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# Allergy

# NEWSLETTER

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Worldwide, anaphylaxis definitions in common use are: "a serious, life-threatening generalized or systemic hypersensitivity reaction" and "a serious allergic reaction that is rapid in onset and might cause death." The true global rate of occurrence of anaphylaxis from all triggers in the general population is unknown because of under-recognition by patients and caregivers and under-diagnosis by healthcare professionals. In addition, under-reporting, use of a variety of case definitions, use of different measures of occurrence such as incidence or prevalence, and under-coding are problematic in many epidemiologic studies. Despite this, anaphylaxis is not rare and the rate of occurrence appears to be increasing, although there are geographic variations. Lifetime prevalence based on international studies is estimated at 0.05–2%.

The evidence base for the assessment and management of patients with anaphylaxis is weak in comparison to, for example, the evidence base for the assessment and management of patients with asthma or allergic rhinitis. It is likely to remain so in the absence of randomized, controlled studies of therapeutic interventions performed during an anaphylactic episode.

## WAO ANAPHYLAXIS GUIDELINES DEVELOPMENT

TheWAOis an international federation of 84 regional and national allergy and clinical immunology societies dedicated to raising awareness and advancing excellence in clinical care, research, education, and training in allergy and clinical immunology. The WAO Anaphylaxis Guidelines were created in response to absence of global guidelines for anaphylaxis.

### Methods

The Guidelines were developed by the Anaphylaxis Special Committee that was appointed by the WAO President in 2007. They are based on the best evidence available, in the absence of randomized, controlled trials with which to answer most clinical questions relevant to anaphylaxis. In determining what is essential and what is not, the Committee drew extensively on the findings of the WAO Survey of Essentials for Assessment and Management of Anaphylaxis.

## ASSESSMENT OF PATIENTS WITH ANAPHYLAXIS

The diagnosis of anaphylaxis is based on clinical findings (Table 1). In this section of the Guidelines, we review patient risk factors for severe or fatal anaphylaxis, other co-factors that amplify anaphylaxis, triggers, the importance of the clinical diagnosis, the use of laboratory tests, and the differential diagnosis.

- Patient Risk Factors for Severe or Fatal
- Anaphylaxis and Co-Factors that
- Amplify Anaphylaxis

Many of the patient factors that increase the risk of severe or fatal anaphylactic episodes are similar worldwide. They include age-related factors, concomitant diseases such as asthma and other chronic respiratory diseases, cardiovascular diseases, mastocytosis or clonal mast

TABLE 1. Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING:
   A) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   B) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg. hypotonia [collapse], syncope, incontinence) OR

2. Two or more of the following that occur rapidly after exposure to a likely allergena for that patient (minutes to several hours)

   A) Involvement of the skin-mucosal tissue (eg, generalized urticaria, itch-flush, swollen lips-tongue-uvula)
   B) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   C) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   D) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) OR

3. Reduced blood pressure after exposure to known allergenb for that patient (minutes to several hours)

   A) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressurec
   B) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

### Triggers of Anaphylaxis

The relative importance of specific anaphylaxis triggers in different age groups appears to be universal. Foods are the most common trigger in children, teens and young adults. Insect stings and medications are relatively common triggers in middle-aged and elderly adults; in these age groups, idiopathic anaphylaxis, a diagnosis of exclusion, is also relatively common.

### The Importance of the Clinical Diagnosis

The diagnosis of anaphylaxis is based primarily on a detailed history of the episode, including information about all exposures and events in the hours preceding the onset of symptoms, for example, exercise, ingestion

of prescription, nonprescription and recreational drugs, ethanol, acute infection such as a cold, emotional stress, travel or other disruption of routine and premenstrual status in females. The key to diagnosis involves pattern recognition: sudden onset of characteristic symptoms and signs within minutes to hours after exposure to a known or potential trigger, often followed by rapid progression of symptoms and signs over hours.

