

New therapeutic approaches to rhinosinusitis

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Lecture outline

- Looking for better evidence
- Meta analyses of antibiotic treatment in acute rhinosinusitis
- Meta analyses of steroid treatment in acute rhinosinusitis
- Meta analyses of steroid treatment in chronic rhinosinusitis with and without nasal polyps
- Meta analyses of nasal lavages trials
- Trials on long-term antibiotics in chronic rhinosinusitis
- Evidence on biologicals in the rhinosinusitis treatment



Looking for better evidence

New treatment approaches

Better evidence in standard treatments

Meta analyses of high quality double blind randomized placebo controlled trial

Subgroup analysis

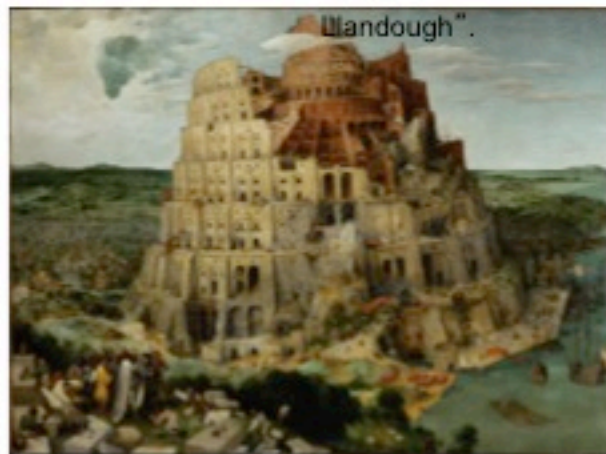
Phenotyping and endotyping

Establishing criteria to evaluate new treatments



Archie
Cochrane

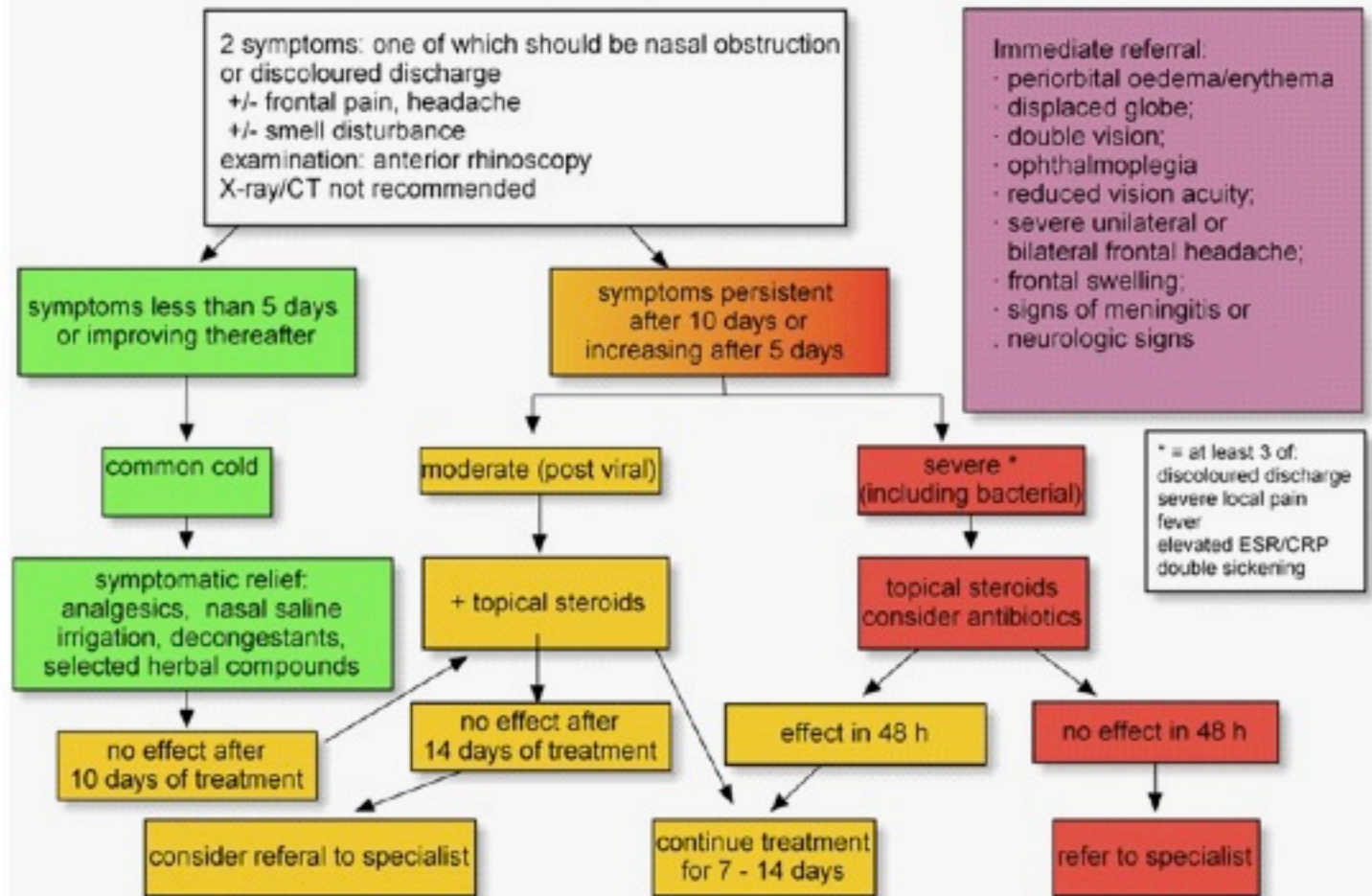
"Cardiff University Library, Cochrane Archive, University Hospital



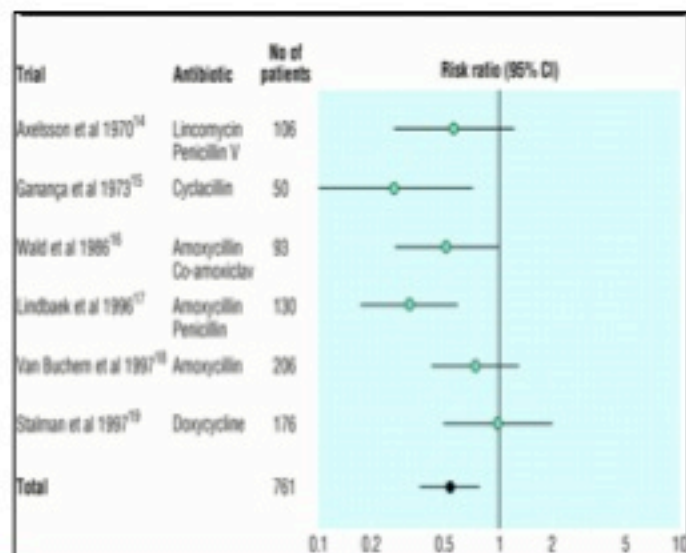
Confusion of tongues

"Sometimes it's not enough to know what things mean, sometimes you have to know what things don't mean." Bob Dylan

