Treatment of CRS in adults
the sandwich of medical and surgical
and medical treatment again

Professor Valerie J LUND CBE
University College London
Menu of Possible Medical Treatments in CRS

- Steroids
- Saline irrigation
- Antibiotics
- Aspirin desensitisation
- Biologics
  - Anti-IgE
  - Anti-IL5
  - Anti-IL4/IL13 etc etc
- Mucoactive agents
- Antihistamines (oral, topical)
- Decongestants
- Bacterial lysates
- Herbal medicine
Menu of Possible Medical Treatments in CRS

- Verapamil
- Furosemide
- Capsaicin
- Anti-fungals
- Proton pump inhibitors
- Probiotics
- Anti-leukotrienes
- Phototherapy
- Figastrim
- Colloidal silver

1b(-) = negative RCT
Figure 1.6.2. EPOS2020 management scheme on diffuse CRS.

**Diffuse / bilateral CRS**

- **Primary diffuse CRS**
  - Presence of:
    - Bleeding / crusting
    - Severe pain
    - Tissue loss
    - Involvement of other organs
  - **Secondary diffuse CRS** (e.g. vasculitis / immune disorder)
    - Serologic investigations
    - Consider biopsy
    - CT scan
    - Involve appropriate specialists to treat underlying disease

**Appropriate medical therapy (AMT)**
- Nasal steroid (drops / spray / rinses)
- Saline rinses
- Educate technique / compliance
- Consider OCS

**6-12 weeks: improvement?**

**Additional work-up:**
CT-scan, SPT, lab; reconsider treatable traits, compliance

**Non-type 2**
- Main complaint often discharge / facial pain
- Less asthma
- Less atopy
- NE: purulence
- Lab: normal IgE, no eosinophilia

**Type 2**
- Main complaint often smell loss or blockage / congestion
- N-ERD and / or asthma
- Atopy
- NE: polyps, eosinophilic mucin
- Lab: elevated IgE, eosinophilia

**AMT (± longterm antibiotics) or FESS**

**AFRS**
- Young
- Atopy
- Warm humid climate
- Asthma
- SPT: positive for fungi

**FESS**
- Tailored (extended) surgery to remove all debris
- Histopathology eosinophils, hyphae, CL crystals
- Culture fungus

**Additional therapy**
- Xylitol rinses
- Longterm antibiotics
- Revision surgery

**Additional investigations**
- Secondary diffuse CRS (e.g. vasculitis / immune disorder)

**6-12 weeks: improvement?**

**ALARM SYMPTOMS**
- Periorbital oedema / erythema
- Displaced globe
- Double vision
- Ophthalmoplegia
- Reduced visual acuity
- Severe headache
- Frontal swelling
- Signs of sepsis
- Signs of meningitis
- Neurological signs
- Unilateral symptoms
- Bleeding
- Crusting
- Cacosmia

**Consider:**
- MRI of sinuses with contrast
- Ophthalmology and neurosurgery consultation
- Preoperative OCS

**OCS taper**

**Additional therapy**
- Biologics
- ATAD in case of N-ERD
- FESS

**6-12 weeks: improvement?**

Saline rinses INCS OCS
Consider immunotherapy
Repeat imaging with concern for recurrence
Meta-analysis of treatment of CRS with topical corticosteroids

- Long term use effective & safe
- All 41 RCTs favour INCS for symptom improvement
- Positive impact on QoL
- Effect size greatest for CRSwNP
- No difference between different steroids
- Min S/E and no increase in infection
- Work best after surgery, reduce recurrence of polyp
INCS irrigation in post-op CRS

- 4 DBPCRCTs
- n=232
- MMNS¹ (1), BUD (3) v saline
- Variable dosage (500mcg to 2mg/day)
- Variable duration (4-52 weeks)
- Outcomes: VAS, SNOT22, endoscopy score, LM score, olfaction, oral steroid use, tissue eosinophilia
- MMNS irrigation sig improved VAS, SNOT22, LM CT
  BUD irrigation – no sig diff shown
- Adrenal function (1 study) – no effect

¹. Harvey et al IFAR 2018

MMNS: mometasone        BUD: budesonide Respules
Improved Nasal Drug Delivery

‘Why treat 70kg when you can treat 2g?’

