkey and fish were tolerated by these patients.

Figure 1 describes the mechanism of meat-induced delayed anaphylaxis. This type of anaphylaxis is mediated through circulating IgE specific to alpha-gal. In classic IgE-mediated anaphylaxis, prior sensitisation with an allergen is a prerequisite for the production of allergen-specific IgE. However, in delayed anaphylaxis to mammalian meat, lone star tick bite sensitises an individual to alpha-gal, who subsequently develops symptoms of anaphylaxis upon ingestion of mammalian meat containing alpha-gal.

The discovery of IgE alpha-gal dates back to 2005, when an oncology group in North Carolina observed anaphylaxis among the recipients of cetuximab, a monoclonal antibody containing alpha-gal, which is used in cancer therapy. Apart from causing cetuximab-induced anaphylaxis, IgE alpha-gal is currently recognised as the cause of meat-induced delayed anaphylaxis. Alpha-gal-associated anaphylaxis differs from the classic anaphylaxis...
The World Allergy Organization (WAO) guidelines for the assessment and management of anaphylaxis were published in March 2011. These guidelines provided a global perspective on patient risk factors, triggers, clinical diagnosis, treatment and prevention of anaphylaxis based on the articles published in indexed, peer-reviewed journals until 2010. The role of allergy/immunology specialists in preventing anaphylactic episodes has been highlighted in these guidelines. Apart from the allergy/immunology domain, these guidelines serve as a resource for other areas such as sports medicine, primary care and allied health. August 2012, update to this guidelines was published based on the relevant articles published during 2011 and early 2012. Important aspects of this update are summarised below.

**Assessment of patients with anaphylaxis**

**Patient risk factors and triggers**

The risk factors for anaphylaxis included age or physiologic state-related vulnerability, associated diseases, concurrent medications and co-factors, which were similar worldwide. Infants, teenagers, pregnant women and the elderly were more vulnerable to anaphylaxis. Risk-taking behaviours were responsible for anaphylaxis among adolescents and young adults. Some of them were either ignorant about the risk or ignored the risk. In young patients, severe and uncontrolled asthma was strongly associated with anaphylaxis. A history of asthma was predictive of dyspnoea, wheezing and respiratory arrest during an anaphylactic episode associated with food. Older age, pre-existing cardiovascular disease or mast cell disorder, elevated serum baseline total tryptase concentrations, due to three distinct reasons. First, anaphylaxis was caused by the primary exposure of an individual to glycoprotein cetuximab. Second, meat-induced anaphylaxis was delayed by several hours (3-6 hours) rather than occurring as an immediate reaction. Third, meat-induced anaphylaxis is the first food-induced anaphylaxis caused by a carbohydrate moiety rather than by a protein.

concurrent treatment with a beta-adrenergic blocker and/or angiotensin-converting enzyme (ACE) inhibitor, a previous severe reaction and the type of stinging insect were the risk factors that increased the severity of insect sting–related anaphylaxis. Exercise, fever, premenstrual status, emotional stress and acute infection such as upper respiratory tract infection were the common co-factors that amplified anaphylaxis.

In children and teenagers, foods were the most common triggers of anaphylaxis. Neuromuscular blocking agents, latex or antibiotics triggered IgE-mediated reactions in both adults and children during anaesthesia. Intrapartum injection of penicillin and exposure to natural rubber latex and other agents in medical or peri-operative settings were the triggers for anaphylaxis during labour and delivery. In individuals more than 50 years of age, the typical triggers of anaphylaxis were stinging insect venoms, medications and other ‘unknown’ factors.

Identification of human IgG-mediated anaphylaxis

Reduced blood neutrophil Fc gamma RIII expression without an increase in the expression of IL-4 R alpha has been proposed as a marker enabling the identification of human IgG-mediated anaphylaxis.

Clinical diagnosis

Figure 2 describes the diagnosis criteria of anaphylaxis that were proposed in the 2011 guidelines. These criteria were well validated in a retrospective cohort study with excellent sensitivity and

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**Figure 2: Diagnosis criteria of anaphylaxis**

1. Sudden onset of illness (minutes to hours) that involve skin, mucosal tissue or both (e.g. generalised hives, itching or flushing, swollen lips-tongue-uvula).

   - At least any one of the following symptoms:
     - Sudden onset of symptoms and signs related to skin and mucosa (e.g. generalised hives, itch-flush, swollen lips-tongue-uvula).
     - Sudden onset of symptoms and signs related to respiratory tract (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia).
     - Sudden reduction in BP or symptoms of end-organ dysfunction (e.g. hypotonia, incontinence).

