

Quinckes edema = angioedema

What is it and how do we treat it?

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CONFLICT OF
INTEREST



Disclosures

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Curriculum vitae

- Specialty registrar in oto-rhino-laryngology in Copenhagen, Denmark
- Published 42 papers since 2012, hereof 22 about angioedema
- Special interest in patients with angioedema with and without complement C1 deficiency
- Defended my PhD thesis on ACE-inhibitor induced angioedema in September 2018

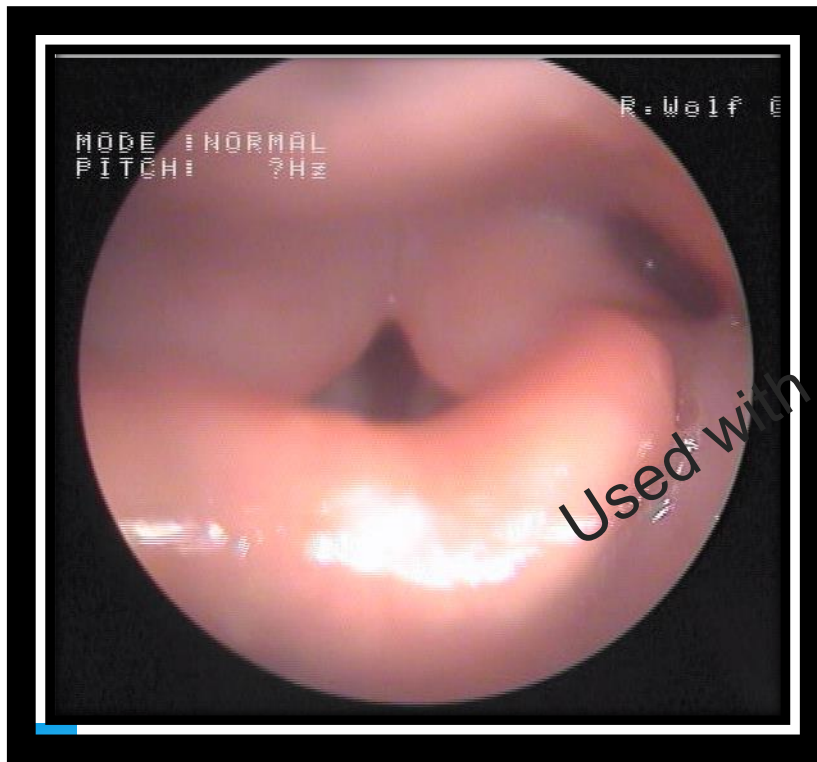
Today's programme

- Angioedema – what is it really?
- Epidemiology and pathophysiology
- Genetic causes – true or false?

