Asthma and co-morbid conditions : nasal polyps

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Prevalence of nasal polyps and association with asthma

- General population
  - by history < 5%
- Asthma population
  - general 7% - 15%
  - non atopic 13 %
  - atopic 5%
- AERD
  - nasal polyps 36 - 96%

Association of CRS with asthma

- CRS coexisted in 34% patients with asthma *(Annesi–Maesano 1999)*
- Abnormal sinus radiographs can be found in 53% of asthmatics *(Berman S 1974)*
- Mucosal thickening (CT scans) can be visualized in 74% of patients with asthma *(Pfister R 1994)*
- Asthmatics with CRS are more likely to have NPs , than non asthmatics with CRS (57.6% versus 25%) *(Pearlman AN 2009)*

Asthma and NP – GA2LEN Survey

- The Global Allergy and Asthma Network of Excellence (GA2LEN) conducted a postal questionnaire in representative samples of adults living in Europe to assess the presence of asthma and CRS defined by the EP3OS criteria.
- Results: Over 52 000 adults aged 18-75 years and living in 19 centers in 12 countries took part.
- In all centers, there was a strong association of asthma with CRS (adjusted **OR: 3.47; 95% CI: 3.20-3.76**) at all ages.
- The association with asthma was stronger in those reporting both CRS and allergic rhinitis (adjusted **OR: 11.85;** 95% CI: 10.57-13.17).

Jarvis D et al. Allergy 2011,

Chronic rhinosinusitis with and without nasal polyps

Sign and Symptoms	CRS with NP	CRS without NP
Symptoms	Nasal obstruction Loss if smell	Headache Postnasal drip
Histopathology	Eosinophylia ECP	MNC,PMN MPO
T cell polarization	TH2 type IL-5	TH1 type IFN γ
T-regulatory cells/factors	FOXP3 decreased TGF β 1 lower	FOXP3 normal TGFβ1 normal
Remodeling	-	+
Association with asthma	Strong	Weak

Huvenne W et al. 2009.

Asthma and eosinophylic inflammation in NP.

- Asthma is more prevalent in white European (mostly eosinophylic polyps) as compared to Asian patients with mostly neutrophylic CRS/NP.
- Eosinophylic inflammation (with IL5 protein production) is associated with asthma in both populations
- Other factors (sIgE to SAE in NP) seem to be associated with asthma

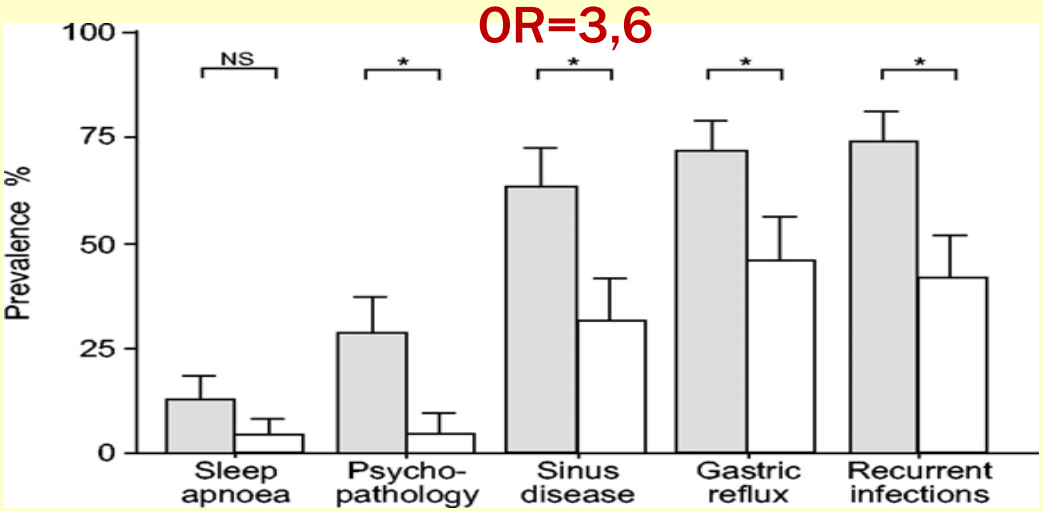
VanBruaene et al. 2008
Bachert et al. al. 2010

