World Allergy Congress 2007 Symposium

2-6 December 2007
Bangkok, Thailand

‘Global Issues in Allergy: Answers for a Worldwide Problem’

Allergic Emergencies

Sunday, November 12, 8:30 a.m. – 10:00 a.m.
Pennsylvania Convention Center, Ballroom AB
ACAAI Annual Scientific Meeting
Philadelphia, Pennsylvania, USA

Sponsored by the

WAO
WORLD ALLERGY ORGANIZATION

WORLD ALLERGY FORUM
A PROGRAM OF THE WORLD ALLERGY ORGANIZATION

Programmed by the
ACAAI American College of Allergy, Asthma & Immunology

Supported through unrestricted educational grants from

Genentech
You Are Invited to Attend

A Global Perspective on Genetics, the Environment and Allergy

AAAAI Annual Scientific Meeting
Monday, February 26, 2007
4:45 p.m. - 6:00 p.m.
San Diego, CA, USA

Moderators:
Thomas A. E. Platts-Mills
Michael A. Kaliner

Is Early Exposure to Allergen Protective?
Adnan Custovic

How Does the Environment Influence Genetic Responses?
Robert F. Lemanske Jr.

Environmental Intervention in the Management of Allergic Diseases
Erika Von Mutius

Supported through an unrestricted education grant from

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‘Global Issues in Allergy: Answers for a Worldwide Problem’

Allergic Emergencies

Moderator:
Michael A. Kaliner, Institute for Asthma and Allergy
Wheaton, Maryland, USA

1. Welcome to the WAC 2007 Symposium and Introduction to “Allergic Emergencies”
Michael A. Kaliner, Institute for Asthma and Allergy
Wheaton, Maryland, USA

2. Acute and Severe Asthma
Bobby Q. Lanier, North Texas Institute for Clinical Trials
Fort Worth, Texas, USA

3. Anaphylaxis: Causes and Treatments
Ruby Pawankar, Nippon Medical School
Tokyo, Japan

4. Angioedema
Michael A. Kaliner, Institute for Asthma and Allergy
Wheaton, Maryland, USA

Acknowledgement:
The Anaphylaxis and Angioedema presentations are based on the WAO GLORIA™ program modules authored by:

Michael A. Kaliner, Anaphylaxis
Allen P. Kaplan, Angioedema
Connie H. Katelaris, Angioedema
Bobby Q. Lanier, Anaphylaxis
Richard F. Lockey, Anaphylaxis
Cassim Motala, Anaphylaxis
F. Estelle R. Simons, Anaphylaxis

Upon completion of this program, participants will be able to:

• Recognize the signs and symptoms of impending respiratory arrest
• Classify by clinical phenotypes the severity of chronic severe asthma
• Integrate international guidelines of classification with therapeutic implications

• Discuss the different mechanisms that underlie anaphylaxis and the agents most likely to cause it
• Recognize the signs and symptoms of anaphylaxis
• Describe the principles of the emergency treatment of anaphylaxis

• Outline the major causes and differential diagnosis of angioedema and hereditary angioedema
• Explain the treatment options for the management of hereditary and acquired angioedemas
About the World Allergy Organization

World Allergy Organization (WAO)
The World Allergy Organization (WAO) is an international umbrella organization of 74 regional and national allergy and clinical immunology societies. By collaborating with member societies, WAO provides direct educational outreach programs, symposia and lectureships to WAO individual members around the globe.

The World Allergy Organization Mission
WAO's mission is to be a global resource and advocate in the field of allergy, advancing excellence in clinical care, education, research and training through a worldwide alliance of allergy and clinical immunology societies.

Programs of the World Allergy Organization

GLORIA Global Resources in Allergy™
The GLORIA program promotes good practice in the management of allergic diseases through programs developed by panels of world experts. GLORIA educates medical professionals worldwide through regional and national presentations and local training initiatives. GLORIA educational modules promote the World Allergy Organization's (WAO) mission – to optimize allergy care worldwide.

GLORIA Modules
Module 1: Allergic Rhinitis and Allergic Conjunctivitis
Module 2: Allergic Conjunctivitis (Expanded Version)
Module 3: Allergic Emergencies
Module 4: Immunotherapy
Module 5: Symptoms and Treatment of Asthma
Module 6: Food Allergy
Module 7: Angioedema
Module 8: Anaphylaxis
Module 9: Diagnosis of IgE Sensitization

World Allergy Forum (WAF) symposia are held at major international allergy meetings. Developed by international expert advisory panels, the symposia provide up-to-the-minute presentations on scientific and clinical developments in the field of allergic disease.

PAAA: Prevention of Allergy and Allergic Asthma
Prevention of Allergy and Allergic Asthma (PAAA) is a collaborative project with the World Health Organization providing guidelines and recommendations for prevention of the allergen-specific immunological sensitization necessary for disease.

Emerging Societies Program
WAO offers advice on initiating and developing allergy societies throughout the world. This proactive initiative aims to expand and improve the specialty of allergy by supporting colleagues working in the field of allergy worldwide. Through sharing practical experiences and alerting new societies to the criteria required for WAO membership, ESM creates relationships with future World Allergy Organization member societies, and educates WAO’s leadership about the challenges and opportunities faced by colleagues in developing countries.

WAO Journals
ACI-International – Journal of the World Allergy Organization (ACII - JWAO) and International Archives of Allergy and Immunology

Read the latest in global allergy and asthma news and research through subscriptions to WAO’s journal partners: ACI International - Journal of the World Allergy Organization (ACII - JWAO) and International Archives of Allergy and Immunology.
### National Member Societies

