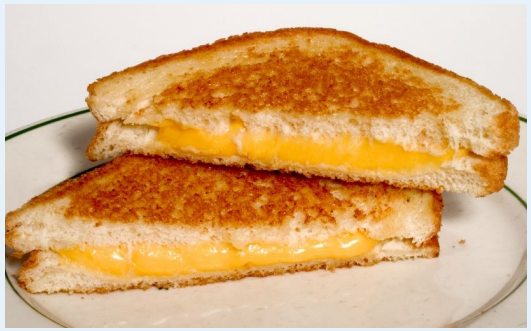
Treatment of CRS in adults the sandwich of medical and surgical and medical treatment again

Professor Valerie J LUND CBE

University College London



Menu of Possible Medical Treatments in CRS

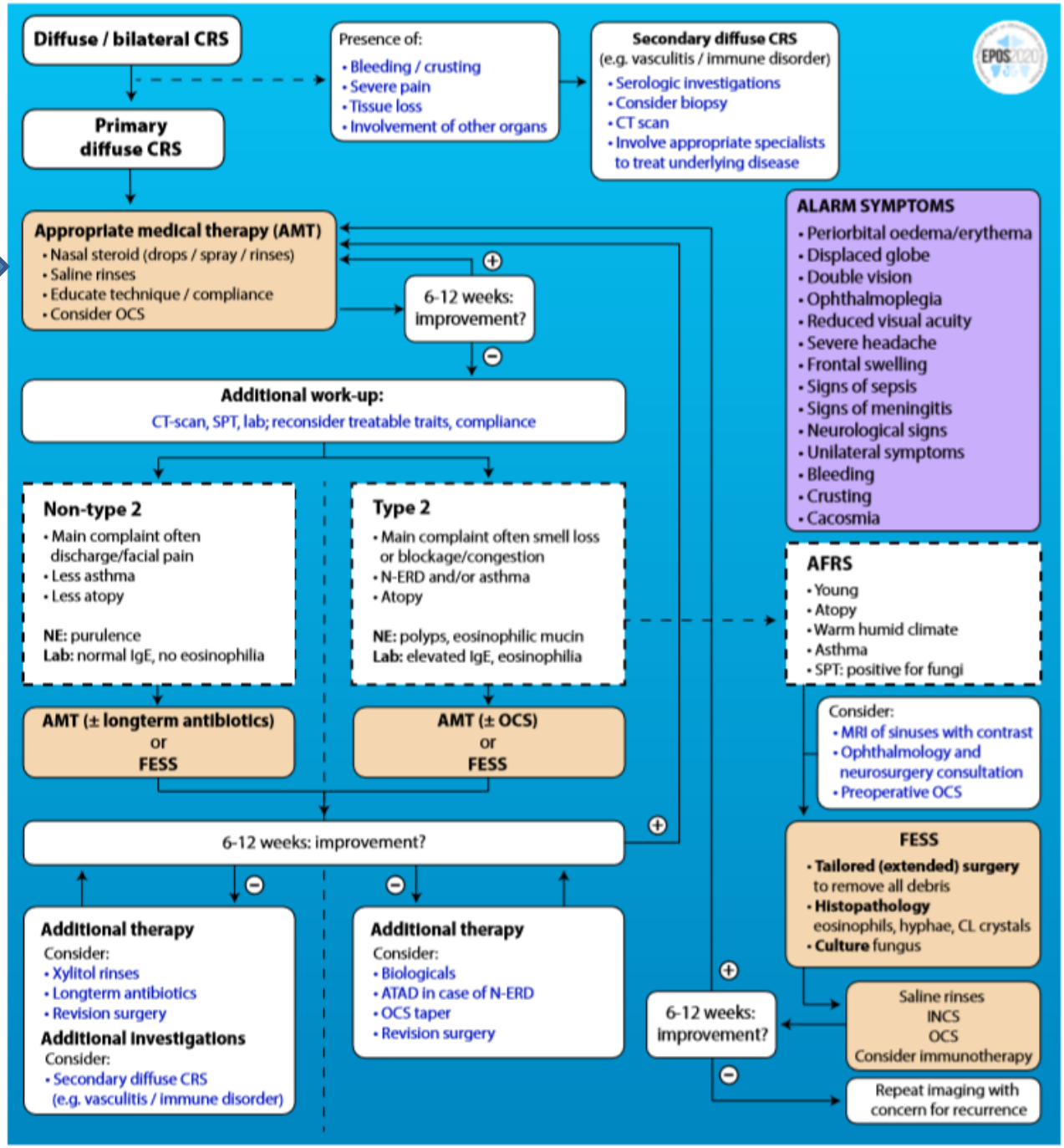
- Steroids
- Saline irrigation
- Antibiotics
- Aspirin desensitisation
- Biologics
  - Anti-IgE
  - Anti-IL5
  - Anti-IL4/IL13 etc etc
- Mucoactive agents
- Antihistamines (oral, topical)
- Decongestants
- Bacterial lysates
- Herbal medicine