CRS/NP and asthma severity

- CRS is associated with more severe asthma *(Liou A et al. Chest 2003)*
- Presence of CRS (but not rhinitis) is associated with multisymptom (more severe asthma) *(Lotvall J et al. Resp res 2010)*
- CRS related to more severe asthma: higher medication use and lower FEV1 (*Aazami et al. Iran JACI 2009)*

CRS as a risk factor for frequent asthma exacerbations

- A group of 136 (63) patients with difficult to control asthma divided in to 2 groups
  - One exacerbation per year
  - Three or more per year



- All patients had at least one of the above factors
- 52% showed three or more factors

Ten Brinke et al. 2005

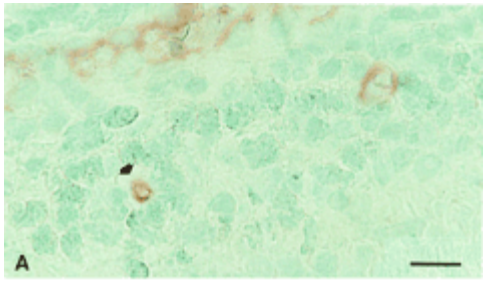
Mechanisms linking CRS/NPs with asthma

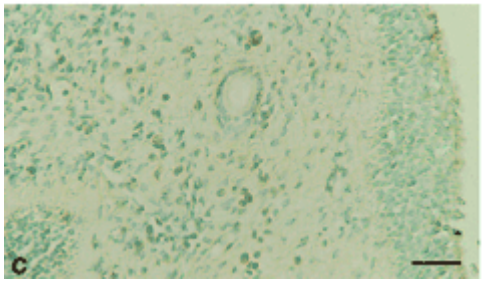
- Neurogenic reflex
- Mouth breathing
- Aspiration
- One airway disease – involvement of bone marrow
- Common triggers
  - Infectious factors
  - Allergens
  - Other environmental (e.g. tobacco smoke)

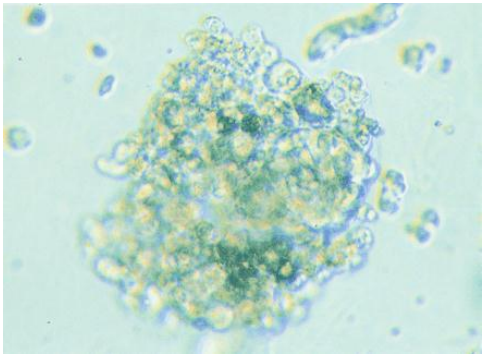
CD34/CD45+ cells and CFC are present in nasal polyps

- Immunoreactive CD34^{+}/CD45^{+} mononuclear cells are present within nasal polyps
- Isolated polyp mononuclear cells demonstrated myeloid colony formation with presence of CD34+/CD45+ cells

  (assessed by flow cytometry)