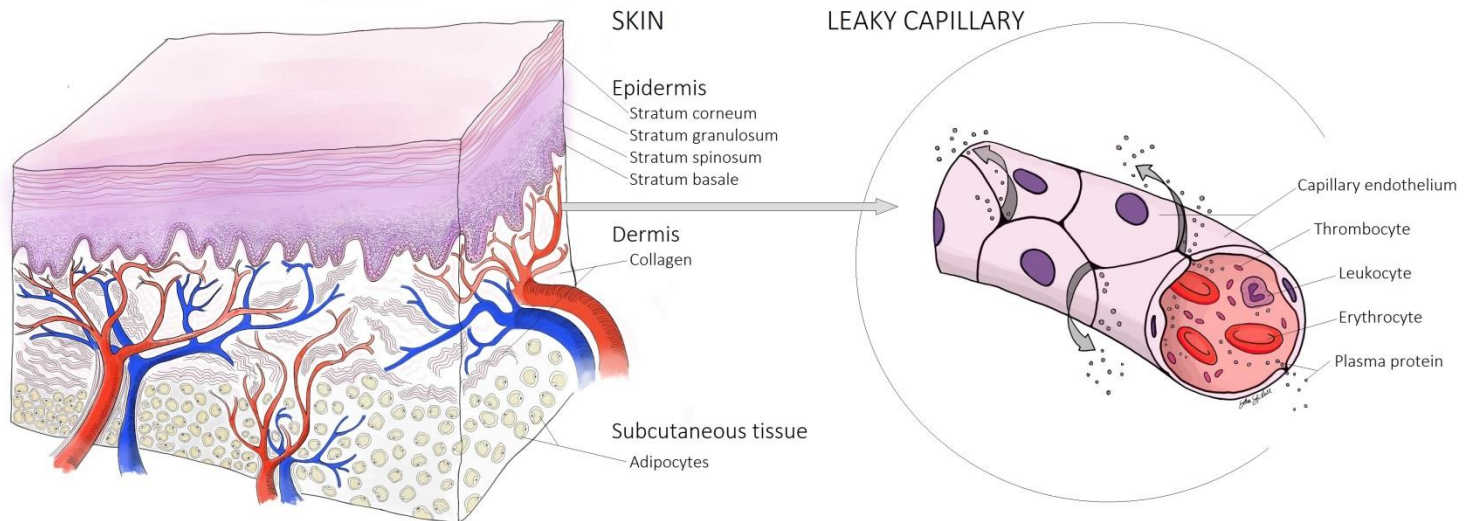
Today's programme

- Treatment – current and those in pipeline
- Future perspectives and new insights
- Discussion and exchange of ideas
- Questions from the audience

Angioedema is a non-pitting non-itching swelling of skin or mucosa and subcutis or submucosa



Plasma leakage from capillaries → swelling



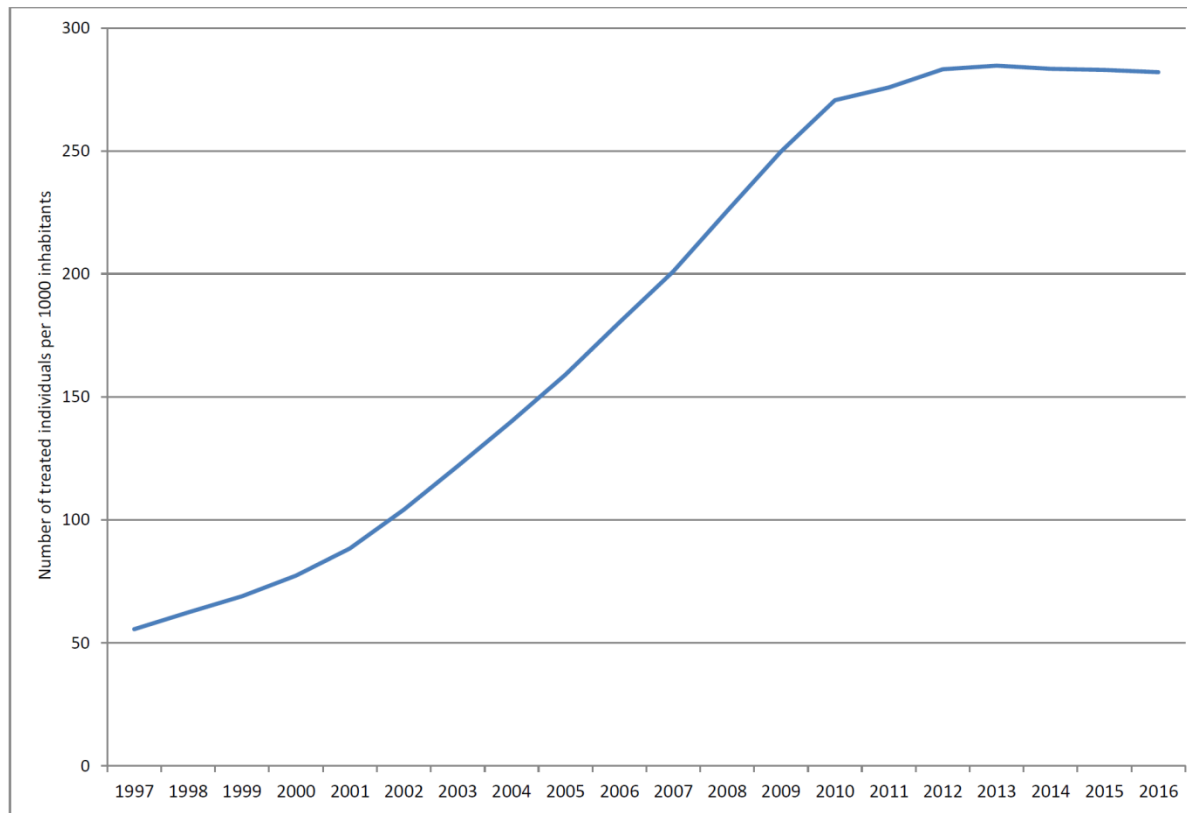
Epidemiology and background

- First mentioned in the 15th century as a symptom of allergy
- In 1882 Dr. Quincke described the symptom hence the name
- Many causes: allergy, pharmaceuticals, complement C1-inhibitor deficiency