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

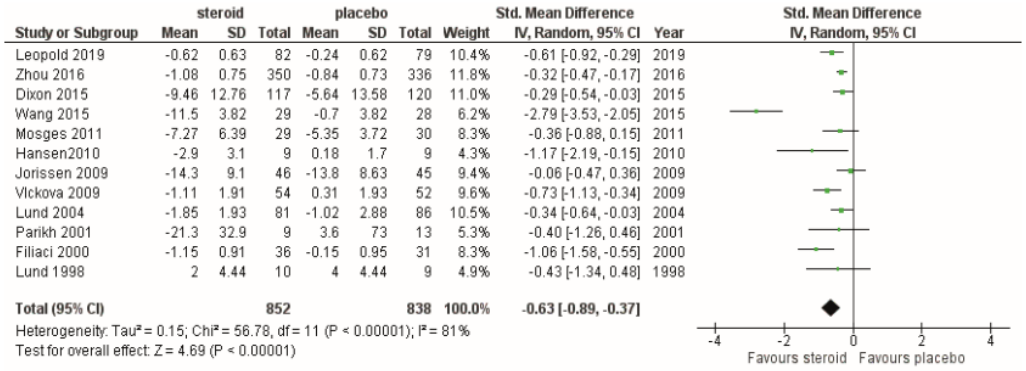
Figure 1.6.2. EPOS2020 management scheme on diffuse CRS.



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

Figure 6.1.5.2. Forest plot of the effect of nasal corticosteroids versus placebo on change in symptom score in patients with CRS compared to placebo.with CRS.



INCS irrigation in post-op CRS

- 4 DBPCRCTs
- n=232
- MMNS[1] (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 eosinophila
- 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

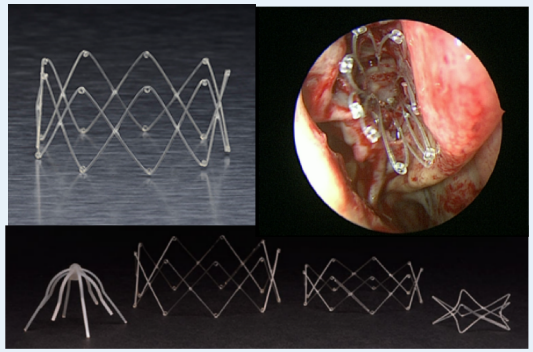
'Why treat 70kg when you can treat 2g? *Niels Mygind*

- **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

Figure 6.1.6.1. Forest plot of the effect of corticosteroid-eluting implants versus placebo on the change from baseline to day 90 in nasal obstruction/congestion score in patients with CRS.