- Albanian Society of Allergology and Clinical Immunology
- American Academy of Allergy, Asthma and Immunology
- American College of Allergy, Asthma and Immunology
- Argentine Association of Allergy and Immunology
- Argentine Society of Allergy and Immunopathology
- Australasian Society of Clinical Immunology and Allergy
- Austrian Society of Allergology and Immunology
- Azerbaijan Society for Asthma, Allergy and Clinical Immunology
- Bangladeshi Society of Allergy and Immunology
- Belgian Society of Allergy and Immunology
- Brazilian Society of Allergy and Immunopathology
- British Society for Allergy and Clinical Immunology
- Bulgarian National Society of Allergology
- Canadian Society of Allergy and Clinical Immunology
- Chilean Society of Allergy and Immunology
- China Allergology Society and Chinese Allergists
- Chinese Hong Kong Institute of Allergy
- Colombian Allergy, Asthma and Immunology Association
- Croatian Society of Allergology and Clinical Immunology
- Cuban Society of Allergology
- Danish Society of Allergology
- Ecuadorian Society of Allergy and Immunology
- Egyptian Society of Allergy and Clinical Immunology
- Finnish Society of Allergology and Clinical Immunology
- French Society of Allergology and Clinical Immunology
- German Society for Allergy and Clinical Immunology
- Georgian Association of Allergology and Clinical Immunology
- Hellenic Society of Allergology and Clinical Immunology
- Hungarian Society of Allergology and Clinical Immunology
- Icelandic Society of Allergy and Clinical Immunology
- Indian College of Allergy, Asthma and Applied Immunology
- Indonesian Society for Allergy and Immunology
- Israel Society of Allergy and Clinical Immunology
- Italian Society for Allergology and Clinical Immunology
- Japanese Society of Allergology
- Korean Academy of Allergy, Asthma and Clinical Immunology
- Lebanese Society of Allergy and Immunology
- Malaysian Society of Allergy and Immunology
- Mexican College of Pediatricians Specialized in Allergy and Clinical Immunology
- Mexican College of Allergy, Asthma and Clinical Immunology
- Mongolian Society of Allergology
- Netherlands Society of Allergology
- Norwegian Society of Allergology and Immunopathology
- Paraguayan Society of Immunology and Allergy
- Peruvian Society of Allergy and Immunology
- Philippine Society of Allergy, Asthma and Immunology
- Polish Society of Allergology
- Portuguese Society of Allergology and Clinical Immunology
- Romanian Society of Allergology and Clinical Immunology
- Russian Association of Allergology and Clinical Immunology
- Allergy Society of South Africa
- Singapore Society of Immunology, Allergy & Rheumatology
- Spanish Society of Allergology and Clinical Immunology
- Swedish Association for Allergology
- Swiss Society for Allergology and Immunology
- Allergy and Immunology Society of Thailand
- Turkish National Society of Allergy and Clinical Immunology
- Ukrainian Association of Allergologists and Immunology
- Uruguayan Society of Allergology
- Venezuelan Society of Allergy and Immunology
- Vietnam Association of Allergy, Asthma and Clinical Immunology
- Zimbabwe Allergy Society

### Associate Member Societies

- Czech Society of Allergology and Clinical Immunology
- Ecuadorian Society of Allergology and Allied Sciences
- Egyptian Society of Pediatric Allergy and Immunology
- Italian Association of Territorial and Hospital Allergists
- Latvian Association of Allergists
- Panamanian Association of Allergology and Clinical Immunology
- Association of Allergy and Clinical Immunology of Serbia and Montenegro

### Regional Organizations

- The Asian Pacific Association of Allergology and Clinical Immunology
- Commonwealth of Independent States Society of Immunology and Allergology
- European Academy of Allergology and Clinical Immunology
- Latin American Society of Allergy, Asthma and Immunology

### Affiliate Organizations

- International Association of Asthmology

*As of June 2006

For WAO membership information please contact the Secretariat

World Allergy Organization (WAO)
555 East Wells Street, Suite 1100 • Milwaukee, WI 53202-3823 USA
Tel: +1 414 276 1791 • Fax: +1 414 276 3349
e-mail: info@worldallergy.org
Web site: www.worldallergy.org
Dear Colleagues,

Welcome to this 30th Symposium in the World Allergy Forum (WAF) Series, ‘Global Issues in Allergy: Answers for a Worldwide Problem’ - Allergic Emergencies. WAO is delighted to bring you the third WAF Symposium for 2006, giving us the opportunity to offer you a flavor of the World Allergy Congress, to be held in Bangkok, Thailand, 2-6 December 2007.

I am delighted to moderate this session today. Faculty member Bob Lanier is a former President of ACAAI and is now a valued member of the WAO Board of Directors, bringing his many years of clinical and communications expertise to our international membership. Dr. Lanier will speak on an allergic emergency that is a source of major morbidity and mortality worldwide, Acute and Severe Asthma.

Ruby Pawankar is a member of the WAO Board of Directors who brings her years of experience of living and working in the Far East to the WAO table, and who is presently working tirelessly to promote the 2007 World Allergy Congress in that region. Prof. Pawankar’s presentation is derived from the new Global Resources in Allergy (GLORIA™) Module, Anaphylaxis, and offers a global perspective on the incidence and management of this acute allergic emergency.

As President of World Allergy Organization, I have the pleasure to present the third lecture of this Symposium, Angioedema, based on another new GLORIA educational module launched this Fall. Acute laryngeal edema resulting from hereditary C1-esterase inhibitor deficiency or abnormality can give rise to serious complications and fatalities for patients needing to undergo surgical procedures. This presentation reviews the need for accurate diagnosis of the underlying pathology in all angioedema patients, and the acute and long-term management of all forms of angioedema.

The World Allergy Forum is the longest-running educational program of the World Allergy Organization, and we are grateful for the unrestricted educational grant from Novartis and Genentech that enables us to bring you this program today.

I am lucky to preside over WAO at this time; the Organization has become very active in a wide range of activities, the leadership is extremely dynamic, and our position in the world of allergy is firmly established. Over the coming years, we plan a global agenda to strengthen allergy, both for patients and allergists. We plan to make WAO more visible, of greater service to our member societies, and to establish strong and broad partnerships with our national and regional societies. WAO will help local allergists to make the governing bodies aware of the need for allergy and work to create an environment where allergy and asthma sufferers can get access to well-trained physicians.

We continue to serve our members through our educational programming. In a 2006 partnership with the American College of Allergy, Asthma and Immunology (ACAAI), we are implementing an American version of the Global Resources in Allergy program (GLORIA) to provide up to 10 lectures per year to Regional, State and Local allergy societies in the US with the GLORIA lecture modules being presented by WAO and ACAAI lecturers. Applications for the US GLORIA can be submitted by all Regional, State and Local allergy societies wishing for the involvement of WAO at their local meeting. The deadline for submitting applications for placements in 2007 is 30 November 2006; applications can be made online at www.worldallergy.org.

We are actively planning the next World Allergy Congress, which will take place 2-6 December 2007, in Bangkok Thailand. The meeting will have several unique features. It will begin with a day-long international symposium on Immunotherapy cosponsored by WAO, EAACI and AAAAI. The meeting will run for 3 days thereafter, ending with a one day international symposium on Food Allergy, cosponsored by ACAAI and WAO.
A global organization will only be as good as its ability to communicate. Our monthly email newsletter, WAO News and Notes, is designed to keep everyone informed of clinical advances in the field and to provide a ready means of rapid communications. If you are not receiving this free of charge communication, please contact us at www.worldallergy.org and share your email information.

As we look to the future, we recognize that allergy is a rapidly developing and expanding field. The importance of allergy is still underappreciated, and the time when allergy is accepted as an important subspecialty of medicine and pediatrics is still on the horizon. WAO is committed to strengthening allergy through active educational and research partnerships with our 74 member societies. In the end, the many millions of patients with asthma and allergy will benefit as the importance of allergic diseases is recognized and taught more widely.

With best regards,

Michael A. Kaliner
President, World Allergy Organization
Bob Lanier, MD is a practicing allergist and past president of the American College of Allergy, Asthma and Immunology (ACAAI). In addition, he is founder and executive vice president of the Society of Principal Investigators, and medical director of North Texas Institute for Clinical Trials. Dr. Lanier is clinical professor of Pediatrics, University of North Texas Health Science Center.