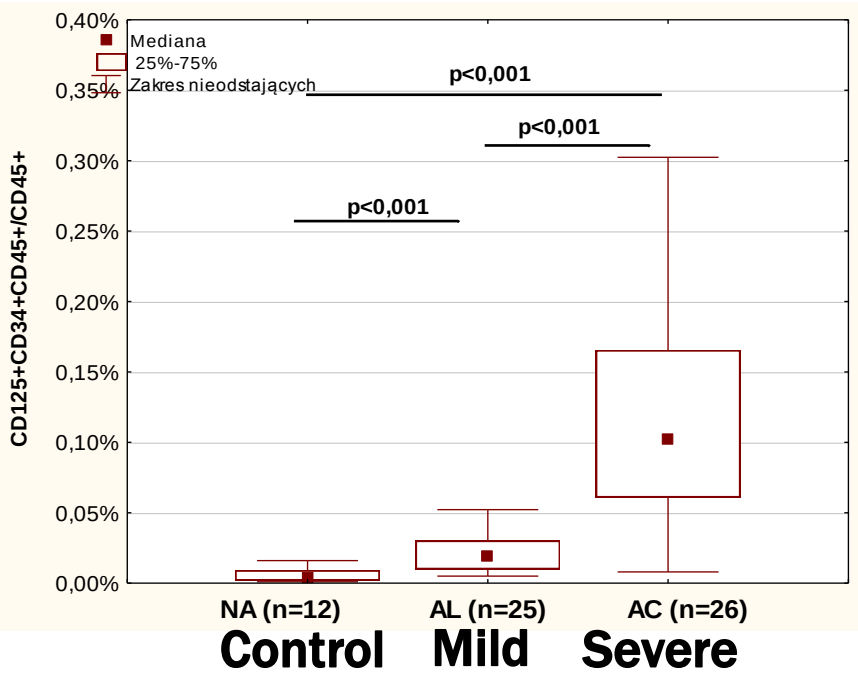




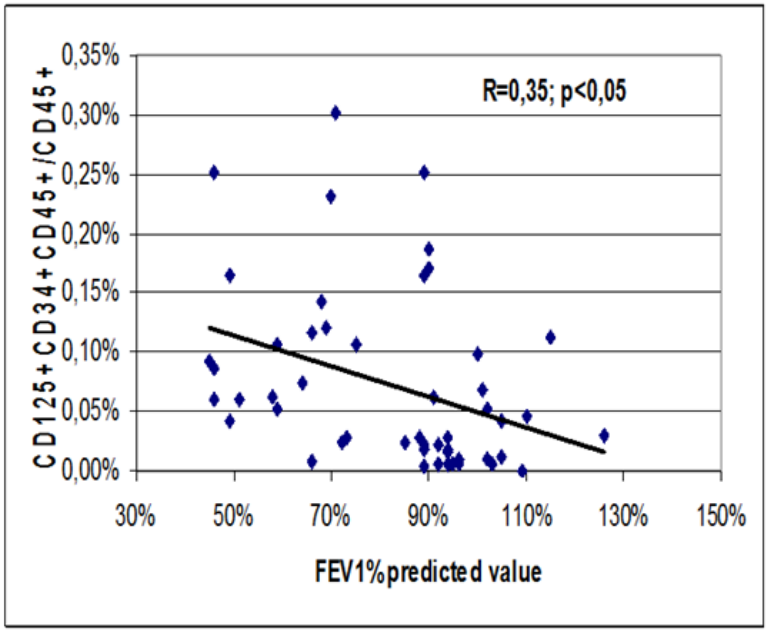
Kim YK et al. AJRCMB 1999,20,388

Eosinophil progenitors in peripheral blood and asthma severity .

Eosinophil progenitors (CD 125+/CD34+/ CD45+)



Correlation of (CD 125+/CD34+/ CD45+) cells with FEV1



J.Makowska Ann Allergy Asthma Immunol. 2008 Oct;101(4):402-6

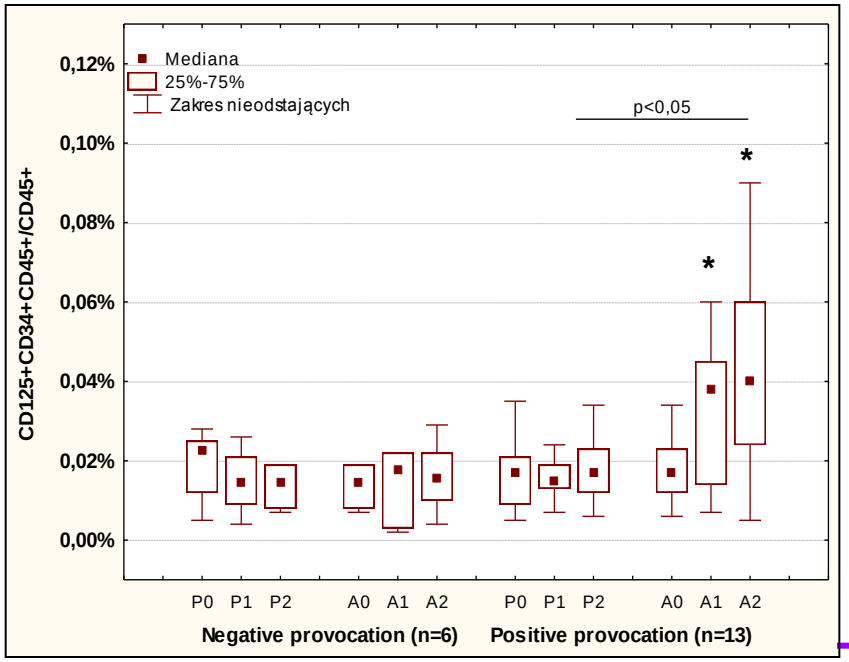
Systemic reaction to aspirin bronchial challenge – recruitement of eosinophil progenitors