Target organ involvement is variable. Typically, symptoms occur in 2 or more body systems: skin and mucous membranes, upper and lower respiratory tract, gastrointestinal tract, cardiovascular system and central nervous system. In certain circumstances, anaphylaxis can be diagnosed when only one body system is involved; for example, after an insect sting, sudden onset of cardiovascular symptoms might be the only manifestations, and after allergen immunotherapy, sudden onset of generalized urticaria might be the only initial manifestation.

Characteristic symptoms and signs of anaphylaxis are listed in Table 2.

TABLE 2. Symptoms and Signs of Anaphylaxis

| |
|---|
| Skin, subcutaneous tissue, and mucosa |
| Flushing, itching, urticaria (hives), angioedema, morbilliform rash, pilor erection |
| Periorbital itching, erythema and edema, conjunctival erythema, tearing |
| Itching of lips, tongue, palate, and external auditory canals; and swelling of lips, tongue, and uvula |
| Itching of genitalia, palms, and soles |
| Respiratorya |
| Nasal itching, congestion, rhinorrhea, sneezing |
| Throat itching and tightness, dysphonia, hoarseness, stridor, dry staccato cough |
| Lower airways: increased respiratory rate, shortness of breath, chest tightness, deep cough, wheezing/bronchospasm, decreased peak expiratory flow |
| Cyanosis |
| Cyanosis |
| Respiratory arrest |
| Gastrointestinal |
| Abdominal pain, nausea, vomiting (stringy mucus), diarrhea, dysphagia |
| Cardiovascular systema |
| Chest pain |
| Tachycardia, bradycardia (less common), other arrhythmias, palpitations |
| Hypotension, feeling faint, urinary or fecal incontinence, shock |
| Cardiac arrest |
| Central nervous system |
| Aura of impending doom, uneasiness (in infants and children, sudden behavioral change, eg. irritability, cessation of play, clinging to parent); throbbing |
| headache (pre-epinephrine), altered mental status, dizziness, confusion, tunnel vision |
| Other |
| Metallic taste in the mouth |
| Cramps and bleeding due to uterine contractions in females |

**Vulnerable Patients**

Anaphylaxis in pregnancy places both mother and baby at increased risk of fatality or hypoxic/ischemic encephalopathy. During the first, second, and third trimesters, potential triggers are similar to those in nonpregnant women. During labor and delivery, anaphylaxis is usually triggered by iatrogenic interventions such as oxytocin or more commonly, an antimicrobial such as a penicillin or a cephalosporin administered to the mother for prophylaxis of group B hemolytic streptococcal infection in the neonate.

In infancy, anaphylaxis can be difficult to recognize. Infants cannot describe their symptoms. Some of the signs of anaphylaxis are also normal daily occurrences in babies; for example, flushing and dysphonia after crying, spitting up after feeding and incontinence. Healthy infants have a lower blood pressure and a higher resting heart rate than older children and adults do; therefore, age-appropriate criteria should be used for documenting hypotension and tachycardia (Table 1).

Teens are vulnerable to anaphylaxis recurrences in the community because of risk-taking behaviors such as failure to avoid their trigger(s) and failure to carry selfinjectable epinephrine.

Middle-aged and elderly patients are at increased risk of severe or fatal anaphylaxis because of known or subclinical cardiovascular diseases and the medications used to treat them.

**Role of Laboratory Tests**

Blood samples for measurement of tryptase levels are optimally obtained 15 minutes to 3 hours after symptom onset. Blood samples for measurement of histamine levels are optimally obtained 15–60 minutes after symptom onset. These tests are not universally available, not performed on an emergency basis and not specific for anaphylaxis.

Increased serum tryptase levels often support the clinical diagnosis of anaphylaxis from insect stings or injected medications and in patients who are hypotensive; however, levels are often within normal limits in patients with anaphylaxis triggered by food and in those who are normotensive.

Serial measurement of tryptase levels during an anaphylactic episode, and measurement of a baseline level after recovery are reported to be more useful than measurement at only one point in time. Normal levels of either tryptase or histamine do not rule out the clinical diagnosis of anaphylaxis. Blood tests for other biomarkers, such as PAF and carboxypeptidase A3 remain experimental.