Dr. Lanier is board certified in Pediatrics and Allergy/Immunology, and he was director of fellowship training at the USAF Wilford Hall Medical Center for pediatric immunology until entering private practice in 1977. He has served as President of the American Association of Certified Allergists, the Texas Medical Association Foundation, and the Tarrant County Medical Association. He has been named a Distinguished Fellow by the ACAAI and a Distinguished Alumnus of Lamar University.

In addition to a long and successful career as a broadcaster on medical topics, Dr. Lanier has served as contributing editor of the Annals of the American College of Allergy, Asthma and Immunology, the John Hopkins Asthma Monitor, and the Proceedings of Allergy and Immunology. He has over 60 contributions in peer reviewed journals as well as textbook chapters in Immunology with emphasis on anti-IgE in allergy.

Abstract

Severe asthma as manifest by the continuous high dose of inhaled corticosteroids, or oral corticosteroids for >50% of the previous year, remains a huge problem despite significant advances in pharmacotherapy. As many as 5-10% of all asthma hospitalizations result in ICU admission, with an overall mortality rate of 0.4%. Hallmarks of severe asthma include polymorphisms in the beta-2 receptor, arginine substitutions at position 16 (Arg/Arg), a female gender, diminished perception of dyspnea, and steroid resistance. A protocol for evaluation and immediate therapy is suggested based on a review of the literature.

References

Acute and Severe Asthma

Definition

Recognition

Management

Definition of severe asthma

- Major (1 or 2)
  - continuous high dose inhaled corticosteroids
  - oral corticosteroids for >50% of the previous year

- Minor (2 or >)
  1. Daily controller
  2. SABA daily
  3. FEV1 < 80%
  4. 1+ Urgent visits
  5. 3 or more steroid "bursts"/yr
  6. Deterioration with ≤25% reduction in oral or inhaled corticosteroid dose.
  7. Near fatal asthma event in the past year

Hallmarks of severe asthma

- Polymorphisms in the beta-2 receptor, arginine substitutions at position 16 (Arg/Arg)
- ~15% Caucasian population ~25% Black
- Severe asthma more common in women
- Diminished perception of dyspnea
- Steroid resistance (dose response shift)
- Late/adult onset asthma
Early and late onset asthma / phenotypes

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Adapted from the work of Sally Wenzel M.D. University of Pittsburgh

How big a problem?

2 million ED visits each year in the United States
2% of all ED visits – in cities asthma up to 10% of all ED visits.
5-10% of all asthma hospitalizations = ICU
0.4% patients succumb
8% mortality in admissions requiring ventilation
10% death after near fatal episode

Take a brief history and perform a rapid physical
Give oxygen and inhaled short-acting beta2 agonist immediately.

Take a more detailed history and do a complete physical examination once therapy has been initiated.

Wheeze is an unreliable indicator of the severity of an asthma attack and may be absent in severe asthma.
Severe Asthma Exacerbations

Natural History
- Most are short-lived - recover in 1-2 hrs of protocol treatment
- More intense the stimulus - longer to resolution
- Differing rates of recovery
- 1/5-1/3 ED patients have poor short term responses to bronchodilators and require admission

Features of a Severe Asthma Exacerbation

One or more present:
- Use of accessory muscles of respiration
- Pulsus paradoxicus >25 mm Hg
- Pulse > 110 BPM
- Inability to speak sentences
- Respiratory rate >25 - 30 breaths/min
- PEFR or FEV1 < 50% predicted
- SaO2 <91 - 92% at sea level

McFadden Am J Respir Crit Care Med 2003

Treatment of Asthma Exacerbations 1

First line therapy- Beta agonists
- Short-acting beta-agonists - SABA’s
- Epinephrine
- Long-acting Beta-agonists - LABAs
Evaluation-Blood Gases

- Typically hypoxemia, hypocapnia and respiratory alkalosis
- Greater severity associated with lower PaO₂
- Resolution of hypoxemia usually slow
- Hypocapnia results from hyperventilation
- Retention is seen in ~10% - usually very low FEV1

Treatment of Asthma Exacerbations 2

SABAs
- Route of administration
  - Inhaled better than systemic
- MDI or spacer just as effective as nebuliser (Cates, Cochrane Nov 2003)
- Degree of improvement is related to how much is given not how it is given
  (Cybulka et al. 2002)
- Optimal dose 5-10mg
- Continuous may be better than intermittent in severe exacerbation

Treatment of Asthma Exacerbations 3
Beta Agonists

- MDI plus spacer, 4-8 puffs Q 20 min x 3
- Nebulizer, 2.5-5 mg albuterol Q 20 min x 3
- Epinephrine SQ, 0.3-0.5ml (0.01 ml/kg children)
- Levalbuterol, 0.63-1.25 mg Q 4-8 hours (if available)
Treatment of Asthma Exacerbations 4
Oral Corticosteroids

- Issues in management
  - No immediate effect
  - Earliest effects 6 hours after high dose
  - May restore epinephrine responses more quickly
  - Use within the first hour reduces admission rate (Rowes et al, Cochrane niv 2006)
  - Route
  - Dose
  - Duration of use
  - Taper or no taper

Treatment of Asthma Exacerbations 5
Corticosteroids

- Oral is as effective as parenteral
- Prednisone (equivalent), 45 – 60 mg
- Methylprednisolone, 1 – 2 mg/kg/24 hours
- Higher doses have increased side effects and no appreciable increased therapeutic benefit

Treatment of Asthma Exacerbations 6

Anticholinergics
ED studies have shown that addition of ipratropium to SABAs reduce hospitalisations and improve lung function (Rodrigo et al 2005)
Treatment of Asthma Exacerbations 7
Anticholinergics

Ipratropium

- Preferred use: combined with beta agonist
- MDI plus spacer, 2 - 4 puffs Q 20 min x 3
- Nebulizer, 500 mcg Q 20 min x 3

Treatment of Asthma Exacerbations 8

Secondary treatment choices

- Methylxanthines-aminophylline or theophylline (oral, parenteral)
- Leukotriene receptor antagonists (oral)
- Oxygen
- Magnesium sulfate

Treatment of Asthma Exacerbations 8
Leukotriene Modifiers

- Montelukast, 10 mg QHS
- Zafirlukast, 20 mg BID, empty stomach
- Zileuton, 600 mg QID

- Intravenous leukotriene montelukast 7 mg IV. may provide bronchodilation within 10 min. Montelukast 10 mg orally may produce an increase in FEV1 in severe asthma exacerbations, in approximately 90 minutes. The role of leukotriene modifiers in acute asthma is an active area of research.
Treatment of Asthma Exacerbations 9
Magnesium Sulfate