Niels Mygind

- **Eluting stents**
  Dexamethasone: Beule et al Am J Rhinol 2009
  Mometasone: Propel, Advance, Resolve, Sinuva etc
  Kern 2018, Han 2014

- **Delivery devices** – Kurve (Controlled Particle Dispersion), OptiNose/EXHANCE
  Fluticasone: – Navigate etc
  Sher..Djupesland Rhinology 2020,58:25-35
Eluting INCS stents in CRS in office

- 3 DBPCRCTs
- n= 301
- Mometasone v placebo
- Dosage 1350mcg over 90 days
- Outcomes: VAS, polyp grade, endoscopy score, need for surgery
- Sig improvement in symptoms, polyp size & need for surgery
- No adverse events
Short course systemic CS in CRSwNP

- 7 DBRCTs using oral CS v placebo +/- INCS
- n=409
- Oral prednisolone mainly
- Variable dosage 25-60mg/day
- Variable duration (7-21 days) & FU
- Outcomes: VAS, SNOT22, LK endoscopy score, polyp grade
  - Improvement overall 2-3 wks, no sig diff at 10-12 wks in syms in 50% pts despite NP score still sig reduced
  - Some S/Es – gi tract, psychological
Short course systemic CS in CRSwNP
Medical treatment of CRS

Saline irrigation or rinsing
Medical Treatment of CRS
Saline irrigation or rinsing

- 33 ‘RCT’s (14 post-op), n= 831
- 20 showed improvement in symptoms, endoscopy, QOL, radiology
- Isotonic or Ringers lactate better than hypertonic
- Method of instillation, concentration, volume, pressure, frequency, temperature or head position?
- Recommended +/- surgery (1a/Grade A) but difficult to recommend one method over another
Medical Treatment of CRS
Additions to saline irrigation/rinsing

Additions to enhance antisepsis and/or biofilm disruption

Evidence for: xylitol, sodium hyaluronate, xyloglucan

Insufficient evidence for: surfactant, baby shampoo, Manuka honey, dexpantenol, hot water, hypertonic soln
Duration of antibiotic courses

- Short-term: applied to anything from 2-3-5-7-10-14 days in the literature.
- Long-term: >2 weeks ie 4,6,8,10,12 etc up to years
- The EPOS panel agreed that 4 weeks or less would be ‘short-term’, accepting that in general practice the duration is usually <10 days, and >4 weeks would be regarded as ‘long-term’.
- Short-term for acute bacterial infection v long term courses for immunomodulatory properties

Fokkens, Lund et al EPOPS2020 Rhinology Suppl 29 pp1-465
Oral antibiotics in CRS 1b(-)

- Short courses (3 RTs: cefaclor or cipro v amoxiclav, cefuroxime v amoxiclav; 9,10 & 14/7)
  ~ acute exacerbations
  - symptom scores
  - microbiology
No placebo and no advantage shown between Rx

Insufficient evidence to recommend & S/E frequent
### Placebo controlled RCTs with oral antibiotics in CRSwNP

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>N=</th>
<th>Time/Dose</th>
<th>Effect symptoms</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schalek 2009</td>
<td>Anti staph antibiotic placebo controlled</td>
<td>23</td>
<td>3 Weeks</td>
<td>No significant effect at 3 and 6 months, endoscopy SNOT-22</td>
<td>1b (-)</td>
</tr>
<tr>
<td>Van Zele 2010</td>
<td>Doxycycline placebo controlled</td>
<td>47</td>
<td>3 weeks/100 mg day</td>
<td>Reduction of polyp size and postnasal secretion, reduction of pro-inflammatory markers</td>
<td>1b</td>
</tr>
</tbody>
</table>

Does not fulfil EPOS criteria of long-term
Oral steroids and doxycycline: Two different approaches to treat nasal polyps

Thibaut Van Zele, MD, PhD, Philippe Gevaert, MD, PhD, Gabriele Holtappels, Achim Beule, MD, Peter John Wormald, MD, Susanne Mayr, MD, Greet Hens, MD, PhD, Peter Hellings, MD, PhD, Fenna A. Ebbens, MD, PhD, Wytske Fokkens, MD, PhD, Paul Van Cauwenberge, MD, PhD, and Claus Bachert, MD, PhD

p<0.05 just!
Long-term Macrolides

- Kudoh\(^1\) improved symptoms & survival in diffuse panbronchiolitis ~ non-eosinophilic lower airway disease in Japan
- Long term low dose erythromycin ↑ 10 year survival from 12\(\rightarrow\)90%, improving clinical and radiological features\(^2\)
- Max serum & sputum levels < MIC supports immunomodulatory effect