Epidemiology and background

- 1980 Wilkin et al stated that with ACEi treatment, cutaneous swellings were observed
 - might be caused by kinin potentiation
- Controversy on whether angiotensin-II receptor blockers (ARBs) can be prescribed to ACEi-AE patients

Epidemiology and background



Epidemiology

- Life-time prevalence 7.4% in a Danish survey-based study (excl. angioedema due to complement C1-inhibitor deficiency)
- Estimate of 100.000 angioedema deaths world-wide yearly due to angiotensin-converting enzyme-inhibitors (ACEi) (Citation: Dr. Nancy Brown)
- >40 mio receiving ACEi world-wide

Epidemiology

- Angioedema caused by ACEis involves upper airways in half the patients
 - risk of suffocation

Piller L et al. *J Clin Hypertens* 2006;8:649–56.
Kostis JB et al. *Arch Intern Med* 2005;165:1637–42.
Miller DR et al. *Hypertension* 2008;51:1624–30.
Rouleau J et al. *Lancet* 2000;356:608–9.
Yde-Holm et al. *Dan med J* 2012.

Epidemiology

- 4.8–10% of hospitalized ACEi angioedema (ACEi-AE) patients require intubation or tracheostomy

Pathophysiology

- Many mediators:
 - Histamine: Allergy
 - Bradykinin and substance P: Not allergy
 - Direct mast-cell activation
- Precipitating factors: allergens, tissue trauma, surgery, intubation, dental treatment, stress, drugs?

Genetic causes – true or false?

Aminopeptidase P

- *XPNPEP2* has been associated with ACEi-AE in small candidate gene studies

Duan, *et al. Am J Hum Genet* 2005;77:617–26.

Woodard-Grice, *et al. Pharmacogenet Genomics* 2010;20:532–6

Cilia La Corte, *et al. Hum Mutat* 2011;32:1326–31.

Genetic causes – true or false?

Neutral endopeptidase/neprilysin

- *MME* has been associated with ACEi-AE in African Americans in a genome-wide association study (GWAS)

Genetic causes – true or false?

Bradykinin receptor type 2

- *BDKRB2* encoding bradykinin receptor type 2 has been associated with ACEi-AE in a candidate gene study in South Africans

Moholisa, *et al. J Clin Hypertens* 2013;15:413–9.
Mukae, *et al. J Hum Hypertens* 2002;16:857–63.
Dhamrait, *et al. Eur Hear J* 2003;24:1672–80.

Genetic causes – true or false?

α -unit of a calcium-activated potassium channel

- *KCNMA1* – effect on the calcium transport in smooth muscle cells and innate immunity

Rasmussen et al. Unpublished data. 2018..



Treatment: always consider how to manage the airway

- Intubation (oral or fiberoptic nasal) or tracheotomy can be needed
- Progresses rapidly and unexpectedly
- Life-threatening



Treatment

- Allergy:
 - Antihistamine
 - Corticosteroids
 - Adrenaline/epinephrine (injection/inhalation)

The difficult airway

- <https://www.youtube.com/watch?v=XpcrsVNGoM4>



Pharmacological treatment of allergic rhinitis: controversial

- Anti-allergic medication
- Bradykinin receptor antagonists
- But



Randomized, Double-blind, Two Arms, Multicenter, Phase III Study of Berinert for Treatment of ACE Induced Angioedema