- 3 meta-analyses and 1 systematic review - “insufficient evidence for routine use”
- Used in very severe asthma in emergency settings:
  - FEV1 < 25% predicted
  - Other signs of severe disease
- 1.2 - 2 gm IV over 10 - 20 min in 50 ml saline
- Minor side effects

Treatment of Asthma Exacerbations
Inhaled corticosteroids

High dose ICS in the ED
- Examined in 4 RCTs and Cochrane review - Edmonds et al 2001
- Repeated high doses of beclomethasone, flunisolide, fluticasone from 5-18 mg in divided doses over a period of hours
- Early high dose ICS use in ED resulted in reduced admission rates and improved lung function to similar extent as standard courses of IV or oral CS

Treatment of Asthma Exacerbations 10
Aminophylline and Theophylline

In children with severe exacerbation addition to SABAs and corticosteroids improves lung function within 6 hours
- no change in hospitalisation rate
- no change in symptom relief
- three times the risk of vomiting

(Mitra et al Cochrane rev 2005)
Treatment of Asthma Exacerbations 12
Aminophylline and Theophylline

- Loading dose for aminophylline: 5 – 6 mg/kg over 20 - 30 min; adjust dose based on age, medications, disease, current use
- Maintenance dose: 0.4 mg/kg/hr (adjust for heart and liver disease)
- Try to achieve 5 - 15 mcg/mL, monitor plasma levels to adjust dose
- Doses for theophylline similar but slightly less

Heliox

- Helium-oxygen (80:20 or 70:30) mixture may provide dramatic benefit for ED patients with severe exacerbations. Helium is about 25% as dense as room air and travels more easily down narrowed passages. This property makes heliox of particular value to patients at risk of intubation by quickly decreasing the work of breathing and better delivery of the inhaled bronchodilator.

Will they come back?

- In one holding unit, asthma study patients were discharged within 12 hours at 50% of predicted PEF if they had no high-risk relapse factors or at 60% of predicted PEF if they had one or more high-risk relapse factors. At 2 weeks following the ED visit, a 9% relapse rate was noted when prednisone tablets handed out (26% for most EDs). Inability to obtain medications due to socioeconomic factors should lower the threshold for hospital admission for patients who have asthma and PEF of 50-69% of predicted or personal best.
**Why do patients die in hospital of a potentially reversible disease???**

**Complicating factors - infrequent**

- Overwhelming obstruction
- Comorbid diseases
- Infection

**Why do patients die in hospital of a potentially reversible disease???**

**Patient factors**

- Lack of understanding
- Misinterpretation of symptoms
- Poor compliance
- DENIAL

Gaps between accepted standards of care and actual performance

- No global assessment
- No objective measures

**ER Discharge**

- The patient may be discharged from the hospital if the PEF or the patient's personal best expiratory flow rate is 70% or more of predicted rate and if symptoms are minimal or absent. Patients who have mild symptoms but have PEF of 50-69% of predicted or personal best could be considered for discharge if high-risk factors for relapse are not present. Patients with PEF of 50-69% of predicted or personal best who may be unable to obtain medications for socioeconomic reasons have a lower admission threshold.
Mild kids die


Death rates drop with steroids

Anaphylaxis: Causes and Treatment

Ruby Pawankar, MD, PhD is with the Department of Otolaryngology at Nippon Medical School in Tokyo, she is guest professor at Kyung Hee University School of Medicine in Seoul, Korea, and she has been guest professor, Division of Allergy, Department of Pediatrics, at Showa University School of Medicine in Tokyo.

Prof. Dr. Pawankar is on the Board of Directors of the World Allergy Organization (WAO), Executive Committee of the WHO Rhinitis Guidelines Initiative (ARIA) and Chair of the ARIA Asia-Pacific Affiliate. She has been the Vice Chair of the Rhinitis Committee of the American Academy of Allergy Asthma & Immunology, and has held several key positions in the organization of international congresses including the International Symposium on Asthma & Allergic Rhinitis (ISBAAR), 10th Biennial Congress of the Transpacific Allergy & Immunology Society and 9th Asian Research Symposium in Rhinology.

Abstract

Anaphylaxis is a severe systemic allergic reaction involving the release of mediators from mast cells, basophils and recruited inflammatory cells, that can involve multiple systems of the body, is often sudden and can have life-threatening consequences. Anaphylaxis manifests as a number of signs and symptoms, alone or in combination, occurring from within minutes to up to a few hours after exposure to a provoking agent. Severe initial symptoms develop rapidly, reaching a peak within 3-30 minutes, with occasionally a quiescent phase lasting for 1-8 hours before the onset of a second reaction (a biphasic response). Protracted anaphylaxis may occur, with symptoms persisting for days. The initial manifestation of anaphylaxis may be loss of consciousness, and the symptoms and signs may be isolated to one organ or involve multiple organs, gastro-intestinal, oral, respiratory, cutaneous, cardiovascular, ocular, and/or genito-urinary. A variety of causes can contribute to the development of anaphylaxis, including foods such as peanuts, tree nuts, shell fish, milk, eggs, fruits and seeds; a severe allergy to pollen that has cross-reactivity with certain foods; food-associated, exercise-induced anaphylaxis; antibiotics and drugs such as muscle relaxants; hymenoptera venoms; latex and foreign proteins; whole blood or its products, including serum or plasma; radiocontrast media; low-molecular weight chemicals; narcotics; modulators of arachidonic acid metabolism; sulfiting agents, and idiopathic causes

The emergency treatment of anaphylaxis comprises:

a) ensuring and establishing a patent airway,
b) assessing the adequacy of ventilation, providing the patient with sufficient oxygen, and treating bronchospasm as necessary, and
c) eliminating the continued exposure to the causative agent.

Assessing the adequacy of perfusion and use of a vasopressor (such as dopamine) may be necessary. Epinephrine is the drug of choice for anaphylaxis and should be given early in the course of the reaction, 0.3-0.5 mg of a 1:1000 w/v solution IM every 10-20 minutes or as necessary for adults, and 0.01 - 0.3 mg/kg IM every 5-30 minutes as necessary for children. Antihistamines are helpful once the patient stabilizes. Although diphenhydramine may be administered IV, IM, or orally, cimetidine (up to 300 mg every 6-8 hours orally or slowly IV) offers the benefit of reducing both histamine-induced cardiac arrhythmias (mediated via H2 receptors), and anaphylaxis-associated vasodilation (mediated by H1 and H2 receptors). Corticosteroids are not effective for acute anaphylaxis but may prevent relapses or protracted anaphylaxis.

To prevent further episodes it is crucial to identify the causative agent/s by obtaining a comprehensive history and performing relevant tests, including allergen skin tests and measurement of allergen-specific IgE in the serum. Risk reduction strategies include avoidance of specific triggers, relevant specific preventive treatment, training of at-risk individuals in the use of self-injectable epinephrine and an anaphylaxis emergency action plan. Anaphylaxis education should be provided for patients, their families, caregivers, health care professionals, and the general public.