19 AERD patients were challenged with lysin aspirin and CD34+cells in PB were determined

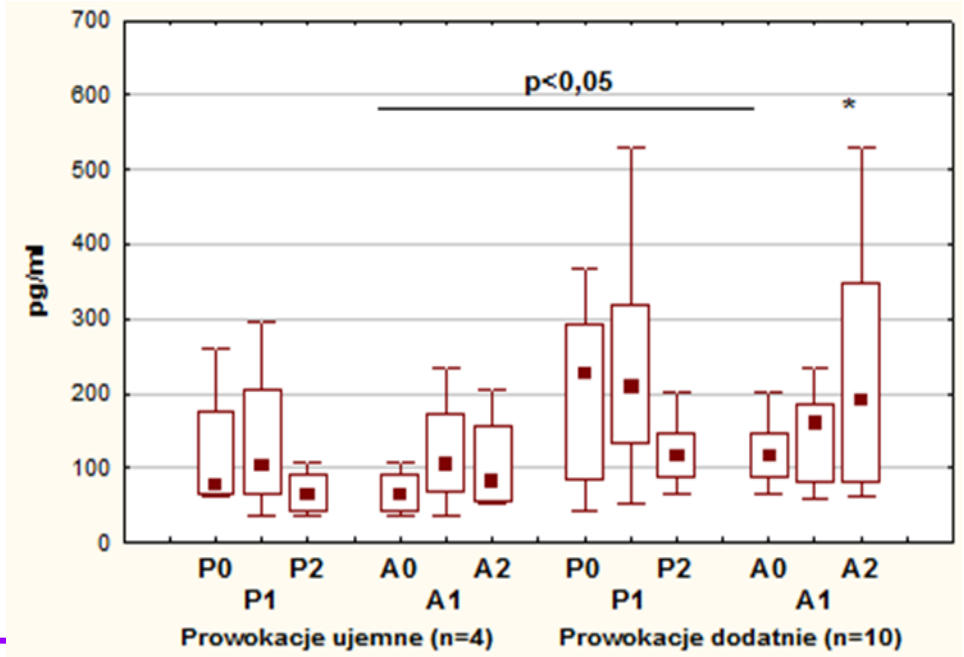
In half of patients positive bronchial reactions were associated with extra bronchial symptoms :

Nasal
Ocular
Cutaneous

CD34+/CD45+/CD125+ cells



Eotaxin-2



Makowska J et al. J Allergy Clin Immunol 2008

Mechanisms linking CRS/NP. with asthma

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Role of Infectious factors in CRS/NPs and asthma exacerbations

	CRS/NP	Asthma
Viruses	Unknown	Important
Fungi	Controversial (EFRS)	Not likely
Bacteria	Superinfections	Controversial – mostly atypical bacteria
Staphylococcal colonization	66-87%	No
Bacterial superantigens	?	?

SAE-IgE and eosinophylic inflammation

- Specific IgE to SAE are present in nasal polyps tissue
- sIgE to SAE are related to eosinophylic inflammation in rhinosinusitis
- Eosinophylic inflammation in NPs (with IL5 protein production) is associated with asthma
- SAE-IgE in NP is associated with asthma
  - OR = 5,8 (95% CI 1.8-29.6%)

Conclusions:

- SAE-IgE may amplify the eosinophylic inflammation and IgE formation increasing the risk of asthma comorbidity

VanBruaene et al. 2008
Bachert eta al. Al. 2010

Characteristics of patients with severe and non-severe asthma (i)