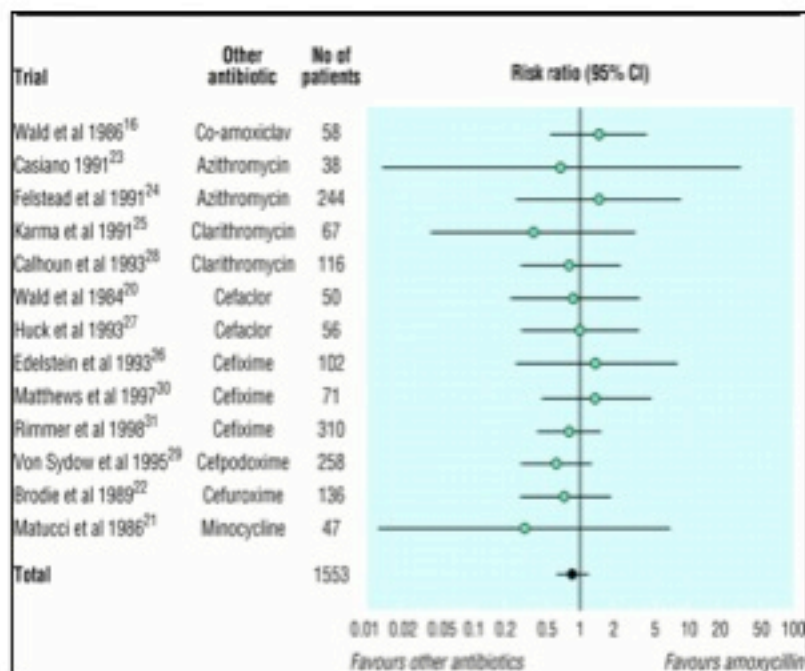
Acute rhinosinusitis in adults management scheme for Primary Care



A need for antibiotic in ARS?



de Ferranti SD et al. BMJ. 1998;317(7159):632-7



(Williams JW et al. Cochrane Database Syst Rev. 2003, Ahovuo-Saloranta A et al. Antibiotics for acute maxillary sinusitis. Cochrane Database Syst Rev. 2008; (2):CD000243. Young J et al. Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data. Lancet. 2008;371(9616):908-14.)

Evidence for antibiotics in acute rhinosinusitis –meta analyses of DBRPCT

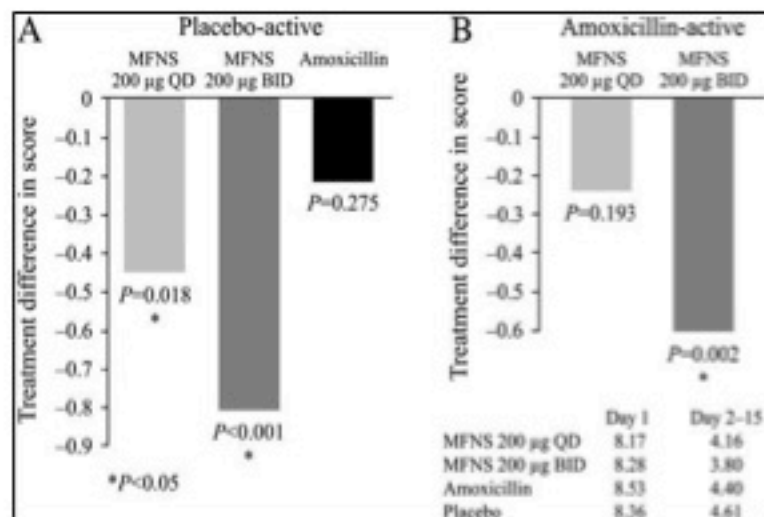
- slight statistical difference in favor of antibiotics, compared to placebo
- cure or improvement rate high in both the placebo group (80%) and the antibiotic group (90%).
- if clinical failure = lack of total cure, significant difference in favor of antibiotics compared to placebo at 7 to 15 days follow up.
- 15 patients with rhinosinusitis-like complaints would have to be given antibiotics before an additional patient was cured.
- *Ahovuo-Saloranta A et al. Antibiotics for acute maxillary sinusitis. Cochrane Database Syst Rev. 2008;(2):CD000243.*
- *Young J et al. Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data. Lancet. 2008;371(9616):908-14.*



Clinicians need to weigh the small benefits of antibiotic treatment against the potential for adverse effects at both the individual and general population level

Evidence on intranasal steroids for acute RS

- Meta analysis of DBRPCT
- Four studies with 1943 participants met the inclusion criteria.
- participants receiving INCS were more likely to have resolution or improvement of symptoms than those receiving placebo (73% versus 66.4%; risk ratio (RR) 1.11; 95% CI 1.04 to 1.18).
- Higher doses of INCS had a stronger effect on improvement or complete relief of symptoms



Meltzer EO et al. *JACI* 116/6: 1289-95, 2006.,
 Merenstein D et al, *J Fam Pract*, 2005., Bucher HC
 et al. *Arch Int Med* 2003

Zalmanovici A, Yaphe J.

Intranasal steroids for acute sinusitis. Cochrane Database Syst Rev. 2009
 Oct 7;(4):CD005149.

Systemic steroids for acute rhinosinusitis

- Four RCTs with a total of 1008 adult participants
- 3 placebo controlled, one NSAID
- participants treated with oral corticosteroids were more likely to have short-term resolution or improvement of symptoms than those receiving the control treatment
- The effect is small, stronger at the earlier days.