References

1. Johansson SGO et al JACI 2004;113:832-6
DEFINITION OF ANAPHYLAXIS

Anaphylaxis is a severe life-threatening generalized or systemic hypersensitivity reaction.

It is commonly, but not always, mediated by an allergic mechanism, usually by IgE.

Allergic (immunologic) non-IgE-mediated anaphylaxis also occurs.

Non-allergic anaphylactic reactions, formerly called anaphylactoid or pseudo-allergic reactions, may also occur.

REVISED NOMENCLATURE FOR ANAPHYLAXIS

- Anaphylaxis
  - Allergic anaphylaxis
  - Non-allergic anaphylaxis
    - IgE-mediated anaphylaxis
    - Immunologic, non-IgE-mediated anaphylaxis
MECHANISMS OF ALLERGIC ANAPHYLAXIS

...a severe, acute, systemic allergic reaction caused by the rapid, IgE-mediated release of potent mediators such as histamine from tissue mast cells and peripheral blood basophils.

- preformed granule-associated substances, eg histamine, tryptase, chymase, carboxypeptidase, and cytokines
- newly-generated lipid-derived mediators, eg prostaglandin D2
- leukotrienes (LT) B4, LTC4, LTD4, LTE4, and platelet activating factor.

PRIMARY SYMPTOMS OF ANAPHYLAXIS

- Skin: (> 90% of patients) flushing, itching, urticaria, angioedema
- Gastrointestinal: (30% of patients) nausea, vomiting, bloating, cramping, diarrhea
- Respiratory: (40% to 70% of patients) dyspnea, cough, stridor, wheezing, dyspnea, chest tightness, asphyxiation, death
- Cardiovascular: tachycardia, hypotension, dizziness, collapse, death (shock occurs in about 15% of patients)
- Other: feeling of impending doom, metallic taste

- skin, oral, and throat symptoms are often the first ones noted
- signs and symptoms are usually seen within 5 to 30 minutes
- the more rapid the onset, the more serious the reaction
- IT CAN AFFECT SINGLE OR MULTIPLE ORGANS

BIPHASIC/LATE-PHASE REACTION

Biphasic anaphylaxis is the return of symptoms after resolution of initial symptoms, without second allergen exposure & usually within 1 to 8 hrs

Cellular infiltrates: 3 to 6 hours (LRB)

Eosinophil
cytokines, GM-CSF, TNF-α, IL-1, IL-6, PAF, MCP, MIP

Basophil
histamine, cysteinyl leukotrienes, TNF-α, IL-1, PAF, LTC4, LTD4

Monocyte
Cysteinyl leukotrienes, TNF-α, PAF, IL-1

Lymphocyte
HIV, TNF-α, IL-1, GM-CSF

Return of Symptoms

EPR 15 min
AGENTS CAUSING ANAPHYLAXIS: IgE-DEPENDENT TRIGGERS

- Foods (eg peanut, tree nuts, seafood)
- Medications (eg, β-lactam antibiotics)
- Venoms
- Latex
- Allergen immunotherapy
- Diagnostic allergens
- Exercise (with food or medication co-trigger)

Estimated risk in US: 1-3%
Females per year in the US: food-induced: 150; antibiotic-induced: 600; venom-induced: 50

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FOOD-INDUCED ANAPHYLAXIS

- Many anaphylactic reactions are caused by food
  - accidental food exposures are common and unpredictable
  - anaphylaxis from food can occur at any age, but children, teens, and young adults are at highest risk
- Prevalence of peanut allergy has doubled in children <5 years of age in the last 5 years
- Seafood allergy is reported by 2.3% of the US population, and is more common in adults than in children

MOST COMMON FOOD ALLERGIES
Peanut, tree nut, seafood, finfish, milk, egg, soy, wheat

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FOOD-DEPENDENT EXERCISE-INDUCED ANAPHYLAXIS

- Reported in USA, Thailand and Japan
- Most common in females, from late teens to mid-30’s
- Triggered by exercise 2-4 hours after ingesting offending food
- Foods implicated: wheat, seafood, fruit, milk, celery, and fish
- Associations: asthma, positive SPT to foods
- Mechanism: two signals required

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VENOM-INDUCED ANAPHYLAXIS

- Causes: bees, wasps, hornets, yellow jackets, fire ants
- Normal reactions: local pain, erythema, mild swelling
  - large local reaction: extended swelling, erythema
- Anaphylaxis: usual onset within 5-30 minutes
  - cutaneous: pruritus, urticaria, flushing, angioedema
  - respiratory: dyspnea, wheezing, stridor, dysphonia
  - cardiovascular: tachycardia, hypotension, dizziness, faintness
- In a patient who has already experienced anaphylaxis from a sting, the risk of anaphylaxis to a subsequent sting is 30%-60%

LATEX-INDUCED ANAPHYLAXIS

- Prevalence is highest among healthcare workers
- Latex gloves, especially if powdered, are a common trigger
- Repeated exposure leads to higher risk
- Incidence increased dramatically in the mid-1980s
- But has decreased progressively with more use of non-powdered latex gloves and use of non-latex gloves

IATROGENIC ANAPHYLAXIS

- Most common drug triggers
  - penicillin (highest number of documented deaths from anaphylaxis)
  - sulfa drugs
  - non-steroidal anti-inflammatory drugs
  - muscle relaxants
- Most common biologic triggers
  - anti-sera for snakobite
  - anti-lymphocyte globulin
  - vaccines
  - allergens

References:
PERI-OPERATIVE ANAPHYLAXIS

- Neuromuscular blocking drugs (muscle relaxants), eg suxamethonium, rocuronium, alcuronium, atracurium
- Induction agents, eg thiopentone, propofol, alfathesin
- Other: including local anesthetics, antibiotics, protamine, and latex
- Predisposing factors: atopy, asthma; previous exposure


ALLERGEN IMMUNOTHERAPY – INDUCED ANAPHYLAXIS

- Fatal reactions are uncommon: 1 per 2,000,000 injections
- Risk factors for fatality include:
  - errors in dosing
  - poorly controlled asthma (FEV₁ < 70%)
  - concomitant β-blocker use
  - lack of proper equipment and trained personnel
  - inadequate epinephrine treatment


ANAPHYLAXIS: NON-IMMUNOLOGIC CAUSES

- Radiocounter media
- Ethylene oxide gas on dialysis tubing (possibly through IgE)
- Protamine (possibly)
- ACE-inhibitor administered during renal dialysis with sulfonated polyacrylonitrile, cuprophane, or polymethylmethacrylate dialysis membranes
ANAPHYLAXIS: NON-IMMUNOLOGIC CAUSES

NONSPECIFIC DEGRANULATION OF MAST CELLS AND BASOPHILS

- Opiates
- Physical factors:
  - exercise (no food or medication as trigger)
  - temperature (cold, heat)