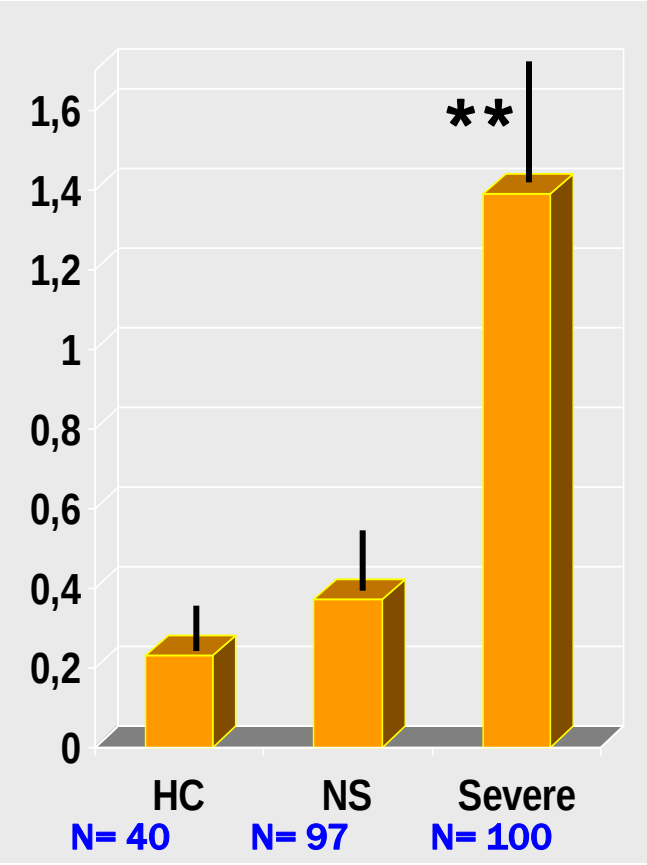
- Patients were recruited from one asthma clinic (Allergy and Asthma Centre in Lodz)
- Severe asthma defined according to the ATS Workshop 2000
- Non-severe asthma – mild and moderate
- Patients were followed up for at least 12 months

	Severe (=109)	NS (n=105)
Exacerbations/year	**1.96±1.48**	**0.37±0.61***
FEV1/FVC%	**63.0±12.5**	**78.8±9***
MEF25-75(l/s)	**43.2 ± 23**	**85.3 ±28***
Inhaled GCS (μg/day)	**1660 ± 0.550**	**590 ± 200***
Oral GCS (mg/day)	**7.8**	**0**

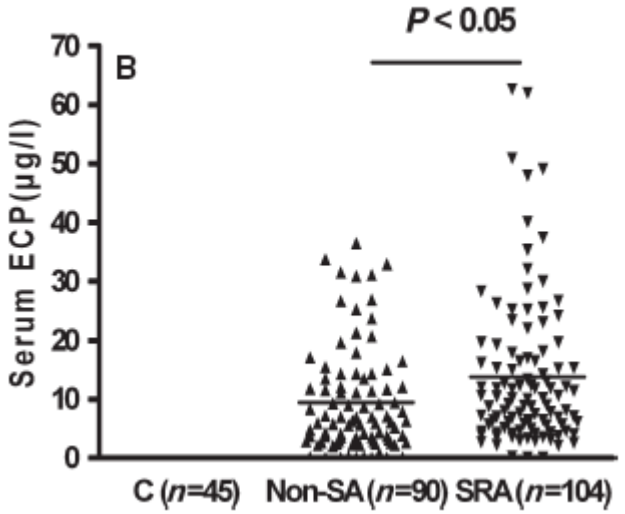
M.L. Kowalski et al. Allergy 2011, 66,32-38

sIgE to Staphylococcus aureus enterotoxins in serum and asthma severity

sIgE to SAE in severe and non-severe asthmatics



Serum ECP in SAE (+) and SAE (-) asthmatics



Serum concentrations of sIgE to SAE was similar in ASA-tolerant and ASA-sensitive asthmatics

M.L. Kowalski et al. Allergy 2011, 66,32-38

Effect of medical treatment of CRS on bronchial asthma

- Improvement in asthma in 4 patients treated for CRS (*Slavin RG 1982*)
- 79% of children stopped using bronchodilators following CRS treatment with antibiotics *(Rachalevsky GS 1984)*
- Spirometry normalized in 67 children with asthma treated for CRS *(Friedman R 1994)*
- Improvement in severity of asthma and PF in 18 children reated with INS/antibiotics *(Tosca 2003)*
- Of 48 patients 18 responded to INCS (600ug/d for 6 wks) and had maintained pulmonary function *(Lamblin C et al. 2000)*