Macrolide duration in CRS

• 4.7% improvement at 2 weeks
• 71% improvement at 12 weeks
• Needs 6-8 weeks to have sig impact
• Improvement at 3 months continues to 12 months

1. Hashiba & Baba Acta Otolaryngol 1996
2. Cervin et al Otolaryngol Head Neck 2002
3. Ragab et al Laryngoscope 2004
### Placebo controlled RCTs in long-term treatment with antibiotics in CRSw/sNP

#### Which patients do best?

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>N=</th>
<th>Time/Dose</th>
<th>Effect symptoms</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wallwork 2006</td>
<td>Roxithromycin</td>
<td>64</td>
<td>12 Weeks/150 mg daily</td>
<td>CRSsNP population only. Significant effect on SNOT-20 score, nasal endoscopy, saccharine transit time, and IL-8 levels.. Improved or cured in treatment group was 67% vs 22% in placebo group. In a subgroup with normal IgE levels 93% were improved or cured in the treatment group.</td>
<td>1b</td>
</tr>
<tr>
<td>Videler 2011</td>
<td>Azithromycin placebo</td>
<td>60</td>
<td>12 weeks/500 mg week</td>
<td>CRSs/wNP. No significant effect. Response rate was 44% in treatment group vs 22% in placebo group. <strong>IgE not measured!</strong></td>
<td>1b (-)</td>
</tr>
</tbody>
</table>

* 1b (-): a level 1b study showing no difference between treatments
**Figure 6.1.2.1.** Forest plot of the effect of macrolides versus placebo on responder scores in CRS patients.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Macrolide</th>
<th>Placebo</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Videler 2011</td>
<td>2.7</td>
<td>2.36</td>
<td>27</td>
</tr>
<tr>
<td>Wallwork 2006</td>
<td>3.11</td>
<td>0.92</td>
<td>29</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>56</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.32; \text{Chi}^2 = 5.59, df = 1 (P = 0.02); I^2 = 82\%$

Test for overall effect: $Z = 1.00 (P = 0.32)$

**Figure 6.1.2.2.** Forest plot of the effect of macrolides versus placebo on SNOT scores in CRS patients.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Videler 2011</td>
<td>2</td>
<td>1.34</td>
<td>27</td>
<td>1.48</td>
<td>0.88</td>
<td>29</td>
<td>49.7%</td>
<td>0.46 [-0.08, 0.99]</td>
</tr>
<tr>
<td>Wallwork 2006</td>
<td>2.34</td>
<td>1.02</td>
<td>29</td>
<td>2.88</td>
<td>0.71</td>
<td>35</td>
<td>50.3%</td>
<td>-0.62 [-1.12, -0.11]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>56</strong></td>
<td></td>
<td></td>
<td><strong>64</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>-0.08 [-1.14, 0.97]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.51; \text{Chi}^2 = 8.24, df = 1 (P = 0.004); I^2 = 88\%$

Test for overall effect: $Z = 0.16 (P = 0.88)$
## Immunomodulation with Long-term Low Dose Macrolides for CRS

<table>
<thead>
<tr>
<th>STUDY</th>
<th>NUMBER</th>
<th>TIME/DOSE</th>
<th>EFFECT symptoms</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ragab, Lund et al 2004</td>
<td>90</td>
<td>500mgbd 2/52 500mg od 10/52 3 mths</td>
<td>Sig improvement in sym, QOL, NO, NMCC, endoscopy, ac rhin., LRT</td>
<td>Ib RT</td>
</tr>
<tr>
<td>Erythromicin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wallwork et al 2006</td>
<td>64</td>
<td>150 mg daily for 12 weeks</td>
<td>Sig improvement SNOT-20, endoscopy, NMCC, IL-8 levels.. Improved or cured in treatment group was 67% vs 22% in placebo group. If IgE normal, 93% were improved or cured in treatment group.</td>
<td>Ib RCT</td>
</tr>
<tr>
<td>Roxithromycin (CRSsNP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fan et al 2014</td>
<td>43</td>
<td>250mg/day for 2 weeks or 500mg bd for 1 week, then 250mg bd for 1 week</td>
<td>Sig improvements in QOL, endoscopy</td>
<td>Ib RCT</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varvyanskaya 2014</td>
<td>66</td>
<td>250mg/day for 12 or 24 weeks</td>
<td>Sig improvement in SNOT-20, rhinomanometry, NMCC, endoscopy, CT</td>
<td>Ib RCT</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Comparator studies of macrolides

Not all macrolides are equal!