IDIOPATHIC ANAPHYLAXIS

- Common in adults who are referred to allergists for evaluation of anaphylaxis
- Uncommon in children
- Negative skin tests, negative dietary history, no associated diseases eg. mastocytosis
- Preventive medication: oral corticosteroids, H1 & H2 antihistamines, anti-leukotrienes
- Deaths rare
- May gradually improve over time

MOST COMMON PRECIPITATING CAUSES

<table>
<thead>
<tr>
<th>Country</th>
<th>Precipitating agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>Insect venom and drugs, immunotherapy, foods, radio contrast media, NSAID</td>
</tr>
<tr>
<td>China, Korea</td>
<td>Drugs - antibiotics and anesthetic agents</td>
</tr>
<tr>
<td>India</td>
<td>Antibiotics, radio contrast agents and anesthetic agents plus blood products, insulin and growth hormones</td>
</tr>
<tr>
<td>Australia</td>
<td>Peanuts</td>
</tr>
<tr>
<td>Japan</td>
<td>Foods in children, insect stings, latex and drugs in adults</td>
</tr>
</tbody>
</table>
**β-ADRENERGIC BLOCKADE**

- By mouth or topically
- Paradoxical bradycardia, severe hypotension and bronchospasm
- Can exacerbate disease and impede treatment
- Selective β-blockers can produce clinically significant adverse respiratory effects even in mild-moderate asthma and COPD; not studied in anaphylaxis

**Diagnosing Anaphylaxis**

- Based on clinical presentation, exposure Hx
- Cutaneous, respiratory Sx most common
- Some cases may be difficult to diagnose
  - Vasovagal syncope
  - Scombroid poisoning
  - Systemic mastocytosis

**Diagnosing Anaphylaxis**

- Careful history to identify possible causes
- Can be confirmed by serum tryptase
  - Specific for mast cell degranulation
  - Remains elevated for up to 6 hours
- Other lab tests to rule out other diagnoses
- Refer to allergist for specific testing
Diagnosing Anaphylaxis

Allergists can identify specific causes by:

- Skin tests/RAST
  - Foods
  - Insect venoms
  - Drugs
- Challenge tests
  - Foods
  - NSAIDs
  - Exercise

Emergency treatment of anaphylaxis

- Place the patient in recumbent position and elevate legs
- Maintain airway (endotracheal tube or cricothyrotomy)
- Administer oxygen, 6-8 L/min to maintain adequate mentation and an oxygen saturation of at least 91%
- Treat bronchospasm with nebulized albuterol (salbutamol)
  2.5-5 mg in 3 ml normal saline
- Administer normal saline IV, volume expanders (colloid solution) for severe hypotension (dopamine if needed)
- Eliminate continued exposure to the causative agent

Treatment of Anaphylaxis

- Immediate treatment with Epinephrine imperative
  - No contraindications in anaphylaxis
  - Failure or delay associated with fatalities
  - IM may produce more rapid, higher peak levels vs SC
  - Must be available at all times
- Dosage:
  0.3-0.5 mg of a 1:1000 w/v solution IM every 15-20 minutes
  or as necessary for adults
  0.01-0.3 mg/kg IM every 5-30 minutes as necessary for children
- Antihistamine when patient stabilizes (oral or parenteral, cimetidine up to 300 mg every 6-8 hours preferred)
- Corticosteroids: Hydrocortisone (100-200 mg) or its equivalent can be administered every 6 to 8 hours for the first 24 hours. Arrange follow-up care, provide epinephrine and education
Food-induced Anaphylaxis: Prevention

I. AVOID ALLERGENS

- Learn to read product labels
  - Identify alternative names for ingredients
  - Find “hidden” ingredients
- Avoid high-risk foods (e.g., baked goods)
- Avoid sharing food, utensils, or food containers
  - Minute amounts can be life-threatening
- Provide educational materials
  - FAAAN (www.foodallergy.org)

Food-induced Anaphylaxis: Prevention

II. RISK MANAGEMENT

- Complete avoidance is impossible
- Must always be prepared to treat a reaction
  - Have an emergency action plan
  - Keep epinephrine on hand at all times
  - Train caregivers and teachers on epinephrine use
  - Wear medical alert bracelet

Risk Management for Anaphylaxis

* EDUCATE

- Teach avoidance measures
- “Accidents are never planned”
- Stress importance of:
  - Always having a current epinephrine on hand
  - Immediate treatment
  - Emphasize the need for follow-up care
SUMMARY

- Anaphylaxis: release of inflammatory mediators from mast cells and basophils (IgE-mediated or non-IgE mediated)
- Symptoms: within minutes of exposure to triggering agent (less commonly can be delayed, biphasic or protracted)
- Common triggers: foods, drugs, latex, hymenoptera stings; idiopathic
- First-line treatment: injected epinephrine (adrenaline)
- Hallmarks of management: education and prevention
**Angioedema**

Michael A. Kaliner, MD is a former President of the AAAAI, ABAI, Allergy Section of ATS, and Head of Allergy at the NIH. He was recently recognized as the AAAAI Distinguished Clinician for 2006. Michael Kaliner was head of the Allergy Training Program at the NIH, and trained over 100 fellows in allergy and immunology. He has published 500 articles related to allergy.

He is the current President of the World Allergy Organization (WAO) and has also written or participated in many of the GLORIA™ lectures.

**Abstract**

*Taken from GLORIA Module 7: Angioedema*

**Authored by:**

Allen P. Kaplan, Medical University of South Carolina
Charleston, South Carolina, USA

Connie H. Katelaris, Westmead Medical Centre
Westmead, NSW, Australia

Angioedema (A/O) was first described by Quincke in 1882. It is caused by the same pathophysiological factors that produce urticaria, but the reaction occurs deeper in the dermis and subcutaneous tissues. A/O is a term used to describe well-demarcated, non-pitting edema that occurs as large, erythematous, swollen areas in the subcutaneous tissues. The face, tongue, lips and eyelids are most commonly affected, but it may also involve the hands, feet, genitalia, mucous membranes and other parts of the body.

Within the spectrum of chronic idiopathic urticaria (CIU) and A/O, 50% of patients experience both urticaria and A/O, while 40% have urticarial lesions alone and 10% will have A/O and no urticaria. Typically, sporadic A/O is idiopathic; however, precipitating factors include physical factors, such as temperature changes and trauma. Other causes include IgE-mediated hypersensitivity to foods, drugs, insect stings and inhalants. Non-IgE-mediated sensitivity to drugs, particularly aspirin and other nonsteroidal antiinflammatory drugs and ACE inhibitors, also occurs. Hereditary A/O is usually familial; however, acquired forms also have been associated with malignancy, in particular, lymphoproliferative disorders.

