Chronic rhinosinusitis: how to implement current and new treatment options, the role of precision medicine

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Amsterdam University Medical Centres, location AMC
CRS: how to implement current and new treatment options, the role of precision medicine

• New classification of CRS, primary versus secondary CRS: consequences for treatment
• New integrated care pathways in CRS in the light of the new classification
• New treatment options with biologicals

Types of inflammation in CRS

web: www.epos2020.com, rhinologyjournal.com
New Classification of CRS

Primary CRS

<table>
<thead>
<tr>
<th>Anatomic distribution</th>
<th>Endotype dominance</th>
<th>Examples of phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized (unilateral)</td>
<td>Type 2</td>
<td>AFRS</td>
</tr>
<tr>
<td>Diffuse (bilateral)</td>
<td>Non-type 2</td>
<td>Isolated sinusitis</td>
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<td></td>
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<td>CRSwNP/eCRS</td>
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<td>Non-type 2</td>
<td>AFRS</td>
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<tr>
<td></td>
<td></td>
<td>CCAD</td>
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</tbody>
</table>

AFRS
Isolated sinusitis
CRSwNP/eCRS
AFRS
CCAD
Non-eCRS

web: www.epos2020.com, rhinologyjournal.com
Unilateral AFRS

- Surgery
- Perioperative systemic corticosteroids
- Immunotherapy?
Isolated frontal chronic rhinosinusitis
Massive CRSwNP

Surgery
Systemic corticosteroids
INCS
Biologicals
New Classification of CRS

Secondary CRS

Anatomic distribution
- Localized (unilateral)
- Diffuse (bilateral)

Endotype dominance
- Local pathology
- Mechanical
- Inflammatory
- Immunity

Examples of phenotypes
- Odontogenic
  - Fungal Ball
  - Tumour
- PCD
- CF
- GPA
- EGPA
- Selective immunodeficiency

web: www.epos2020.com, rhinologyjournal.com
Bilateral odontogenic CRS

Teeth first
CRS second
ANCA positive GPA

Retuximab
local ointments
CRS in patients with IgA deficiency

Long term antibiotics
EPOS 2020: Care pathways for CRS

SelfCare Pharmacy
- Two CRS symptoms
  - One of which should be nasal obstruction and/or discoloured discharge
  - Facial pain/pressure
  - Reduction or loss of smell
  - >12 weeks
- Self-Care
  - Self-education / e-Health
  - Saline spray/rinses
  - INCS (if not OTC)
  - Avoid antibiotics
  - Avoid exacerbating factors

Primary Care
- Primary care follow-up
  - Saline rinses
  - INCS (if not OTC)
  - Educate compliance/technique
  - Avoid antibiotics
  - Check treatable traits and comorbidities
- Refer to Secondary / Tertiary Care

Secondary / Tertiary Care
- Check treatable traits / comorbidities
  - History and full ENT exam
  - Nasal endoscopy
  - Diffuse / bilateral CRS
    - Follow EPOS 2020 management scheme on diffuse / bilateral CRS
  - Localized / unilateral CRS
    - CT scan (urgent if suspicion of tumour)
    - Diagnosis rejected
      - Reconsider differential diagnosis
    - Diagnosis confirmed
      - Surgery likely
      - Refer if necessary / suspected malignancy
    - No (apparent) CRS
      - Consider CT scan
      - Reconsider differential diagnosis

Immediate Referral
- Presence of 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

6-12 weeks: improvement?

Anatomic distribution
- Localised
  - T1/2
  - Non-T1/2
  - CCAD
  - cCRS/sinusitis NP
- Diffuse
  - T1/2
  - Non-T1/2
  - Non-CRS

Endotype dominance
- Examples of phenotypes
  - AHR
  - CNM

web: www.epos2020.com, rhinologyjournal.com
Diffuse bilateral CRS management scheme

**Diffuse / bilateral CRS**

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

- 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
- N/E: purulence
  - Lab: normal IgE, no eosinophilia

**AMT (± long-term antibiotics)**
- or FESS

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

**AMT (± OCS)**
- or FESS

- 6-12 weeks; improvement?

