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

“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

2 symptoms: one of which should be nasal obstruction or discoloured discharge
- +/- frontal pain, headache
- +/- smell disturbance
- examination: anterior rhinoscopy
- X-ray/CT not recommended

Symptoms less than 5 days or improving thereafter
- Common cold
  - Symptomatic relief: analgesics, nasal saline irrigation, decongestants, selected herbal compounds
  - No effect after 10 days of treatment
  - Consider referral to specialist

Symptoms persistent after 10 days or increasing after 5 days
- Moderate (post viral)
  - Topical steroids
  - No effect after 14 days of treatment
  - Continue treatment for 7 - 14 days

Severe *
- (including bacterial)
  - Topical steroids
  - Consider antibiotics
  - Effect in 48 h
  - Refer to specialist

Immediate referral:
- Periorbital oedema/erythema
- Displaced globe
- Double vision
- Ophthalmoplegia
- Reduced vision acuity
- Severe unilateral or bilateral frontal headache
- Frontal swelling
- Signs of meningitis or neurologic signs

* = At least 3 of: discoloured discharge, severe local pain, fever, elevated ESR/CRP, double sickening
A need for antibiotic in ARS?

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.

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.


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


• 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

2 symptoms: one of which should be nasal obstruction or discoloured discharge
+/- frontal pain, headache
+/- smell disturbance
ENT examination including endoscopy
consider CT scan
check for allergy
consider diagnosis and treatment of co-morbidities eg. asthma

mild
VAS 0-3
no serious mucosal disease at endoscopy

- topical steroids nasal saline irrigation
- improvement

- follow-up + topical steroids nasal saline irrigation
- consider long term antibiotics

moderate/severe
VAS >3-10
mucosal disease at endoscopy

topical steroids nasal saline irrigation culture
consider long term antibiotics (if IgE is not elevated)

- CT scan
- if not done before
- no improvement

consider surgery

CT scan
consider surgery
follow up + topical steroids nasal saline irrigation culture
consider long term antibiotics

consider other diagnosis
unilateral symptoms
bleeding
crusting
cacosmia

orbital symptoms: peri-orbital oedema/erythema
displaced globe
double or reduced vision
ophthalmoplegia

severe frontal headache
frontal swelling
signs of meningitis
neurological signs

urgent investigation and intervention
**Meta analysis – nasal steroids in CRS s/NP**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Steroids n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovigiane</td>
<td>2/15</td>
<td>5/15</td>
<td></td>
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<td></td>
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<tr>
<td>Sylves</td>
<td>8/70</td>
<td>9/10</td>
<td></td>
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<tr>
<td>Quammborg</td>
<td>12/20</td>
<td>12/20</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dijkstra</td>
<td>21/26</td>
<td>12/20</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lund et al.</td>
<td>38/67</td>
<td>50/67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>186</strong></td>
<td><strong>190</strong></td>
<td></td>
<td><strong>100.00</strong></td>
<td><strong>0.96 [0.80, 1.13]</strong></td>
</tr>
<tr>
<td>Total events: 81 (Steroids), 93 (Control)</td>
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</table>

Test for heterogeneity: $\chi^2 = 11.82, df = 4 (P = 0.02), I^2 = 88.2\%$

Test for overall effect: $Z = 1.46 (P = 0.14)$

**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.

Topical steroid in CRSsNP

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

CRSwNP management scheme for ENT-specialists

2 symptoms: one of which should be nasal obstruction or discoloured discharge
+/- frontal pain, headache
+/- smell disturbance
ENT examination including endoscopy (size of polyps)
consider CT scan
consider diagnosis and treatment of co-morbidities

mild
VAS 0-3
no serious mucosal disease at endoscopy

topical steroid spray
nasal saline irrigation

review after 3 months
improvement
continue with topical steroids
nasal saline irrigation
review every 6 months

moderate
VAS >3-7
mucosal disease at endoscopy

topical steroid spray
nasal saline irrigation
consider increase dose
consider drops
consider doxycycline

review after 1 month
improvement
no improvement

severe
VAS >7-10
mucosal disease at endoscopy

topical steroids
nasal saline irrigation
oral steroids
(short course)

review after 1 month
improvement
no improvement

follow up
+ nasal irrigation
+ topical ± oral steroids
+ long term antibiotics

consider other diagnosis
unilateral symptoms
bleeding
crusting
cacosmia

orbital symptoms:
peri-orbital oedema
displaced globe
double or reduced vision
ophthalmoplegia

severe frontal headache
frontal swelling
signs of meningitis or focal neurological signs

urgent investigation and intervention

CT scan
surgery
Meta analysis – topical steroid in CRS with nasal polyps

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

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.

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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>N</th>
<th>Mean (SD)</th>
<th>Control</th>
<th>N</th>
<th>Mean (SD)</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratago 2000</td>
<td>12.7 (24.43)</td>
<td>26</td>
<td>12.8 (16.29)</td>
<td>23</td>
<td>12.2 (16.78)</td>
<td>0.0111 %</td>
<td>0.47 [-0.04, 0.97]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>23</td>
<td>46</td>
<td>12.7 (24.43)</td>
<td>23</td>
<td>12.2 (16.78)</td>
<td>100.0 %</td>
<td>0.47 [-0.04, 0.97]</td>
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</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 1.81 (P = 0.071)

Hypertonic vs. isotonic saline

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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Std. Mean Difference (95% CI)</th>
<th>Weight</th>
<th>Std. Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (Mean(SD))</td>
<td>N (Mean(SD))</td>
<td></td>
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<tr>
<td>Bachmann 20000</td>
<td>20 (0.7 (0.5))</td>
<td>20 (0.6 (0.48))</td>
<td>5.1% [0.12, 0.83]</td>
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<tr>
<td>Cordray 2005</td>
<td>5 (1.3 (0.2))</td>
<td>5 (0.16 (0.23))</td>
<td>7.2% [0.24, 2.7]</td>
<td></td>
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</tr>
<tr>
<td>Skoetz 2000</td>
<td>15 (1.2 (0.52))</td>
<td>15 (1.13 (0.59))</td>
<td>39.7% [0.49, 0.95]</td>
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</tr>
<tr>
<td>Total (95% CI)</td>
<td>40 (1.26 (0.52))</td>
<td>40 (1.13 (0.59))</td>
<td>100.0% [0.34, 0.11, 0.60]</td>
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</tbody>
</table>

Heterogeneity: Chi² = 4.12, df = 2 (P = 0.13); I² = 51%
Test for overall effects: Z = 1.49 (P = 0.14)

Long term low dose macrolides

- Randomized controlled prospective study – 1 year follow up – erythromycin + 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 roxythromicline vs. placebo – active better in symptom score, endoscopy, sacharine test and II-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

Doxycycline in CRS w. NP

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

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.

What is the evidence for surgery?


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


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

- 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  

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

Still no solution

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