Table 6.1.2.5. Long-term clarithromycin vs. erythromycin for the treatment of patients with CRS.

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Drug</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashiba 1997(35)</td>
<td>Single</td>
<td>59 CRS</td>
<td>Clarithromycin 400mg twice daily vs. erythromycin 600mg three times daily for 8-12 weeks</td>
<td>Efficacy assessed (symptoms and endoscopic signs) after 2, 4, 8 and 12 weeks.</td>
<td>Clarithromycin was significantly more effective when compared to erythromycin.</td>
</tr>
</tbody>
</table>

CRS, chronic rhinosinusitis.
Managing Cardiovascular Risk of Macrolides: Systematic Review and Meta-Analysis; Wong A et al In Drug Safety 2017

- The **short-term** risk of cardiovascular outcomes associated with macrolides was found in observational studies (estimated 1.79 excess MI per 1000 patients, 95% CI 0.88 -3.20)

- This risk is **not found** in RCTs; however the authors comment trials were likely underpowered for this

- **No long-term cardiovascular risk** (ranging from 30 days to 3 years) associated with macrolides was observed

*NB: Studies all assess risk in full dose, short term studies in acute lower respiratory tract infections*
Factors $\rightarrow$ good response to macrolides

*Oakley, Harvey & Lund* Curr Allergy Asthma Rep (2017) 17: 30

- Low serum eosinophilia
- Low tissue eosinophilia
- Normal or low serum IgE – less reliable
- Poor response in LRT to inhaled steroids
- Absence of squamous metaplasia ie lack of remodelling
- Lack of childhood asthma, skin or eye symptoms
- Poor systemic corticosteroid response

Macrolides most beneficial in T1-mediated non-eosinophilic CRS
‘The EPOS2020 steering group, due to the low quality of the evidence, is uncertain whether or not the use of long-term antibiotics has an impact on patient outcomes in adults with CRS, particularly in the light of potentially increased risks of cardiovascular events. There is a need for the larger high-quality trials that are presently being undertaken in Europe.’
Figure 1.6.2. EPOS2020 management scheme on diffuse CRS.

**Diffuse / bilateral CRS**
- Primary diffuse CRS
- Presence of:
  - Bleeding / crusting
  - Severe pain
  - Tissue loss
  - Involvement of other organs

**Secondary diffuse CRS**
- (e.g. vasculitis / immune disorder)
- Serologic investigations
- Consider biopsy
- CT scan
- Involve appropriate specialists to treat underlying disease

**Appropriate medical therapy (AMT)**
- Nasal steroid (drops / spray / rinses)
- Saline rinses
- Educate technique / compliance
- Consider OCS

**6-12 weeks: improvement?**

**Additional work-up:**
- CT-scan, SPT, lab; reconsider treatable traits, compliance

**Non-type 2**
- Main complaint often discharge/facial pain
- Less asthma
- Less atopy
- NE: purulence
- Lab: normal IgE, no eosinophilia

**Type 2**
- Main complaint often smell loss or blockage/congestion
- N-ERD and/or asthma
- Atepy
- NE: polyps, eosinophilic mucin
- Lab: elevated IgE, eosinophilia

**AMT (± longterm antibiotics) or FESS**

**AFRS**
- Young
- Atopy
- Warm humid climate
- Asthma
- SPT: positive for fungi

**Consider:**
- MRI of sinuses with contrast
- Ophthalmology and neurosurgery consultation
- Preoperative OCS

**FESS**
- Tailored (extended) surgery to remove all debris
- Histopathology
- eosinophils, hyphae, CL crystals
- Culture fungus

**Saline rinses**
- INCS
- OCS
- Consider immunotherapy

Repeat imaging with concern for recurrence
Surgical treatment
Primary ESS

• When to operate – ‘after appropriate medical treatment’
  but wide variation in rates of surgery 0.33- 1.8/1000 pop
• 3 groups: medical; surgical; crossover from medical to surgical
• Surgical cohort sig higher symptomatic improvement than medical cohort
• >30% of medical cohort crossed-over to ESS during 1 year follow up
• Patients in the crossover group had stagnant or worsening QoL, which improved after ESS
Economic evaluation of ESS v continued medical therapy for refractory CRS