**Differential Diagnosis**

In anaphylaxis, some of the most common diagnostic dilemmas involve acute asthma, syncope, and

anxiety/panic attacks. A severe asthma episode can cause diagnostic confusion because wheezing, coughing, and shortness of breath can occur in both asthma and anaphylaxis; however, itching, urticaria, angioedema, abdominal pain and hypotension are unlikely in acute asthma.

## MANAGEMENT OF ANAPHYLAXIS IN A HEALTH-CARE SETTING

Anaphylaxis is a medical emergency. Prompt assessment and management are critically important. In this section of the Guidelines, we discuss a systematic approach to the basic initial management of anaphylaxis, emphasizing the primary role of epinephrine in treatment. We discuss the importance of having an emergency protocol, removing exposure to the trigger if possible, assessing the patient rapidly, simultaneously calling for assistance, injecting epinephrine intramuscularly and positioning the patient appropriately. We review the initial management of respiratory distress and of hypotension and shock. We describe use of second-line medications such as antihistamines, beta-2 adrenergic ago-nists and glucocorticoids. We also discuss management of anaphylaxis refractory to basic initial treatment, management of anaphylaxis in vulnerable patients and duration of monitoring in a healthcare setting.

### Systematic Approach to Anaphylaxis Treatment

A systematic approach is critically important. The principles of treatment apply to all patients with anaphylaxis, from all triggers, who present at any time during an acute episode. Basic initial treatment (what all healthcare professionals should be able to provide, even in a low resource environment, is outlined in (Table 3). Preparation involves having a written emergency protocol, posting it, and rehearsing it regularly. Throughout these Guidelines, a child is defined as a prepubertal patient weighing less than 35– 40 kg, rather than by age.

### Epinephrine (Adrenaline): Evidence-Base for Use as First-Line Treatment

The World Health Organization (www.who.int) classifies epinephrine (adrenaline) as an essential medication for the treatment of anaphylaxis. Previous WAO publications and anaphylaxis guidelines published in indexed, peer-reviewed journals consistently emphasize prompt injection of epinephrine as the first-line medication of choice in anaphylaxis.

Epinephrine is life-saving because of its alpha-1 adrenergic vasoconstrictor effects in most body organ systems (skeletal muscle is an important exception) and its ability to prevent and relieve airway obstruction caused by mucosal edema, and to prevent and relieve hypotension and shock.

The evidence base for prompt epinephrine injection in the initial treatment of anaphylaxis is stronger than the evidence base for the use of antihistamines and glucocorticoids in anaphylaxis. It consists of: observational studies performed in anaphylaxis, randomized, controlled clinical pharmacology studies in patients at risk for anaphylaxis but not experiencing it at patients at risk for anaphylaxis but not experiencing it at the time of the investigation, studies in animal models of anaphylaxis, in vitro studies, and retrospective studies, including epidemiologic studies and fatality studies. The latter provide particularly compelling evidence for prompt epinephrine injection. For example, in one study, only 14% of 164 people with fatal anaphylaxis had received epinephrine before cardiorespiratory arrest. The median times to cardiorespiratory arrest were minutes after administration of a diagnostic or therapeutic intervention, minutes after an insect sting, and 30 minutes after food ingestion.

#### *Epinephrine Dosing and Route of Administration*

Epinephrine should be injected by the intramuscular route in the mid-anterolateral thigh as soon as anaphylaxis is diagnosed or strongly suspected, in a dose of 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution, to a maximum of 0.5 mg in adults (0.3 mg in children). This achieves peak plasma and tissue concentrations rapidly. Depending on the severity of the episode and the response to the initial injection, the dose can be repeated every minutes, as needed. Most patients respond to 1 or 2 doses of epinephrine injected intramuscularly promptly; however, more than 2 doses are occasionally required.