Other treatments for ARS

- **selected herbal compounds** (Ponikau JU, et al. An exploratory trial of Cyclamen europaeum extract for acute rhinosinusitis. *Laryngoscope*. 2012; Pfaar O, et al. Cyclamen europaeum nasal spray, a novel phytotherapeutic product for the management of acute rhinosinusitis: a randomized double-blind, placebo-controlled trial. *Rhinology*. 2012 Mar; 50(1):37-44.; Bachert C, Schapowal A, Funk P, Kieser M. Treatment of acute rhinosinusitis with the preparation from Pelargonium sidoides EPs 7630: a randomized, double-blind, placebo-controlled trial. *Rhinology*. 2009 Mar;47(1):51-8.)
- **bacterial lysates** (Cazzola M, et al. Polyvalent mechanical bacterial lysate for the prevention of recurrent respiratory infections: a meta-analysis. *Pulm Pharmacol Ther*. 2012 Feb;25(1):62-8.
- **saline** (Kassel JC, King D, Spurling GK. Saline nasal irrigation for acute upper respiratory tract infections. *Cochrane Database Syst Rev*. 2010 Mar 17;(3):CD006821.)

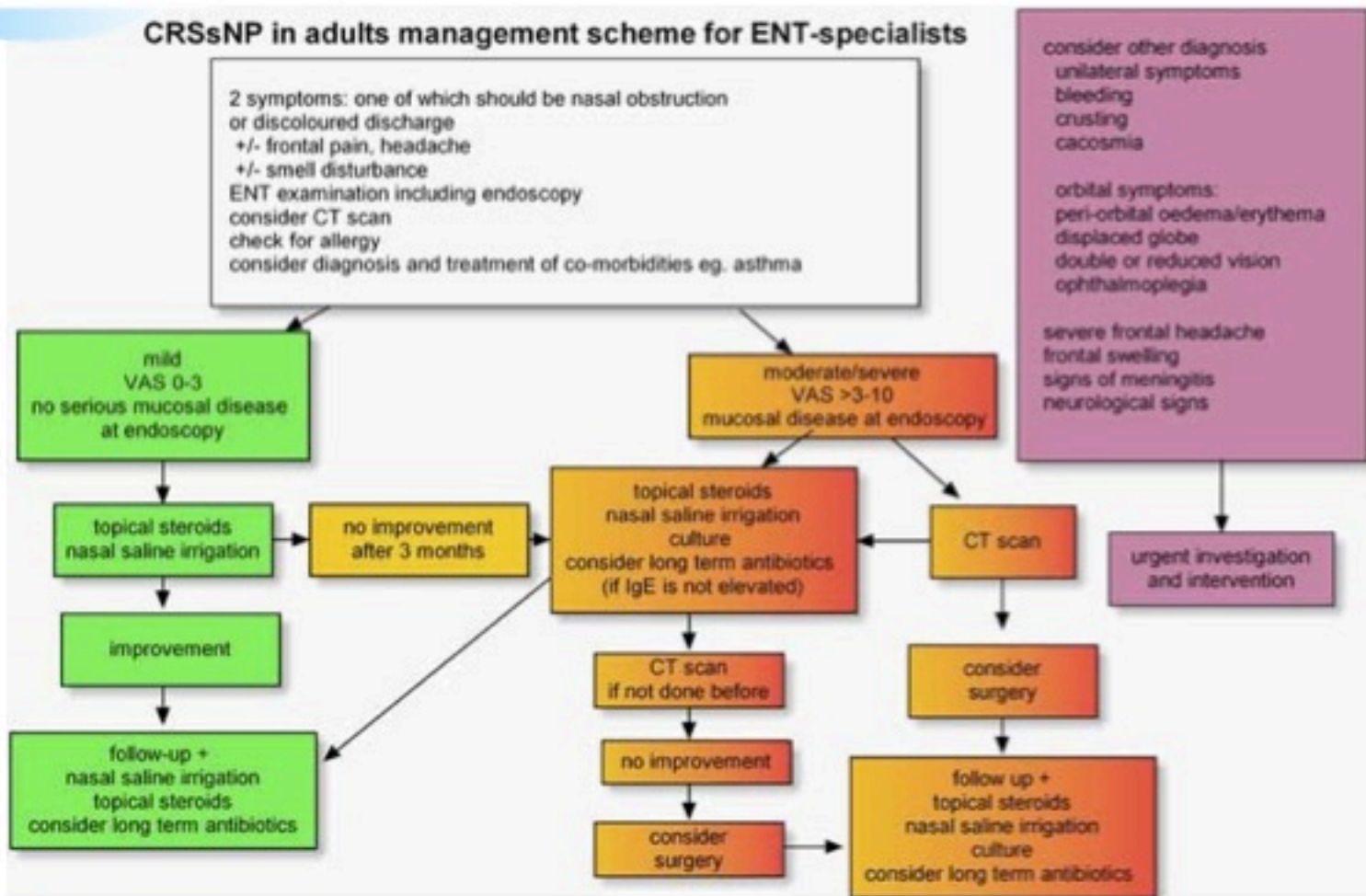
Treatment of CRS – what is the evidence?

- nasal lavage
 - nasal steroids
 - systemic steroids
 - antibiotics – long term low dose
 - surgery
-
- Problem of placebo control for saline and surgery.
 - Ethical issue of placebo (sham) surgery



I learned a long time ago that minor surgery is when they do the operation on someone else, not you. ~Bill Walton

CRSsNP in adults management scheme for ENT-specialists



Meta analysis – nasal steroids in CRS s/NP

Review: Topical steroids in CRS without polyps
 Comparison: 02 Topical steroids compared to controls
 Outcome: 01 Number of patients NOT responding to treatment

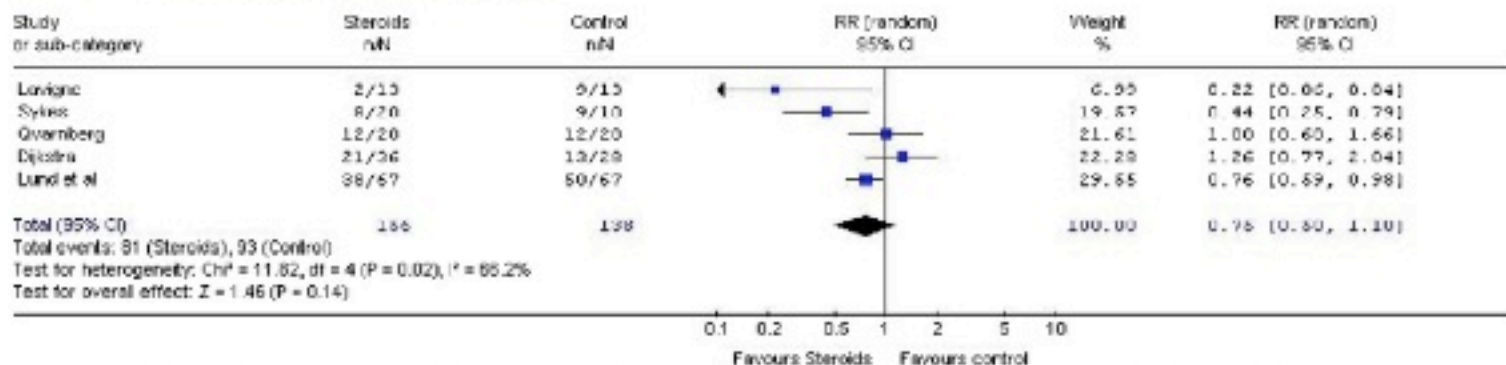


Figure 2 Effects of topical steroids compared with no topical steroids (outcome, treatment nonresponse).