Study or Subgroup	corticosteroid Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kern 2018	0.93	0.8	177	0.69	0.79	89	89.5%	0.24 [0.04, 0.44]
Han 2014	1.33	1.5	53	0.67	1.5	47	10.5%	0.66 [0.07, 1.25]
Total (95% CI)			**230**			**136**	**100.0%**	**0.28 [0.09, 0.48]**

Heterogeneity: $Chi^2 = 1.75$, df = 1 (P = 0.19); $I^2 = 43\%$
Test for overall effect: Z = 2.91 (P = 0.004)

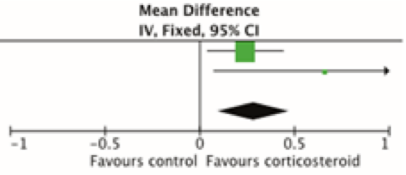
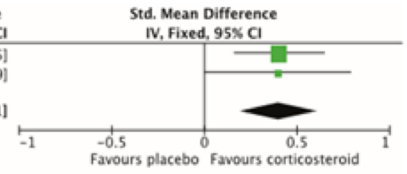


Figure 6.1.6.2. Forest plot of the effect of corticosteroid-eluting implants versus placebo on the change from baseline to day 90 in bilateral Nasal Polyp Score (NPS) in patients with CRS.

Study or Subgroup	corticosteroid Mean	SD	Total	placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Kern 2018	0.56	1.06	195	0.15	0.91	97	72.3%	0.40 [0.16, 0.65]
Han 2014	1	2.26	53	0.1	2.26	47	27.7%	0.40 [-0.00, 0.79]
Total (95% CI)			**248**			**144**	**100.0%**	**0.40 [0.19, 0.61]**

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0\%$
Test for overall effect: Z = 3.77 (P = 0.0002)



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 (7-21days) & 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

Figure 6.1.7.1. Forest plot of the effect of short course of systemic corticosteroid therapy versus placebo on total symptom score 2 weeks after start of the therapy in CRS patients.at day 90 (%).

Study or Subgroup	Systemic corticosteroid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Ecevit 2015	11.1	10.8	10	29.3	16	12	7.4%	−1.26 [−2.19, −0.33]	2015
Kirtsreesakul 2012	6.51	14.16	67	17.28	13.83	47	43.4%	−0.76 [−1.15, −0.38]	2012
Vaidyanathan 2011	1.03	1.68	29	3.22	3.48	28	22.1%	−0.80 [−1.34, −0.25]	2011
Van Zele 2010	3.62	3.89	14	8.64	3.44	19	10.8%	−1.35 [−2.12, −0.57]	2010
Hissaria 2006	0.9	2.2	20	2.3	3.1	20	16.3%	−0.51 [−1.14, 0.12]	2006
Total (95% CI)			**140**			**126**	**100.0%**	**−0.83 [−1.08, −0.57]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.65$, df = 4 (P = 0.46); $I^2 = 0\%$
Test for overall effect: Z = 6.39 (P < 0.00001)

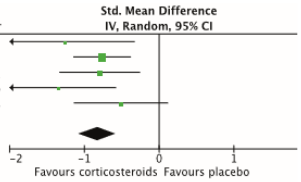


Figure 6.1.7.2. Forest plot of the effect of short course of systemic corticosteroid therapy versus placebo on total symptom score 10-12 weeks after start of the therapy in CRS patients.

Study or Subgroup	Systemic corticosteroid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Kirtsreesakul 2012	7.73	14.16	67	9.75	13.83	47	56.4%	−0.14 [−0.52, 0.23]
Vaidyanathan 2011	1.14	1.14	27	1.3	1.51	26	27.1%	−0.12 [−0.66, 0.42]
Van Zele 2010	7.62	3.89	14	7.94	3.44	19	16.5%	−0.09 [−0.78, 0.60]
Total (95% CI)			**108**			**92**	**100.0%**	**−0.13 [−0.41, 0.15]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 2 (P = 0.99); $I^2 = 0\%$
Test for overall effect: Z = 0.89 (P = 0.38)

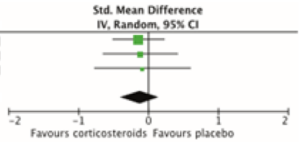


Figure 6.1.7.3. Forest plot of the effect of short course of systemic corticosteroid therapy versus placebo on polyp score 2-3 weeks after start of the therapy in CRS patients.