Epinephrine is under-used in anaphylaxis treatment. Failure to inject it promptly is potentially associated with fatality, encephalopathy because of hypoxia and/or ischemia, and biphasic anaphylaxis in which symptoms recur within hours (usually within 8 –10 hours) after the initial symptoms have resolved, despite no further exposure to the trigger.

Epinephrine in a dose of 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution injected promptly by the intramuscular route is effective and safe in the initial treatment of anaphylaxis. In other anaphylaxis scenarios,this low first-aid dose is unlikely to be effective. For example, if shock is imminent or has already developed, epinephrine needs to be given by slow intravenous infusion, ideally with the dose titrated according to noninvasive continuous monitoring of cardiac rate and function. If cardiac arrest is imminent or has already occurred, an intravenous bolus dose of epinephrine is indicated; however, in other anaphylaxis scenarios, this route of administration should be avoided, for the reasons listed below.

#### *Advers e Effects of Epinephrine*

Transient pharmacologic effects after a recommended dose of epinephrine by any route of administration include pallor, tremor, anxiety, palpitations, dizziness

TABLE 3. Basic Management of Anaphylaxis

Preliminary Steps

1) Have a posted, written emergency protocol for recognition and treatment of anaphylaxis and rehearse the protocol regularly

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

3) Assess circulation, airway, breathing, mental status, skin, and body weight (mass)

Promptly and simultaneously

4) Call for help (resuscitation team in hospital or other healthcare setting, or emergency medical services in community setting), if available

5) Inject epinephrine (adrenaline) intramuscularly in the mid-anterolateral aspect of the thigh, 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution, to a maximum of 0.5 mg (adult) or 0.3 mg (child); record the time of the dose and repeat it in 5–15 minutes, if needed; most patients respond to 1 or 2 doses

6) Place patient on the back, or in a position of comfort if there is respiratory distress and/or vomiting; elevate the lower extremities; fatality can occur within seconds if a patient stands or sits suddenly

When indicated at any time during the episode

7) Give high flow supplemental oxygen (6-8 L/min) by face mask or oropharyngeal airway

8) Establish intravenous access using needles or catheters with wide-bore cannulae (14 or 16 gauge for adults). When indicated, give 1-2 litres of 0.9% (isotonic) saline rapidly. (eg. 5–10 mL/kg in the first 5–10 minutes to an adult; or 10 mL/kg to a child)

9) When indicated at any time, prepare to initiate cardiopulmonary resuscitation with continuous chest compressions.

In addition

10) At frequent and regular intervals, monitor patient's blood pressure, cardiac rate and function, respiratory status and oxygenation and obtain electrocardiograms; start continuous non-invasive monitoring, if possible

and headache. These symptoms indicate that a therapeutic dose has been given. Serious adverse effects such as ventricular arrhythmias, hypertensive crisis and pulmonary edema potentially occur after an overdose of epinephrine by any route of administration.

***Epinephrine and the Heart***

The heart is a potential target organ in anaphylaxis. ACS can occur in anaphylaxis in the absence of epinephrine injection in patients with known coronary artery disease, and those in whom subclinical coronary artery disease is unmasked by the anaphylactic episode. ACS can also occur in those of any age, including children, who have no cardiovascular abnormalities as determined by electrocardiogram and echocardiography after complete recovery from the anaphylactic episode in which the ACS developed. Although caution is necessary and dosing errors need to be avoided, epinephrine is not contraindicated in the treatment of anaphylaxis in patients with known or suspected cardiovascular disease, or in middleged or elderly patients without any history of coronary artery disease who are at increased risk of ACS only because of their age.40,97 Through its beta-1 adrenergic effects, epinephrine actually increases coronary artery blood flow because of an increase in myocardial contractility and in the duration of diastole relative to systole. Concerns about the potential adverse cardiac effects of epinephrine therefore need to be weighed against concerns about the cardiac 8 of untreated anaphylaxis.