**Table 1: Classification of A/O**

**Hereditary**

- Type 1: C1 esterase inhibitor deficiency
- Type 2: functional abnormality of C1 esterase inhibitor

**Acquired**

- Idiopathic (most common)
- IgE-mediated (most commonly with urticaria)
- Drugs
  - Foods
  - Stings
  - Infections (viral - Epstein Barr virus; hepatitis A, B; helminthic)
  - Non-IgE-mediated
    - Cyclooxygenase inhibition
    - ASA, NSAIDs
    - Angiotensin-converting enzyme inhibition
    - Systemic diseases, eg:
      - Systemic lupus erythematosus
      - Hypereosinophilia
      - Lymphoma: Abnormal antibodies activate complement system

**Physical causes**

- Cold
- Cholinergic
- Solar
- Vibratory

**Other**

- Some contact reactions
  - Autoantibodies to C1 esterase inhibitor (associated with malignancy, connective tissue diseases)

Acute laryngeal edema resulting from hereditary C1-esterase inhibitor deficiency or abnormality can cause life-threatening respiratory distress, leading to serious complications and fatalities for patients needing to undergo surgical procedures. Asphyxiation is the most common cause of mortality in hereditary angioedema. Time for onset of swelling to death can be dramatically short, from as little as 20 minutes, with intervals between 1-14 hours (mean, seven hours) being reported. Early symptoms reported by those affected include
a tight sensation in the throat, feeling of a lump in the throat, hoarseness, dysphagia and progressive dyspnea. Mortality from HAE has significantly decreased since the advent of long-term prophylactic treatment with attenuated androgens.

This presentation will review the acute and long-term management of all forms of angioedema.

References
Angioedema

- First described by Quincke in 1882
- Well-demarcated non-pitting edema
- Often caused by same pathological factors that cause urticaria
- Reaction occurs deeper in dermis and subcutaneous tissues
- Face, tongue, lips, eyelids most commonly affected
- May cause life-threatening respiratory distress

Causes of Angioedema - 1

- Like urticaria – foods, drug allergy, radiocontrast media, insect stings/bites, infection, NSAIDs
- Associated with anaphylaxis of any cause
- Autoimmune – accompanying chronic urticaria
- Idiopathic:
  - Accompanying chronic idiopathic urticaria
  - Angioedema alone (no urticaria, no evident cause)
- ACE inhibitors – Typically without urticaria;
- C1 inhibitor deficiency – no urticaria:
  - Hereditary – Types I and II
  - Acquired – Types I and II

Causes of Angioedema – 2

- Physical causes
  - Cold
  - Cholinergic
  - Solar
  - Vibratory
- Other causes
  - Some contact reactions
  - Systemic diseases (e.g., systemic lupus erythematosus)
Angiotensin Converting Enzyme (ACE) – Induced Angioedema – 1

- Now most common exogenous cause of angioedema seen in emergency rooms
- Usually has no associated urticaria
- Due to increased bradykinin levels because kinin degradation is inhibited
- Can cause dramatic swelling of tongue, pharynx, or larynx – may require intubation or tracheostomy acutely

ACE-Induced Angioedema - 2

- Angioedema develops in 0.1% to 0.5% of those receiving the drug
- Onset from 1st week of use to 2-3 years of use
- Symptoms resolve within 24-48 hours of cessation of drug
- Most commonly seen with captopril and enalapril, but described with all ACE inhibitors
- Genetic factors may be important
- Subjects with a history of angioedema from other causes are more susceptible to ACE-induced angioedema

Slater JAMA 1988

ACE-Induced Angioedema - 3

- Face and lips most commonly involved but laryngeal edema reported
- Risk factors include obesity, prior endotracheal intubation and face and neck surgery
- ACE inhibitors will trigger attacks in those with HAE, so avoid in these patients

Joint Chest 1992
Bradykinin Degradation – Site of ACE Inhibition

Bradykinin = Arg Pro Pro Gly Phe Ser Pro Phe Arg

Arg Pro Pro Gly Phe Ser Pro Phe Arg → Arg Pro Pro Gly Phe + Ser Pro + Phe Arg

ACE

ACE

Carboxypeptidase N

Arg Pro Pro Gly Phe Ser Pro Phe + Arg

ACE Inhibitors and Angioedema - 4

Management

- Stop drug and use other classes of antihypertensive agents
- ALL ACE inhibitors are to be avoided
- Management of angioedema depends on site of involvement – securing the airway by intubation may be necessary
- ACE receptor antagonists are generally considered to be safe


Angioedema
**Hereditary Angioedema (HAE) - 1**

- 1888 – family described by William Osler
- 1963 – Donaldson and Evans described the biochemical defect responsible – absence of C1 inhibitor
- Defective gene located on chromosome 11

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**Epidemiology and Clinical Presentations of HAE**

**Epidemiology**
- 1:10,000 – 1:150,000 with no racial or gender predilection

**Clinical Presentations**
- Usually manifests in 2nd decade
- May be seen in young children
- Edema may develop in one or several organs
- Presentation depends upon site of swelling
- Attacks last 2–5 days before spontaneous resolution

_Novak Arch Intern Med, 2001_

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**HAE Clinical Manifestations - 1**

- Angioedema may develop in subcutaneous tissues of extremities, genitalia, face, trunk
HAE Clinical Manifestations - 2

- Symptoms of bowel wall edema can be confused with an acute abdominal emergency
  - White blood count is normal and symptoms resolve within 72 hours.
- Submucosal edema of larynx (or, rarely, pharynx) may cause asphyxiation – this may occur on first presentation

HAE Clinical Manifestations - 3

Laryngeal Edema

Commonest cause of mortality in HAE

- Time from onset of swelling to death 1–14 hours (mean 7 hours)
- May be presenting feature
- Death may occur in those with no previous laryngeal edema episodes
- Increased risk within certain families
- Early symptoms: lump in throat, tightness in throat
- Hoarseness, inspiratory stridor, progressive dyspnoea

Bark Mayo Clin Proc 2000

Genetics of HAE - 1

- Hereditary – Autosomal dominant
  - 85% decreased C1 inhibitor protein and function – often gene deletion, insertion, stop codon, frame shift mutation (Type 1 HAE)
  - 15% normal or increased C1 inhibitor protein but decreased function typically due to single nucleotide mutation (Type 2 HAE)
  - Suppression of the one normal gene product (theoretically should be 50%) to 25% or less causes swelling
Genetics of HAE - 2

- Autosomal dominant; all patients heterozygous
- 25% no prior family history – spontaneous mutations
- More than 100 different mutations reported
- Varied clinical pattern may be explained by variable effect of mutations on C1 inhibitor synthesis

Agostino Medicine (Baltimore) 1992

Diagnosis of Hereditary Angioedema (HAE)

- Clinical presentation
- For screening – quantitative and functional assays of C1 inhibitor
- C4 and C2 levels reduced in acute attack
- C4 persistently low in most patients

Nzeako Arch Intern Med 2001

Pathophysiology of HAE – 1

C1 Inhibitor
- Single chain glycoprotein; molecular weight 104,000; serine protease family
- Important regulatory protein of complement cascade
- Inactivates C1 esterase complex
- Regulates coagulation, fibrinolytic, kinin, complement systems