Study or Subgroup	systemic corticosteroid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Ecevit 2015	2.2	0.42	10	2.8	0.49	12	19.9%	−1.26 [−2.19, −0.32]	2015
Kirtsreesakul 2012	1.92	1.37	67	3.13	1.09	47	32.4%	−0.95 [−1.35, −0.56]	2012
Vaidyanathan 2011	2.6	1.31	29	4.7	0.79	29	26.7%	−1.92 [−2.54, −1.29]	2011
Van Zele 2010	3.46	1.01	14	5.96	1.26	19	21.0%	−2.10 [−2.98, −1.22]	2010
Total (95% CI)			**120**			**107**	**100.0%**	**−1.51 [−2.12, −0.90]**	

Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 9.86$, df = 3 (P = 0.02); $I^2 = 70\%$
Test for overall effect: Z = 4.88 (P < 0.00001)

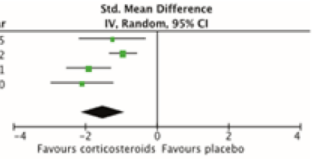


Figure 6.1.7.4. Forest plot of the effect of short course of systemic corticosteroid therapy versus placebo on polyp score 10-12 weeks after start of the therapy in CRS patients.

Study or Subgroup	systemic corticosteroid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Kirtsreesakul 2012	1.79	1.37	67	2.22	1.09	47	55.9%	−0.34 [−0.71, 0.04]	2012
Vaidyanathan 2011	2.2	1.5167	27	3.2	0.7887	29	27.3%	−0.82 [−1.37, −0.28]	2011
Van Zele 2010	5.61	1.01	14	6.26	1.26	19	16.7%	−0.55 [−1.25, 0.16]	2010
Total (95% CI)			**108**			**95**	**100.0%**	**−0.51 [−0.80, −0.21]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.08$, df = 2 (P = 0.35); $I^2 = 4\%$
Test for overall effect: Z = 3.40 (P = 0.0007)

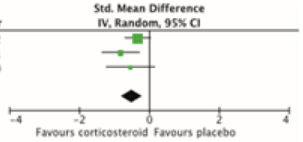


Figure 6.1.7.3. Forest plot of the effect of short course of systemic corticosteroid therapy versus placebo on polyp score 2-3 weeks after start of the therapy in CRS patients.

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, dexpanthenol, 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

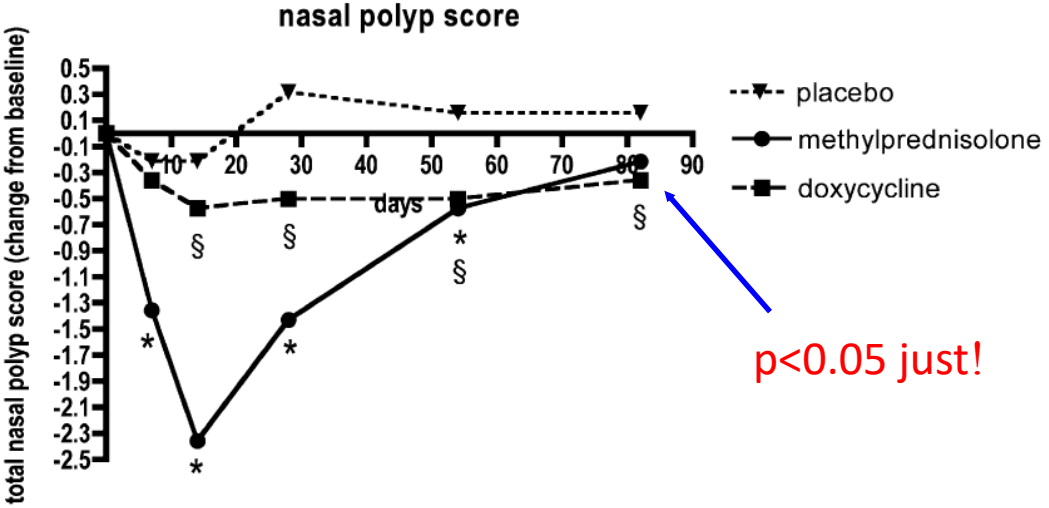
Placebo controlled RCTs with oral antibiotics in CRSwNP