- Positioning the Patient
- Management of Respiratory Distress
- Management of Hypotension and Shock
- Second-Line Medications
- $H_1$-Antihistamines
- Beta-2 Adrenergic Agonists
- Glucocorticoids
- $H_2$-Antihistamines

**Treatment**

A minority of patients do not respond to timely, basic initial anaphylaxis treatment with epinephrine by intramuscular injection(s), positioning on the back with lower extremities elevated, supplemental oxygen, intravenous fluid resuscitation, and second-line medications. If possible, such patients should be transferred promptly to the care of a specialist team in emergency medicine, critical care medicine, or anesthesiology. These physicians, nurses and technicians are typically trained, experienced and equipped to provide skilled management of the airway and mechanical ventilation and to provide optimal shock management by safely administering vasopressors through an infusion pump with frequent dose titration based on continuous noninvasive monitoring of cardiovascular and respiratory outcomes.

Anaphylaxis education should be personalized according to the needs of the individual patient, taking into consideration their age, concomitant diseases, concurrent medications, relevant anaphylaxis trigger(s), and likelihood of encountering such trigger(s) in the community.

***Ref:* 1.** *Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004;113:832– 836.*

**2.** *Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report: Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol. 2006;117:391–397.*

**3.** *Simons FER, for the World Allergy Organization. World Allergy Organization survey on global availability of essentials for the assessment and management of anaphylaxis by allergy/immunology specialists in healthcare settings. Ann Allergy Asthma Immunol. 2010;104: 405–412.*

According to the World Allergy Organization, allergic disorders affect 30–40% of the world's population and the prevalence is escalating to epidemic proportions. Much of the pathology of chronic allergic disorders such as atopic dermatitis and asthma is the long-term result of chronic allergic inflammation at the site of allergen exposure. Thus, to explore additional possibilities to treat chronic allergic disorders, it is of importance to understand the distinct pathomechanisms and properties of chronic inflammation.

Inflammation in general is the response of tissues to harmful stimuli such as infectious agents, antigens or physical and chemical damage. Besides the increased inflammatorycell infiltration into the inflamed tissue, it has become clear in the recent years that acute and chronic inflammatory processes are associated with pronounced vascular remodeling. Angiogenesis and lymphangiogenesis, the growth of new blood vessels and of lymphatic vessels from preexisting ones, are involved in a number of physiological and pathological conditions such as wound healing, tumor growth and metastatic spread. Angiogenesis and lymphangiogenesis also occur in several chronic inflammatory conditions, including rheumatoid arthritis, inflammatory bowel disease, asthma, chronic airway inflammation, atopic dermatitis, and psoriasis.

**The Function of Blood Vessels and Lymphatic Vessels in Tissue Homeostasis**

In vertebrates, there are two vascular systems: the cardiovascular and the lymphatic system. To exert their functions, both vascular systems build highly branched, tree-like tubular structures. In the cardiovascular system, the heart pumps the blood through arteries into smaller arterioles and into capillary beds. From there, the blood returns via venules and veins to the heart to proceed to the lungs for new oxygen loading. Under physiological conditions, the major functions of blood vessels include the supply of gases, fluid, nutrition and signaling molecules to the tissues with the capillaries as the actual sites of exchange. At these sites, plasma leaks from the capillaries into the interstitium, driven by blood pressure and osmotic gradients. The lymphatic capillaries take up this protein-rich fluid, thereby maintaining not only tissue fluid homeostasis but also exerting immune surveillance. The lymphatic network is composed of blindbeginning thin-walled capillaries without pericyte coverage and with incomplete basal lamina as well as of collecting lymphatic vessels with a smooth muscle cell layer, a basement membrane and valves, which prevent back flow of lymph. The largest collecting lymphatic vessel, the thoracic duct, connects the lymphatic system with the cardiovascular system. In adults, physiological angiogenesis and lymphangiogenesis are uncommon. However, new lymphatic and blood vessels form during the female reproductive cycle, the hair cycle and in healing wounds.