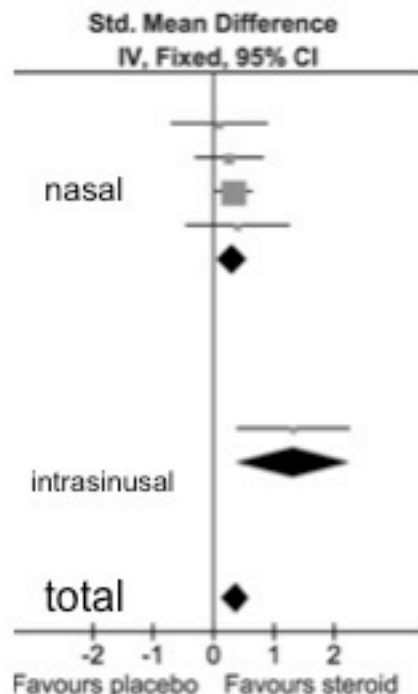
Topical steroid is a beneficial treatment for CRS without polyps and the adverse effects are minor. Direct delivery of steroid to the sinuses may bring more beneficial effect. No beneficial effect of previous surgery.

•Kalish LH, Arendts G, Sacks R, Craig JC. Topical steroids in chronic rhinosinusitis without polyps: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg.* 2009;141(6):674-83.

Snidvongs K, Kalish L, Sacks R, Craig JC, Harvey RJ. Topical steroid for chronic rhinosinusitis without polyps. *Cochrane Database Syst Rev.* 2011 Aug 10;(8):CD009274.

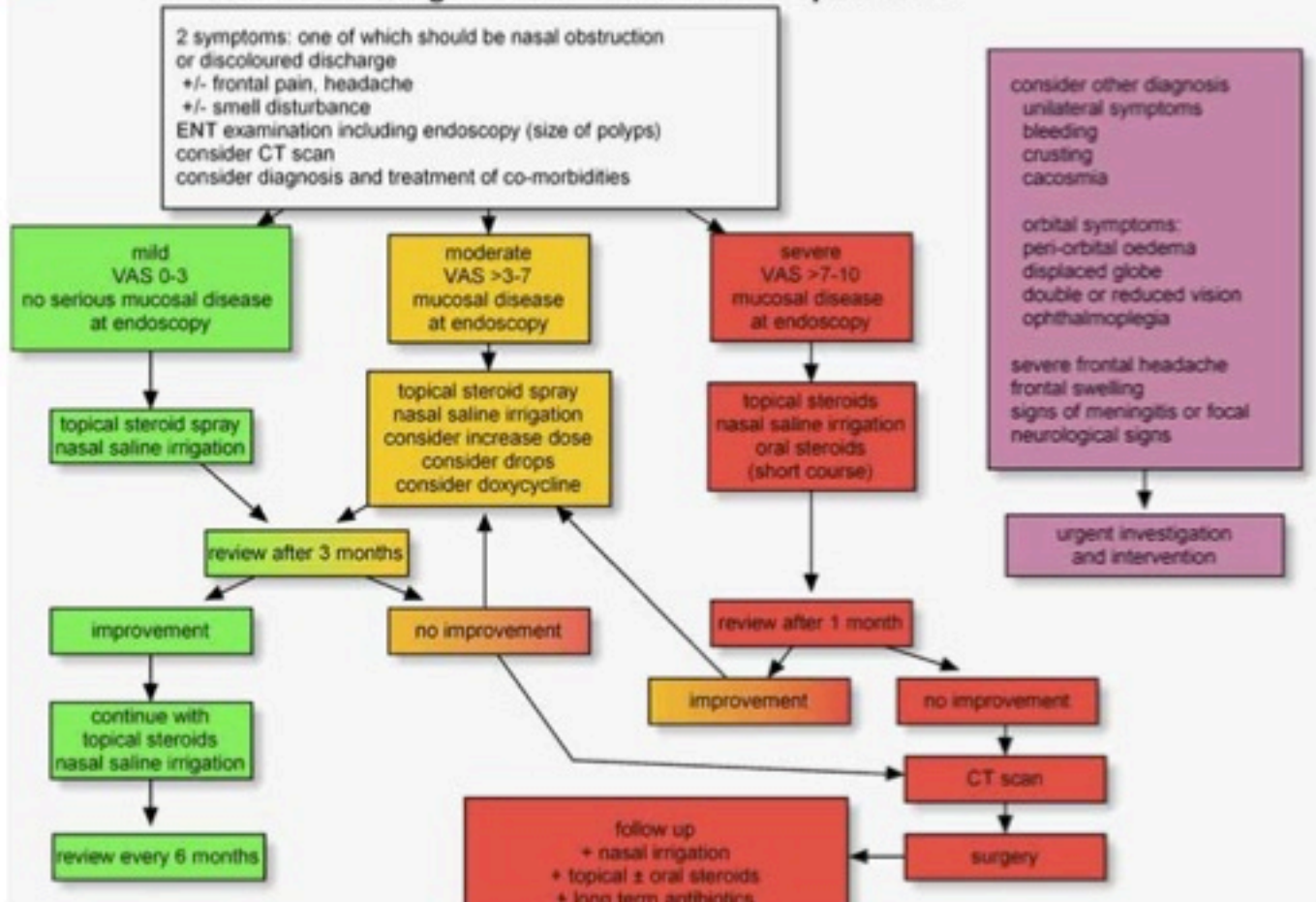
Topical steroid in CRSsNP

- Meta analysis of 5 double blind randomized placebo controlled trials confirms efficacy of nasal and endosinusual application
- Previous surgery does not seem to have significant effect
- Endosinusual application seem to bring more benefit
- Nasal application modality does not have impact