Nielsen Immunopharmacology 1996
Pathophysiology of HAE - 2

- Lack of C1 inhibitor leads to abnormal activation of complement pathway, reduced C2 and C4 levels
- Hageman factor induces formation of kallikrein from prekallikrein
- Bradykinin is released from high molecular weight kininogen
- All these mediators increase capillary permeability and are responsible for attacks of angioedema

Kaplan MCI 2002

Role of C1 Inhibitor in Controlling Bradykinin Formation

Management of HAE - 1

Principles
- Action plan for acute episodes
- Strategy for long term prophylaxis
- Short term prophylaxis for high risk procedures
- Regular follow up for education and monitoring side effects of therapy
Management of HAE - 2

Acute Attacks
- Treatment of choice is C1 inhibitor concentrate, 500 – 1,000 units per intravenous infusion
- Safe and effective – no longer term side effects reported
- Excellent and prompt response in most patients
- Not universally available, but clinical trials ongoing in USA

Bork Arch Intern Med 2001

Management of HAE - 3

- Acute attacks when C1 inhibitor concentrate not available:
  - Intubation and respiratory support may be necessary when laryngeal edema present
  - Fresh frozen plasma (FFP) has been used successfully for acute attacks. Exacerbation of symptoms by supplying more kallikrein substrate is a consideration and is occasionally seen

Bork Arch Intern Med 2001

Management of HAE - 4

Long Term – Adults
- Monthly C1 inhibitor concentrate, where available
- Attenuated androgens (danazol, stanozol, oxandrin) can prevent attacks. Methyl testosterone can be used in treating males.
- Aim to increase levels of C1 inhibitor, C4 and C2
- Titrate to lowest effective dose to control attacks – for danazol may be able to reduce to 200 mg every second day
- Regular monitoring necessary

Nzeako Arch Intern Med 2001
Management of HAE - 5

Long Term - Children
- Antifibrinolytic agents have been used as first line prophylaxis
- Low dose danazol

Management of HAE - 6

Short Term Prophylaxis
- Necessary for high risk interventions, e.g., dental procedures, tonsillectomy
- C1 inhibitor concentrate, where available, given before procedure
- Increased dose of attenuated androgen for 3-5 days beforehand, the day of the procedure, and 1-2 days thereafter
- Fresh frozen plasma (FFP) may be added to an increased androgen dosage, as noted above

Management of HAE - 7

Other
- No response to steroids or antihistamines
- Avoid oral contraceptives, ACE inhibitor medications
- Premedicate before procedures requiring radiocast media or streptokinase as they may decrease C1 inhibitor levels
- Reassurance; address issues such as ongoing stress
- Treat infections promptly
- Genetic counseling and screening
Future Management Considerations

- Kallikrein inhibitors for acute episodes
- Purified or cloned C1 INH for acute treatment and prophylaxis
- Bradykinin antagonists
- Future management strategies aim to address pathogenesis more specifically and to decrease adverse reactions (for example, viral contamination of blood products)

Acquired C1 Inhibitor Deficiency

- Type I: Caused by massive amounts of immune complex (IgG antibody to lymphoma cell surface antigen, cryoglobulins, autoimmune diseases), which activates C1 so that C1 inhibitor is depleted
- Type II: Circulating antibody (IgG) to C1 inhibitor, which prevents its ability to inactivate enzymes such as Factor XII and kallikrein

Markovic Ann Int Med 2000

Acquired C1 Inhibitor Deficiency - 2

- Decreased C1q levels distinguish AAE from HAE, where C1q is usually normal
- Treatment of underlying condition may result in resolution
- For acute attacks, C1 inhibitor concentrate, where available, should be used
- Attempted androgen may be useful in Type 1
- Immunosuppressive therapy for Type 2, but can be particularly refractory to treatment. Plasmapheresis may be tried

Laurent Clin Rev Allergy Immunol 1999
C1 Inhibitor Deficiency – Hereditary vs. Acquired - 1

- All forms have low C4 levels, which may decrease to zero during attacks of swelling. C2 also decreases, but only during episodes of swelling.
- All forms have low C1 inhibitor function
- All forms have low C1 inhibitor protein except Type II - HAE

C1 Inhibitor Deficiency – Hereditary vs. Acquired - 2

- C1Q is normal in both forms of HAE, but diminished in both forms of acquired C1 inhibitor deficiency
- Type II acquired C1 inhibitor deficiency (IgG C1 inhibitor) has a decrease in C1 inhibitor size on SDS gel electrophoresis from 105 Kd to 95 Kd

Idiopathic Angioedema

- Recurrent angioedema, no recognized exogenous precipitant, normal C4 levels, unassociated with concomitant urticaria
- Typically: episodes of swelling of lips, cheeks, eyes, tongue, pharynx, extremities, genitalia
- Sub-types:
  - Respond to antihistamines
  - Non-responsive to antihistamines. Uncertain role of bradykinin

### Laboratory Features of Idiopathic Angioedema

- Normal Complement – CH50, C4, C1 inhibitor. Negative testing for antibody to IgE receptor – May have different pathogenesis from chronic urticaria with or without angioedema
- Anti-thyroid antibodies elevated in some; perhaps less frequently than in chronic urticaria

### Treatment of Acute Episodes of Angioedema

- Diphenhydramine 50 mg – repeat in 4 hours
- Prednisone 50 mg X 2 doses and stop without any taper
- Epinephrine – if rapidly advancing
- H2 antihistamines

### Preventive Therapy of Frequent but Mild Episodes of Angioedema

- A non-sedating antihistamine; may double the dose or combine them, e.g. fexofenadine 180 mg or loratadine 10 mg in a.m. and cetirizine 10 mg mid-day and bedtime
- Add H2 - antagonist, BID
- If ineffective, diphenhydramine at 50 mg QID, plus H2 antagonist
- If antihistamines alone are ineffective, try adding a leukotriene antagonist (BID)
Prevention of Frequent and/or Severe Episodes of Angioedema

• Diphenhydramine at 50 mg qid. If successful, taper to lowest effective dose. Consider non-sedating antihistamines at BID dosing
• H2 - antagonists at BID dosing may be added
• Leukotriene antagonists; if ineffective try leukotriene synthesis inhibitors
• If refractory to above:
  – Tranexamic acid or epsilon amino caproic acid (empiric therapy for non-histamine induced idiopathic angioedema)
  – Corticosteroid at 10-20 mg every other day
  – Azulfidine (up to 3 grams per day) can be tried as well

Angioedema - Conclusions

• Most often occurs in association with urticaria
• When angioedema occurs alone, consider idiopathic angioedema, ACE inhibitors, hereditary and acquired C1 inhibitor deficiencies
• HAE is a rare disease, but must be identified as it can be life-threatening
• Refer to appropriate specialist for ongoing management
• ACE-inhibitor induced angioedema is an important cause in older people