**Anatomy of the Cutaneous and Pulmonary Vascular Systems**

The epidermal layer of the skin is free of blood and lymphatic vessels. In the dermis, the blood vascular system is organized into a deep and a superficial horizontal plexus with capillaries arising from the latter one. The lymphatic vasculature also forms two plexuses in vicinity to the blood vessels. Branches from the superficial lymphatic vessel plexus extend into the dermal papillae and descend into the larger lymphatic vessels in the lower dermis. The bulk of blood microvascular vessels is located immediately below the epidermis, whereas the lymphatic vessels reside more distant to the epidermis.

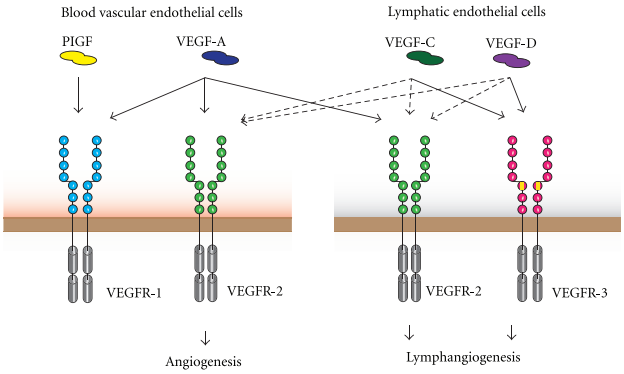
**The Role of Blood and Lymphatic Vessels in inflammation**

Both the blood and the lymphatic vascular system contribute to the body's inflammatory response. In acute inflammation, blood vascular endothelial cells are activated by several inflammatory mediators (e.g., vascular endothelial growth factor- (VEGF-)A, tumor necrosis factor (TNF-), interleukin (IL)-6, and IL-1), leading to the typical signs of inflammation, increased blood flow as a consequence of vessel dilation and edema formation due to increased permeability of the blood vessels. Furthermore, the expression of adhesion molecules, such as intercellular adhesion molecule- (ICAM-)1 vascular cell adhesion molecule- (VCAM-)1 and E-selectin on activated blood vascular endothelial cells, enables the interaction between leukocytes and endothelium, a major event in the inflammatory process. In chronic inflammation, the blood vasculature remains enlarged, hyperpermeable and activated with high expression of adhesion molecules, leading to continuous extravasation of inflammatory cells and fluid into the inflamed tissue. A number of inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, asthma, atopic dermatitis and psoriasis are characterized by pronounced angiogenesis. Besides the blood vasculature, also the lymphatic vasculature plays an important role in inflammation.

**Mediators of Angiogenesis and Lymphangiogenesis in inflammation**

In recent years, the understanding of inflammatory angiogenic and lymphangiogenic processes such as endothelial cell growth, migration and survival has increased and a variety of involved mediators have been

identified. The most important molecule that controls inflammation-driven angiogenesis is VEGF-A, a member of a family of angiogenic and lymphangiogenic drivers such as VEGF-C, VEGF-D and placenta growth factor (PlGF). VEGF-A signals via its receptor tyrosine kinases VEGFR-1 and VEGFR-2 and thereby induces angiogenesis and lymphangiogenesis.




**Blood and Lymphatic Vessels in Chronic skin inflammation**

Several skin diseases such as atopic dermatitis, contact dermatitis, UV damage, and psoriasis are associated with increased vascular remodeling . In the lesional skin of atopic dermatitis and psoriasis, levels of the angiogenic growth factor VEGF-A are elevated and in psoriasis patients, the plasma levels of VEGF-A correlate positively with the disease severity . In recent years, a number of mouse models have been developed to study vascular remodeling in chronic skin inflammation, for example, the epidermal specific JunB/CJun knockout mice, human psoriatic skin transplantation onto severe combined immunodeficiency- (SCID-)mice and K14 (keratin14) VEGF-A transgenic micewhich have been developed in our laboratory. In these mice, murine VEGF-A164 is continuously expressed in epidermal keratinocytes under the control of the K14 promoter. Mice homozygous for this transgene develop a chronic cutaneous inflammation at the age of approximately 5-6 months, which has most of the features of human psoriasis, namely epidermal hyperplasia and abnormal terminal differentiation of epidermal keratinocytes, typical leukocyte infiltration including dermal CD4+ T cell and epidermal CD8+ T-cell accumulation as well as a pronounced increase in the number and size of blood and lymphatic vessels. In hemizygous K14-VEGF-A transgenic mice, the chronic skin inflammation is inducible by applying the contact sensitizer oxazolone.