Rudmik et al Laryngoscope 2015;125:25-32

- Cohort-style Markov decision-tree economic evaluation over 30 year horizon
- Primary outcome ~ QALY
- ESS + post-op medication v medication alone
- ESS: $49k, 20.50 QALYs
- Medical: $29k, 17.13 QALYs

C/E ratio in favour of ESS

$6k per QALY

- 74% certainty that ESS is more cost-effective and becomes so by 3rd year post-op
Evidence-Based ESS for Rhinosinusitis

More than 200 reviewed case series (level IV) with highly consistent results suggest that patients with CRS with and without nasal polyps benefit from endoscopic sinus surgery

~ 89% success

BETTER THAN MANY OF THE MEDICAL TREATMENTS!
Long Term Outcomes from the English national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis

*Hopkins, Slack, Lund et al Laryngoscope 2009, 119;2459-2465*

- Improvement from surgery maintained over 5 years
- Mean post-op SNOT-22 ~ 28.2, improvement of 13.8 over pre-op mean = effect size of 0.68
  (>MCID 9)

NB ‘Normal’ SNOT-22 score = 9.1

Patients with SNOT-22 <20 unlikely to benefit from treatment
Long Term Outcomes from the English national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis

*Hopkins, Slack, Lund et al Laryngoscope 2009, 119;2459-2465*

- CRSwNP patients do better than CRSsNP at all time points
- Revision surgery more frequent after less extensive surgery eg endoscopic polypectomy
  
  **BUT**

  more extensive surgery only demonstrated to be statistically better at 5 years
Percentage change from baseline greater in Early than Late at all time points (p<0.005 at 60 months) when other demographic factors (pre-op SNOT-22, LM score, age, gender, asthma, allergy) and extent of surgery are controlled for.
Why?

Surgery
Reduces inflammatory load ~ ‘IL5-ectomy’?
Prevent irreversible mucosal change & remodelling?
Reduces biofilm density/formation?
Reduces microbiome disturbance?
Reduces development of osteitis?

Earlier surgery allows better irrigation and instillation of topical steroids?
Postoperative intervention

- Debridement – evidence poor  
- Saline irrigations – effective 1b
- Antibiotics – ineffective 1b(-)
- Corticosteroids – oral, topical  effective 1b
- Anti-leukotrienes – ineffective 1b(-)
- Decongestants – ineffective 1b(-)
- Anti-mycotics – ineffective 1b(-)
Potential target areas in pathophysiology of CRS

After Kariyawasam Exp Rev Clin Immunol 2019
Medical Treatment of CRSwNP
Aspirin Desensitisation

Oral 1b

- **N-ERD** = asthma, CRSwNP and hypersensitivity to inhibitors of Cox-1 eg aspirin, NSAIDs
- Challenge to confirm (oral, bronchial, nasal), urinary LTc4
- Oral or nasal (lysine aspirin drops)
- Mainly given post-op
- 4 DBPCT, n=179
- Oral aspirin increasing up to 624mg/day then maintenance (100-325mg)
- SNOT22, VAS, medication, CT, serum IL4, IL5, IL10, eosins etc, smell, asthma control, nasal airway
- Improvement in most parameters to 6 months
- S/E 0-34% - gi tract mainly
Revision Surgery

Only 2 out of every 3 patients having surgery derive a clinically significant benefit

Of those who do, 10% will deteriorate >6 months

\[\text{revision surgery}\]

<table>
<thead>
<tr>
<th></th>
<th>CRSwNP</th>
<th>CRSsNP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>3.6%</td>
<td>4.1%</td>
<td>3.7%</td>
</tr>
<tr>
<td>36 months</td>
<td>11.8%</td>
<td>10.4%</td>
<td>11.4%</td>
</tr>
<tr>
<td>60 months</td>
<td>15.1%</td>
<td>9.5%</td>
<td>13.3%</td>
</tr>
</tbody>
</table>

Hopkins, Slack, Lund et al Laryngoscope 2009, 119;2459-2465
Comprehensive management!

NOT CURE BUT CONTROL

CRS is a medically managed disease in which surgery plays an important role

PATIENT & PHYSICIAN EDUCATION