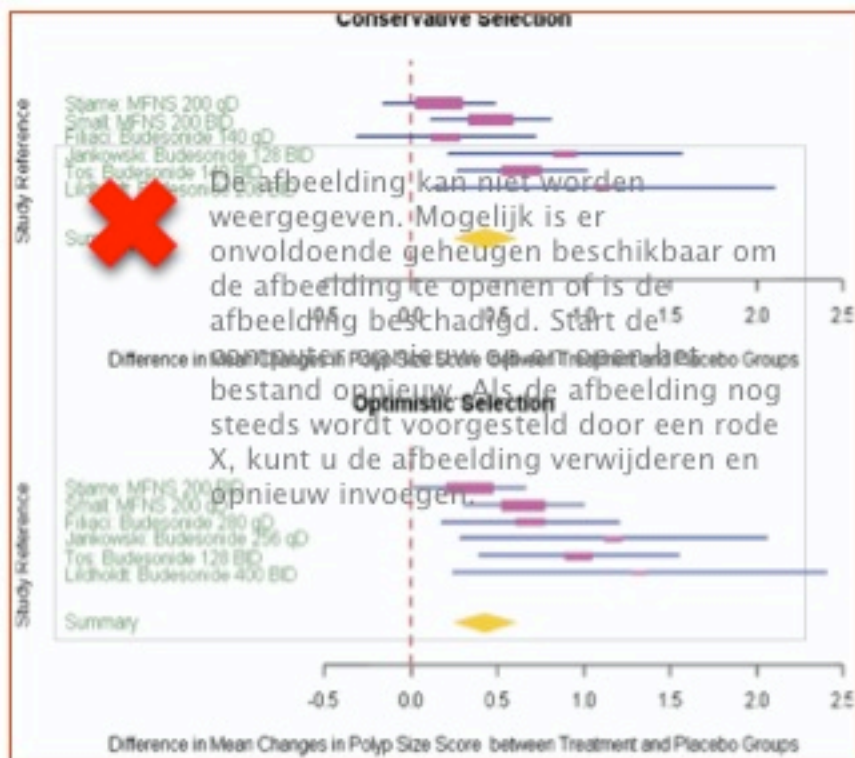
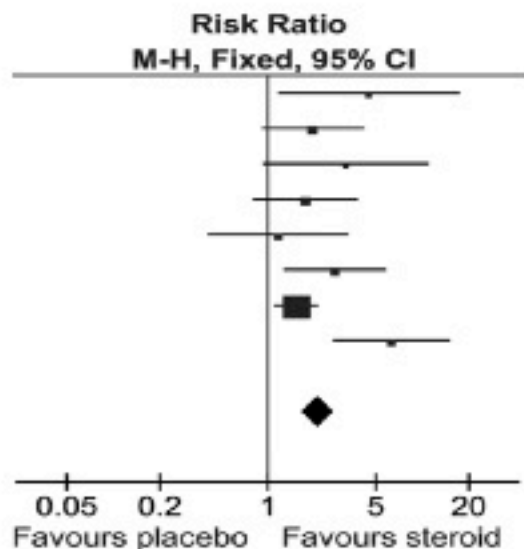
Snidvongs K, Kalish L, Sacks R, Craig JC, Harvey RJ. Topical steroid for chronic rhinosinusitis without polyps. Cochrane Database Syst Rev. 2011 Aug 10;(8):CD009274.

CRSwNP management scheme for ENT-specialists



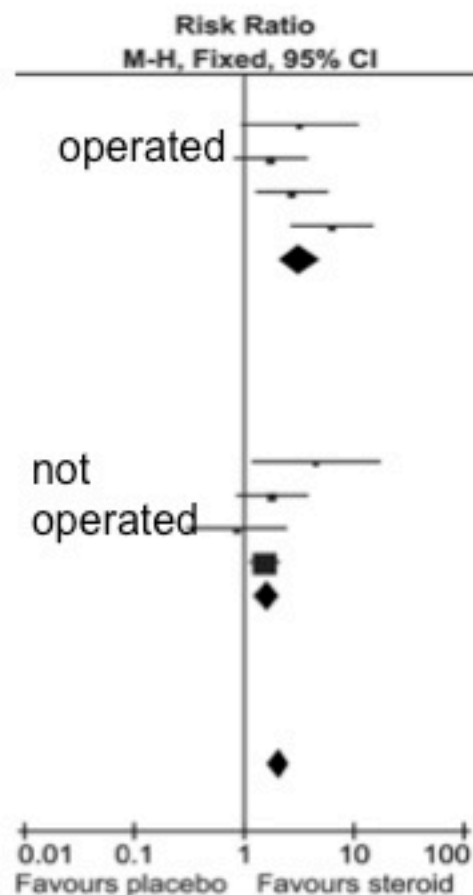
Meta analysis – topical steroid in CRS with nasal polyps

- No study without response
- Surgical cases excluded
- Mean reduction is 0,6



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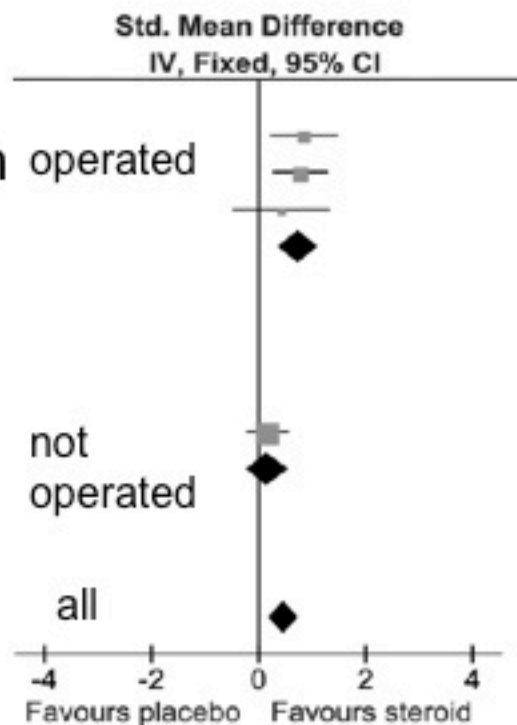
Nasal steroid treating CRSwNP



Meta analysis of subgroups

Operated have better outcomes than non-operated

Improvement according to polyp size and subjective symptoms reduction



Oral steroids for CRSwNP

- Three trials (166 patients) - short-term benefit of a short (two to four-week) course of oral steroids compared to placebo
- There was an objective reduction of polyp size and a subjective improvement of nasal symptoms and quality of life
- Moderate to low quality of these trials
- No report of significant adverse effects of treatment with a short course of steroids.