**Additional therapy**
- Consider:
  - Xyitol rinses
  - Longterm antibiotics
  - Revision surgery
- Additional investigations
  - Consider:
  - Secondary diffuse CRS (e.g. vasculitis / immune disorder)

**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

**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

**AMT**, appropriate medical treatment; **INCS**, intranasal corticosteroids;


web: www.epos2020.com, rhinologyjournal.com
Treatment of Type 2 Inflammation in Chronic Rhinosinusitis

- anti-IL-5
  - mepolizumab
  - reslizumab.
- anti-IL-4/anti-IL-13
- dupilumab
- anti-IgE
- omalizumab

Dupilumab in CRSwNP
Responder Analysis: Percent of Patients With NPS Improvement from Baseline

- Improvement by at least 1 point in NPS from baseline
- Improvement by at least 2 points in NPS from baseline

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Dupilumab 300 mg Q2W</th>
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<tbody>
<tr>
<td>Improvement by at least 1 point in NPS from baseline</td>
<td>12%</td>
<td>66%</td>
</tr>
<tr>
<td>Improvement by at least 2 points in NPS from baseline</td>
<td>5%</td>
<td>54%</td>
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</table>

Proportion of Patients (%)

**SINUS-52 Week 52**

All P-values <0.0001
NPS, nasal polyp score; Q2W, every 2 weeks.
Data on file.

Bachert, Fokkens et al. Lancet 2019
Comparison of biologicals

**SNOT-22 (0-110)**
- Baseline
- Treatment
- Placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>P n=30</th>
<th>D n=30</th>
<th>D n=103</th>
<th>D n=143</th>
<th>P n=103</th>
<th>D n=150</th>
<th>P n=63</th>
<th>M n=64</th>
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<th>O n=82</th>
<th>P n=69</th>
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**Nasal polyp score (NPS) (0-8)**
- Baseline
- Treatment
- Placebo

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<tr>
<td>Treatment</td>
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**Nasal congestion score (NCS) (0-3)**
- Baseline
- Treatment
- Placebo

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**Hellings, Verhoeven, Fokkens Rhinology, in press**

Bachert C., JAMA, 2016, n=60
Bachert C., Lancet, 2019, n=276
Bachert C., Lancet, 2019, n=448
Bachert C., J Allergy Clin Immunol, 2017, n=109
Gevaert P., J Allergy Clin Immunol, 2013, n=24
POLYP2, 2020, n=127
POLYP1, 2020, n=138
Comparison of biologicals

**Loss of smell (LOS) (0-3)**

<table>
<thead>
<tr>
<th>Trial</th>
<th>N =</th>
<th>Year</th>
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<tbody>
<tr>
<td>1</td>
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<td>2016</td>
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<tr>
<td>2</td>
<td>276</td>
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<td>2019</td>
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<tr>
<td>7</td>
<td>138</td>
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</tbody>
</table>

**Dupilumab**
**Mepolizumab**
**Omalizumab**

**UPSIT (0-40)**

**Hellings, Verhoeven, Fokkens Rhinology, in press**
Indications for biological treatment in CRSwNP

Presence of bilateral polyps in a patient who had ESS*

THREE criteria are required

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Cut-off points</th>
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<tr>
<td>Evidence of type 2 inflammation</td>
<td>Tissue eos ≥10/hpf, OR blood eos ≥250, OR total IgE ≥100</td>
</tr>
<tr>
<td>Need for systemic corticosteroids or contraindication to systemic steroids</td>
<td>≥ 2 courses per yr, OR long term (&gt;3 months) low dose steroids</td>
</tr>
<tr>
<td>Significantly impaired quality of life</td>
<td>SNOT-22 ≥ 40</td>
</tr>
<tr>
<td>Significant loss of smell</td>
<td>Anosmic on smell test (score depending on test)</td>
</tr>
<tr>
<td>Diagnosis of comorbid asthma</td>
<td>Asthma needing regular inhaled corticosteroids</td>
</tr>
</tbody>
</table>

*exceptional circumstances excluded (e.g., not fit for surgery)
Defining response to biological treatment in CRSwNP

Evaluation of 5 criteria
- Reduced nasal polyp size
- Reduced need for systemic corticosteroids
- Improved quality of life
- Improved sense of smell
- Reduced impact of co-morbidities

Evaluate treatment response after 16 weeks

Evaluate treatment response after 1 year

Excellent response
5 criteria

Moderate response
3-4 criteria

Poor response
1-2 criteria

No response
0 criteria

Discontinue treatment if no response in any of the criteria
Diffuse bilateral CRS management scheme

AMT, appropriate medical treatment; INCS, intranasal corticosteroids;