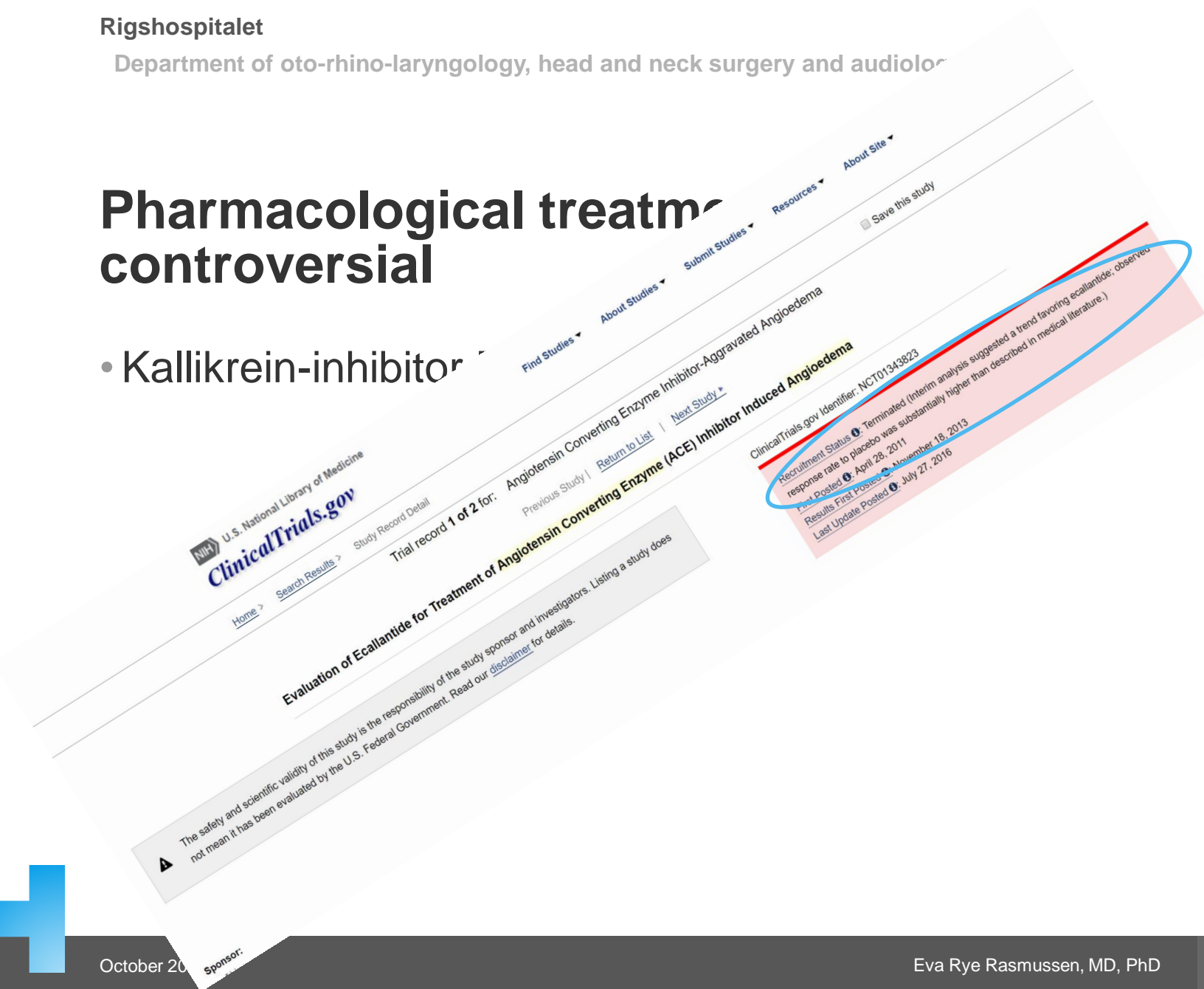
ClinicalTrials.gov Identifier: NCT01643530
 Recruitment Status: Unknown
 Verified April 2016 by Technische Universität München.
 Recruitment status was: Recruiting
 First Posted April 30, 2013
 Last Update Posted April 29, 2016

Controversial
 Clinical point of view
 Indicate?

Sinert R *et al.* Acad Emerg Med 2015;22:S3–425
 Baş M *et al.* Ann Emerg Med 2010;56:278–82.
 Baş M *et al.* N Engl J Med 2015;372:418–25

Pharmacological treatment controversial

- Kallikrein-inhibitor



More treatment options are coming?

- The range of drugs designed to treat other types of bradykinin-mediated angioedema is expanding
- Use of these drugs for other types of angioedema?

To sum up

- Quinckes edema = angioedema = angioneurotic edema = giant urticaria
- Treatment should target the mediator
- Airway management is essential
- Can progress rapidly and cause asphyxiation

Questions and answers



Thank you for coming

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