Martinez-Devesa P, Patiar S. Oral steroids for nasal polyps. Cochrane Database Syst Rev. 2011 Jul 6;(7):CD005232.

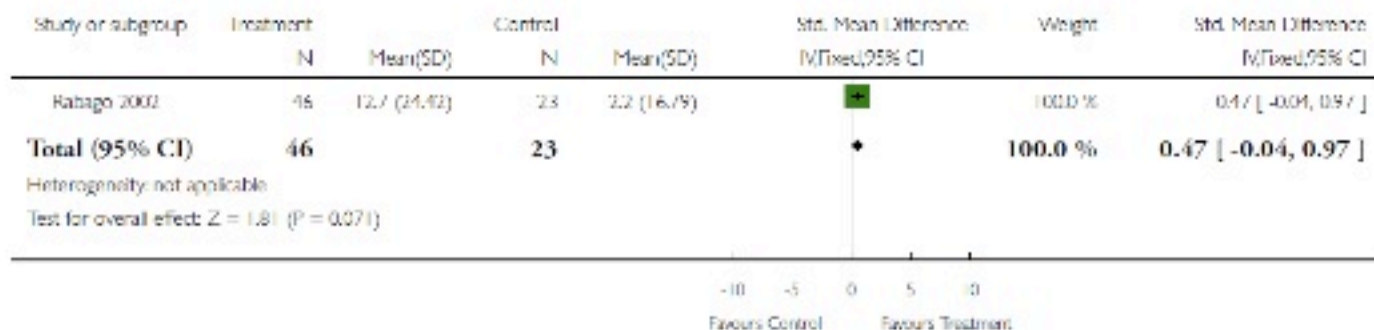
Patiar S, Reece P. Oral steroids for nasal polyps. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD005232. Review. Update in: Cochrane Database Syst Rev. 2011;(7):CD005232.

Analysis 1.3. Comparison 1 A: Comparison of saline versus no treatment, Outcome 3 Quality of Life scores (general).

Review: Nasal saline irrigations for the symptoms of chronic rhinosinusitis

Comparison: 1 A: Comparison of saline versus no treatment

Outcome: 3 Quality of Life scores (general)



Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD006394.

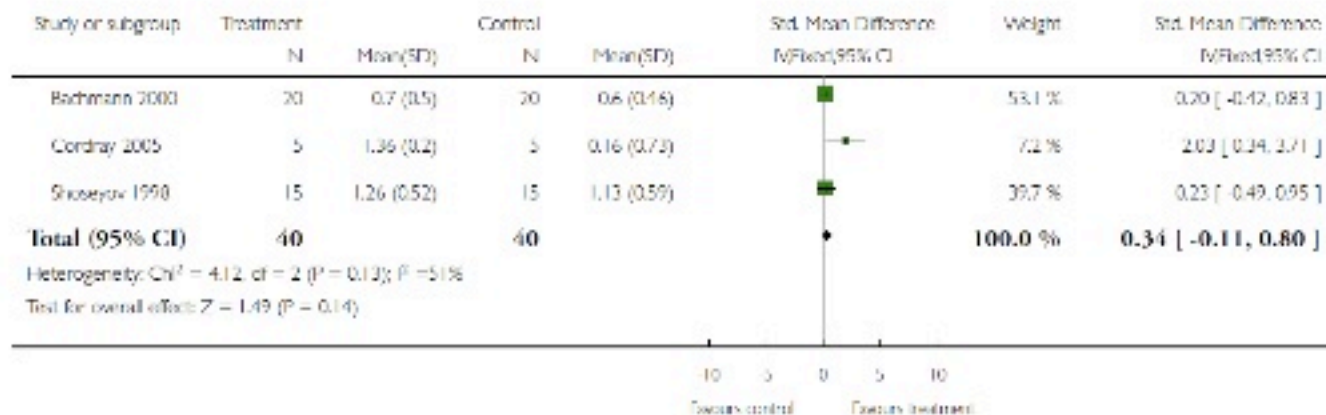
Hypertonic vs. isotonic saline

Analysis 4.1. Comparison 4 E: Hypertonic versus isotonic saline, Outcome 1 Symptom scores.

Review: Nasal saline irrigations for the symptoms of chronic rhinosinusitis

Comparison: 4 E: Hypertonic versus isotonic saline

Outcome: 1 Symptom scores



Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD006394.

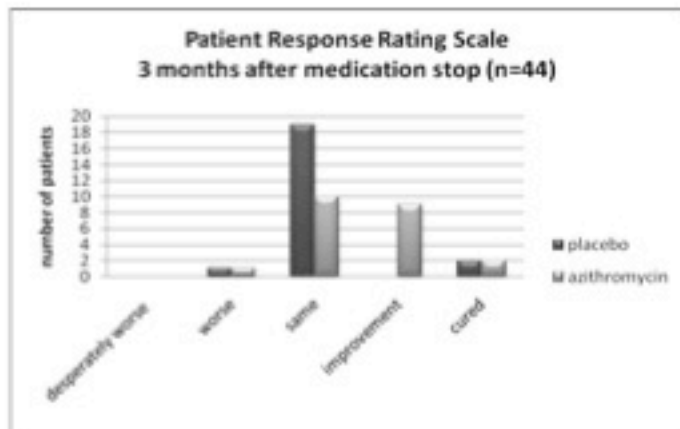
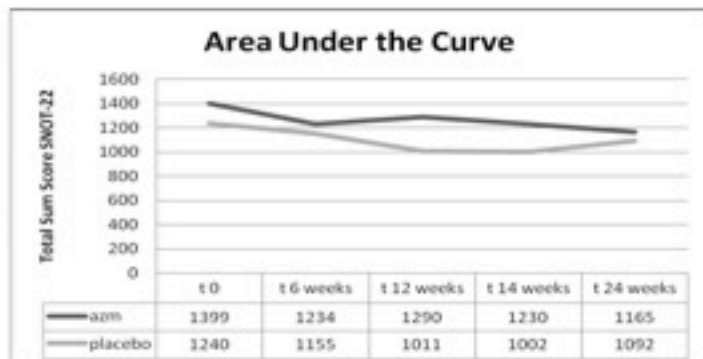
Long term low dose macrolides