Effect of endoscopic sinus surgery (ESS) on asthma

- Significant reduction in asthma severity (65%), hospitalizations (75%) and emergency visits (81%) (*Nishioka GJ 1994)*
- ESS improved pulmonary function in patients with asthma *(Ikeda K 1999)*
- Improvement in asthma symptoms and oral steroids one year after ESS *(Palmer JN 2001)*
- Decrease in non-specific BHR after ESS *(Okayama M 1998)*
- Improvement in asthma symptoms and PEFR *(Enhage A 2009)*
- Improvement in symptoms, decrease in asthma medication and in hospitalizations *(Proimos E 2010)*

Effect of medical versus surgical CRS/NP therapy on asthma

Patients

- 43 patients with and without NPs and concomitant asthma were randomized to either medical (erythromycin, nasal douches, INCS) or surgical treatment (ESS followed by erythromycin ,nasal douches) and were assessed at 6 and 12 months

Results

- Both medical and surgical treatment were associated with subjective and objective improvement in asthma
- Improvement in CRS symptoms correlated with improvement in asthma symptoms and control

Ragab S et al. ERJ 2006,28,68

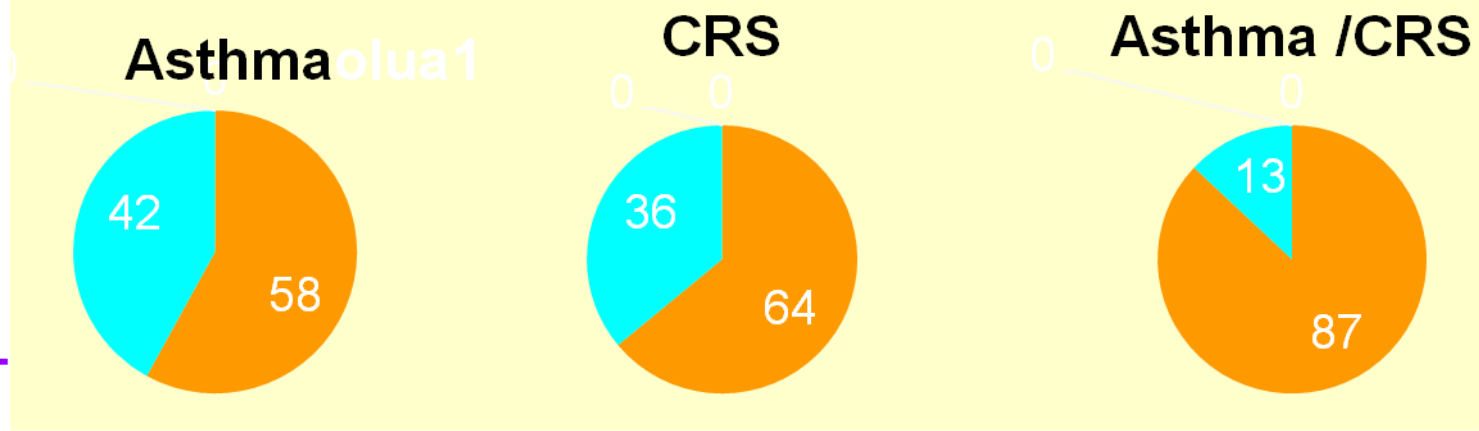
Aspirin desensitization in patients with AERD

- 1923 F. Vidal reported „desensitization” to aspirin
- 1976 C. R. Zeiss & R.F. Lockey described refractory period to aspirin
- 1981 D.D. Stevenson reported clinical benefits of prolonged treatment with aspirin after desensitization

Clinical efficacy of ASA-desensitization in AERD

- 11 studies assessed clinical efficacy of ASA after desensitization
- Total 474 patients were successfully desensitized
- Only 1 study was placebo controlled ***(Stevenson 1984)***
- Duration of treatment: 2 weeks - 6 years
- Dosing of aspirin: 325 mg-2600 mg
- Clinical assessment : symptoms; need for medicines; exacerbations, polyps recurrence
- Full data available for limited number of patients

% of patients with clinical improvement while on aspirin



Conclusions

- CRS with NP is associated with bronchial asthma and may affect asthma severity
- The pathomechanisms of CRS/NP and asthma association is complex
- Proper management of CRS/NP may improve asthma symptoms
- New treatment modalities common for both diseases are needed

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