   Or

   2. Sudden onset (minutes to hours) of 2 or more of the following symptoms that occur after exposure to the possible allergen or trigger* for the patient

   - Sudden onset of symptoms and signs related to skin and mucosa (e.g. generalised hives, itch-flush, swollen lips-tongue-uvula).
   - Sudden onset of symptoms and signs related to respiratory tract (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia).
   - Sudden decrease in BP or symptoms of end-organ dysfunction (e.g. hypotonia, incontinence).
   - Sudden onset of gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting).

   Or

   3. Reduction in BP following exposure to a known allergen** for the patient (minutes to several hours)

   - Infants and children: low systolic BP (SBP) specific to age or >30% reduction in SBP***

   - Adults: SBP <90 mmHg or >30% decrease from that person’s baseline

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*For example, immunologic but IgE-independent, or non-immunologic (direct mast cell activation)

** For example, reduced BP might be the only manifestation of anaphylaxis following an insect sting, or, generalized hives might be the only initial manifestation of anaphylaxis after allergen immunotherapy.

*** Low SBP for children is defined as <70 mmHg from 1 month to 1 year, <70 mmHg + (2 × age) from 1 to 10 years, and <90 mmHg from 11 to 17 years. Normal heart rate per minute ranges from 80–140 beats at age 1-2 years, from 80–120 beats at age 3 years, and from 70–115 beats after age 3 years. In infants and children, respiratory compromise is more likely than hypotension or shock. Shock is more likely to be manifested initially by tachycardia than by hypotension.

BP, blood pressure.
Figure 3: Initial treatment of anaphylaxis

1. Ensure a written emergency protocol for recognition and treatment of anaphylaxis with a regular rehearsal.

2. Remove exposure to the trigger if possible, e.g. discontinue an intravenous diagnostic or therapeutic agent that seems to be triggering symptoms.

3. Perform steps 4, 5 and 6 promptly and simultaneously.

4. Call for help: resuscitation team (hospital) or emergency medical services (community) if available.

5. Inject epinephrine (adrenaline) (0.01 mg/kg of a 1:1,000 [1 mg/mL] solution) intramuscularly in the mid-anterolateral aspect of the thigh. The maximum dose is 0.5 mg for an adult and 0.3 mg for a child. The time of the dose to be recorded. Dose to be repeated in 5–15 minutes, if required. Majority of the patients respond to 1 or 2 doses.

6. Place the patient on the back or in a comfortable position in case of respiratory distress and/or vomiting. Elevate the lower extremities. If the patient stands or sits suddenly, fatality can occur within seconds.

7. Give high-flow supplemental oxygen when indicated (6-8 L/minute), by face mask or oropharyngeal airway.

8. Establish intravenous access using needles or catheters using wide-bore cannulae (14 - 16 gauges). Give 1–2 litres of isotonic (0.9%) saline rapidly (e.g. 5-10 ml/kg in the first 5-10 minutes to an adult; 10 ml/kg to a child) when indicated.

9. Perform cardiopulmonary resuscitation at any time when indicated, with continuous chest compressions and rescue breathing.

10. Patient’s BP, cardiac rate and function, respiratory status, and oxygenation to be monitored at frequent, regular interval (continuous monitoring is suggested if possible).
specificity. Application of these guidelines in epidemiological studies significantly improved the identification of patients with anaphylaxis. Based on newer evidence, in 2012 update, identification of tissue mast cells, by staining for immune histochemical markers such as CD117 was proposed to facilitate post-mortem diagnosis of anaphylaxis.

**Management of anaphylaxis in health care settings**

Initial treatment of anaphylaxis proposed in 2011 guidelines is summarised in Figure 3. Development and implementation of an anaphylaxis protocol significantly improved the rate of epinephrine administration, the rate of admission to an observation unit and the duration of observation in the unit in paediatric population with no epinephrine-associated adverse events.

**Management at the time of discharge from health care settings**

The WAO guidelines released in 2011 have provided recommendations for the prevention and treatment of anaphylaxis recurrences at the time of discharge from health care settings. However, information on preparation for self-treatment in the community, confirmation of the anaphylaxis triggers, allergen avoidance and immune modulation was updated in 2012.

- Novel investigations on the treatment of anaphylaxis recurrences have provided additional support to the recommendation that patients should be taught how to recognise the signs and symptoms of anaphylaxis and how to use self-injectable epinephrine.
- The role of allergy/immunology specialists in the identification of clinically relevant allergen triggers by performing and interpreting skin tests and measuring specific IgE levels has been emphasised in this update.
- Strict avoidance of the causative allergens such as implicated food, medication and cross-reacting substances is recommended.
- New strategies for immune modulation to prevent food- and venom-induced anaphylaxis have been described.

To summarise, the evidence-based recommendations for assessment, management and prevention of anaphylaxis made in the 2011 WAO Anaphylaxis Guidelines were supported by the subsequently published research reviewed in this 2012 update.

**Reference:**