- Randomized controlled prospective study – 1 year follow up – erythromycine + lavage vs. endoscopic sinus surgery = improvement 51 i 54% surgical group, 50,4 i 61,2% medication group (*Ragab, Lund, Scadding, Laryngoscope, 2004*)
- Double blind randomized placebo controlled trial 150 mg/ 3 months roxythromicine vs. placebo – active better in symptom score, endoscopy, sacharine test and Il-8, not in olfaction and PNIF, better in patients with normal IgE (<200) (*Wallwork et al, Laryngoscope, 2006*)



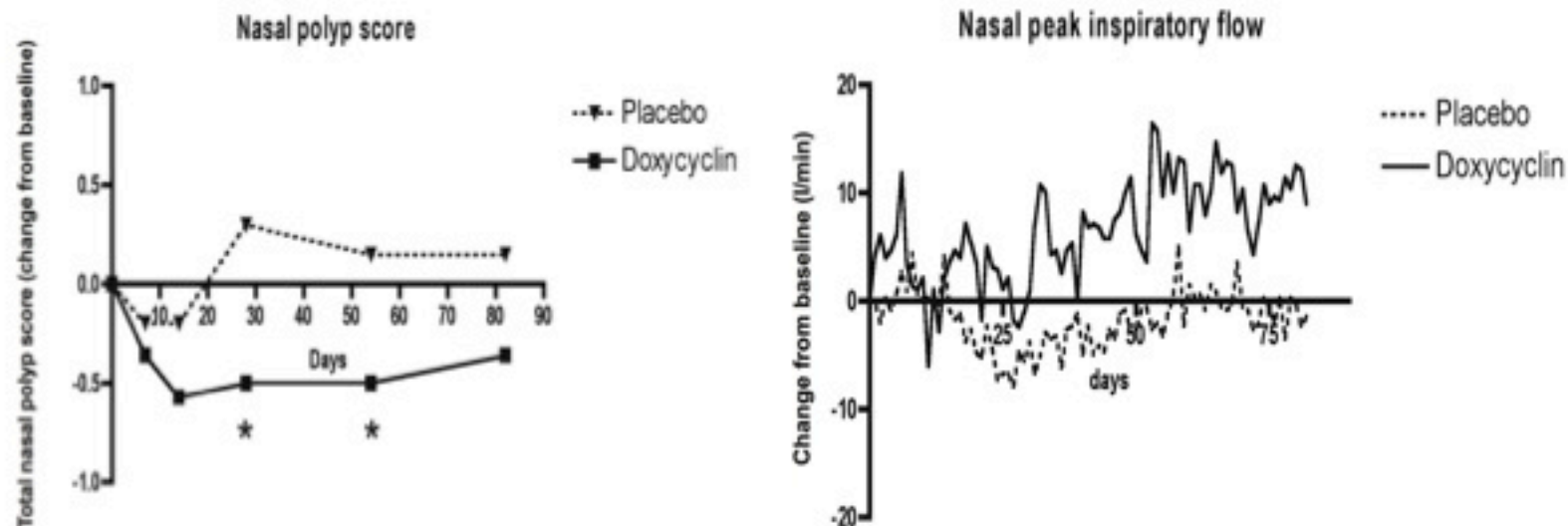
MACS – azithromycin vs. placebo - 3 months

- Multicentric study
- Azithromycin 500 mg weekly (first 3 days daily)
- Symptoms (EPOS) + Lund Mackay <5 on the worse side
- 60 patients (30+30), 50% asthma, 58% revision
- No effect on symptoms or objective measures
- Videler WJ et al. Lack of efficacy of long-term, low-dose azithromycin in chronic rhinosinusitis: a randomized controlled trial. *Allergy*. 2011 ; 66(11):1457-68.



Doxycycline in CRS w. NP

20 days doxy (100mg/d) vs. placebo



Van Zele T et al. Oral steroids and doxycycline: two different approaches to treat nasal polyps. *J Allergy Clin Immunol*. 2010 May;125(5):1069-1076.e4.

Antifungals for CRS

- Six studies (380 participants)
- 5 studies - topical, 1 systemic antifungals.
- All trials being double-blinded and randomised.
- Pooled meta-analysis showed no statistically significant benefit of topical or systemic antifungals over placebo for any outcome
- Symptom scores in fact statistically favoured the placebo group. Adverse event reporting was statistically significantly higher in the antifungal group



Sacks PL 4th, et al. Antifungal therapy in the treatment of chronic rhinosinusitis: a meta-analysis. *Am J Rhinol Allergy*. 2012 Mar-Apr;26(2):141-7.

Sacks PLet al.. Topical and systemic antifungal therapy for the symptomatic treatment of chronic rhinosinusitis. *Cochrane Database Syst Rev*. 2011 Aug 10; (8):CD008263.

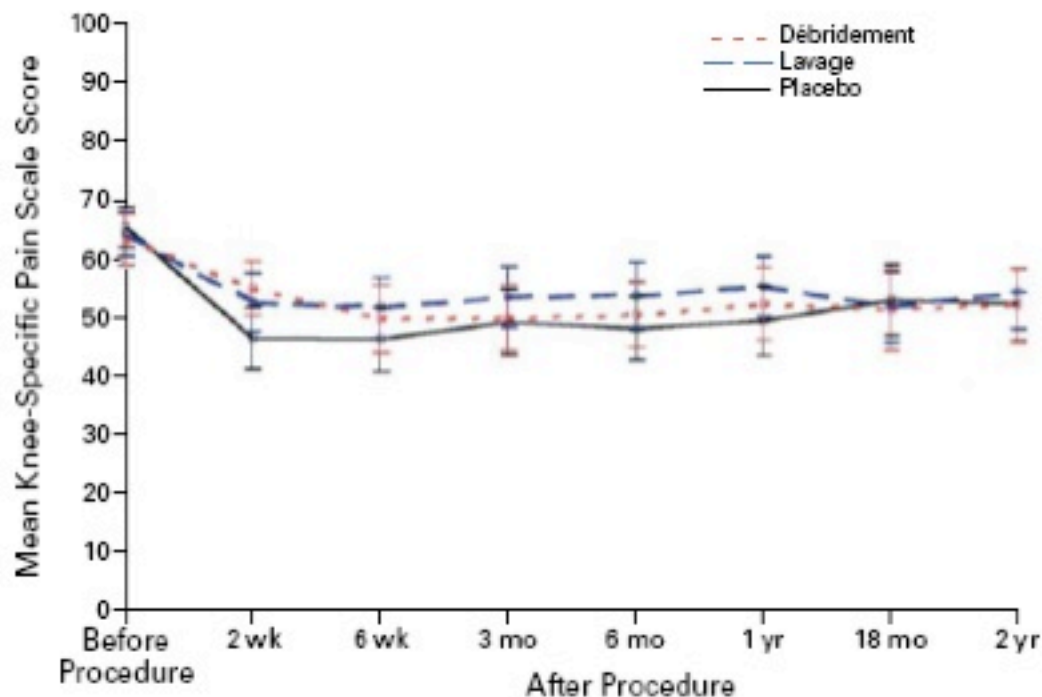
What is the evidence for surgery?