**Blood Vessels in Asthma**

Asthma is a chronic inflammatory disease of the airways that is characterized by airway hyperresponsiveness, episodic airflow limitations and a decline in lung function. These symptoms are caused by chronic inflammation and airway remodeling, including increased thickness of the lamina reticularis, smooth muscle hyperplasia/hypertrophy and increased vascularity in small and large airways.

McDonald and colleagues established the *Mycoplasma pulmonis* infection model of chronic airway inflammation as a valuable tool for investigation of chronic inflammatory airway diseases in mice. This model shows several-though not all—characteristic features of asthma such as inflammatory cell influx, angiogenesis, mucosal edema, epithelial changes, fibrosis and bronchial hyperreactivity. Shortly after *M. pulmonis* infection, mucosal blood vessels enlarge by endothelial cell proliferation and angiogenesis reaches a plateau at 14 days after infection. Surprisingly, VEGF receptor blocking studies showed that this pathological angiogenesis might not be driven by VEGF-A. However, blocking of TNF signaling by an anti-TNF antibody dramatically reduced blood vessel remodeling 14 days after *M. pulmonis* infection, suggesting that TNF signaling is involved in this angiogenic process.

**Lymphatic Vessels in Chronic Airway Disease**

Edema formation results when the amount of leakage from the blood vessels exceeds the capacity of lymphatic vessels for drainage. Such edemas are a cardinal sign of chronic inflammation, and indeed increased microvascular permeability as well as edema are features of asthma. However, knowledge of lymphatic involvement in edema formation in asthma is remarkably sparse. In the M. pulmonis driven mouse model of chronic airway inflammation, there is also a dramatic remodeling of lymphatic vessels. In contrast, adenoviral overexpression of VEGF-C in the murine trachea leads to enhanced lymphatic filopodia formation and to sprouts similar to those seen in the *M. pulmonis* infected mice.

**Conclusions and Outlook**

There is clear evidence that in humans, vascular remodeling occurs in many chronic inflammatory disorders. Even though different anti-inflammatory drugs are on the market, there is no specific therapy that interferes with the pathological vascular changes that occur during inflammation. Angiogenesis and lymphangiogenesis are tightly linked to chronic inflammation, and targeting the blood vessels and lymphatic vessels has been shown to be an effective strategy in different experimental mouse models of chronic inflammation. Nonetheless, antiangiogenic and prolymphangiogenic therapies might represent new approaches to treat chronic inflammatory disorders, including those due to chronic allergic inflammation.

*Ref: S. J. Galli, M. Tsai, and A. M. Piliponsky, "The development of allergic inflammation," Nature, vol. 454, no. 7203, pp. 445–454, 2008.*

## Congratulations!

The winner of **Allergy** NEWSLETTER

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2. **Dr. Md. Atiquel Islam Chowdhury**, MBBS, MCPS, FCPS (Medicine), Medicine specialist, Assistant Professor, Dept. of Medicine, USTC.
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5. **Dr. Hasan Zafar Rifat**, MBBS, MS (ENT), Consultant, ENT, Labaid centre, Jail road, B. Baria.



**Dear Doctor**

We are happy to present you the "Allergy News Letter" Vol. 02 No. 1. In this issue we have concentrated on "World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis" and "An Important Role of Blood and Lymphatic Vessels in Inflammation and Allergy". We hope you will enjoy reading the publication!

We appreciate your comments and queries.

Please participate in Quiz competition & win prizes.