- Khalil HS, Nunez DA. Functional endoscopic sinus surgery for chronic rhinosinusitis. Cochrane Database Syst Rev. 2006 Jul 19;3: CD004458.
- Ahmed J, et al. Functional endoscopic balloon dilation of sinus ostia for chronic rhinosinusitis. Cochrane Database Syst Rev. 2011 Jul 6; (7):CD008515.
- Saleh AM, et al. Prophylactic Perioperative Antibiotic Use in Endoscopic Sinus Surgery: A Systematic Review and Meta-analysis. Otolaryngol Head Neck Surg. 2012 Jan 12.
- Mallardi V, et al. Traditional endonasal and microscopic sinus surgery complications versus endoscopic sinus surgery complications: a meta-analysis. Eur Arch Otorhinolaryngol. 2012;269(3): 721-9.

Level of evidence is low not only as there is no placebo control, but the quality of the most of the trials does not meet EBM criteria.

Power of placebo surgery

Moseley JB et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. NEJM 347, 2002



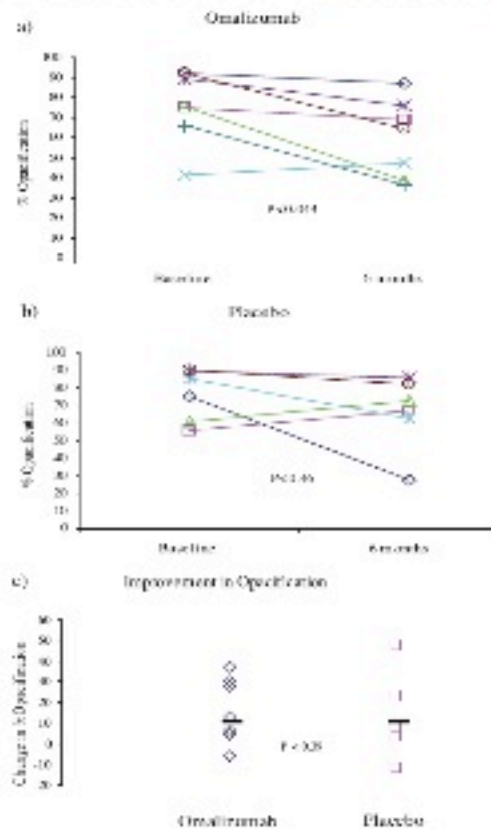
No difference between surgery, lavage and placebo at any term in 2 years.

- Anti IgE (omalizumab) monthly for 6 months – 14 patients with refractory CRS (12 wNP) – no significant response in reduction of sinus opacification on CT, SNOT 20, endoscopy - underpowered

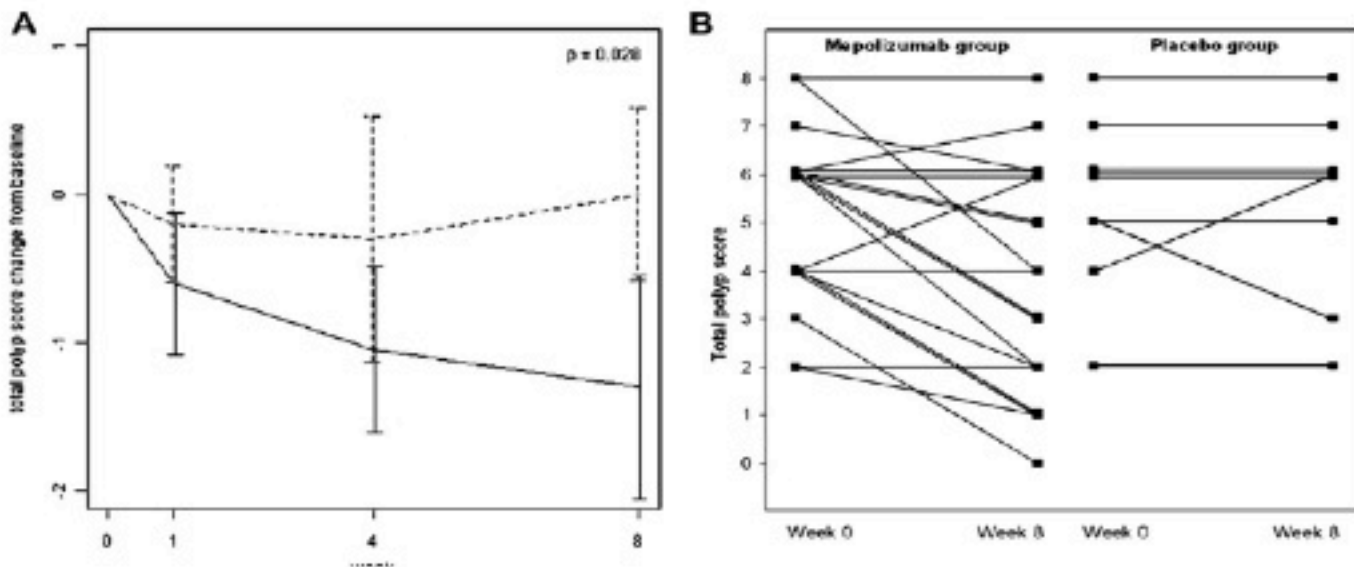
Pinto JM, et al. A randomized, double-blind, placebo-controlled trial of anti-IgE for CRS. Rhinology. 2010;48:318-24

- Anti IL-5 (reslizumab 3 or 1 mg/kg or placebo) 24 patients, DBRPCT (16/8), no improvement in polyp scores, 50% pats responders

Gevaert P, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. J Allergy Clin Immunol. 2006;118(5):1133-41.)



Anti-IL5



- Anti IL-5 30 (20/10 pts) 2x750mg in 2 months, observed 6 months – polyp scores improved for 1,3 pts in active and CT improvement
Gevaert P, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. J Allergy Clin Immunol. 2011 Nov; 128(5):989-95.e1-8.

Still no solution

- biofilm
- steroid resistant CRSwNP
- empty nose – facial pain
- genetic disorders (PCD, CF)
- aggressive surgeons