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

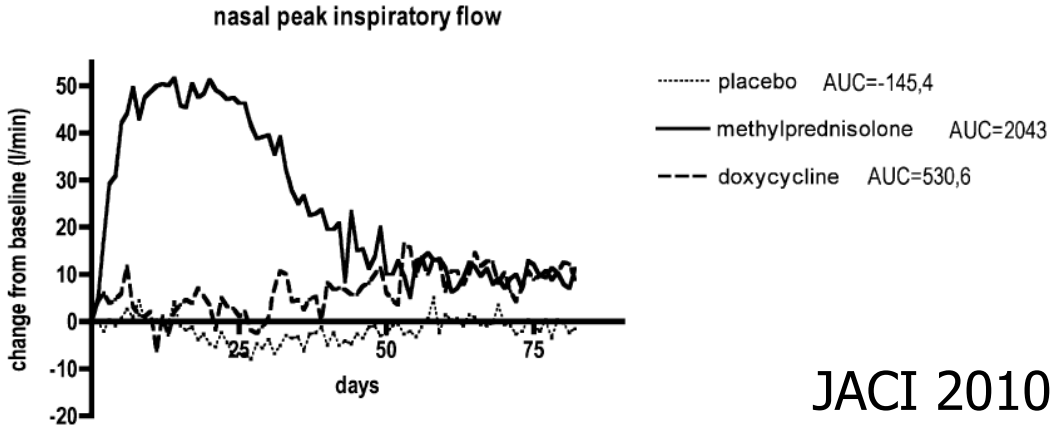
Does not fulfil EPOS criteria of long-term

Oral steroids and doxycycline: Two different approaches to treat nasal polyps

Thibaut Van Zele, MD, PhD,[a]* Philippe Gevaert, MD, PhD,[a]* Gabriele Holtappels,[a] Achim Beule, MD,[d] Peter John Wormald, MD,[d] Susanne Mayr, MD,[c] Greet Hens, MD, PhD,[b] Peter Hellings, MD, PhD,[b] Fenna A. Ebbens, MD, PhD,[e] Wytske Fokkens, MD, PhD,[e] Paul Van Cauwenberge, MD, PhD,[a] and Claus Bachert, MD, PhD[a]



p<0.05 just!



JACI 2010

Long-term Macrolides

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

1. *Kudoh et al Jpn J Thoracic Dis 1987;25:632-42*
2. *Nagai et al Respiration 1991;58:145-9*

Macrolide duration in CRS

- 4.7% improvement at 2 weeks
- 71% improvement at 12 weeks[1]
- Needs 6-8 weeks to have sig impact

- Improvement at 3 months continues to 12 months[2,3]

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?

Study	Drug	N=	Time/Dose	Effect symptoms	Level of Evidence
Wallwork 2006	Roxithromycin	64	12 Weeks/150 mg daily	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.	1b
Videler 2011	Azithromycin placebo controlled	60	12 weeks/500 mg week	CRSs/wNP. No significant effect. Response rate was 44% in treatment group vs 22% in placebo group. IgE not measured!	1b (-)*

* 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.

Study or Subgroup	Macrolide Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Videler 2011	2.7	2.36	27	2.7	1.67	29	49.9%	0.00 [-0.52, 0.52]
Wallwork 2006	3.11	0.92	29	3.84	0.71	35	50.1%	-0.89 [-1.41, -0.37]
Total (95% CI)			**56**			**64**	**100.0%**	**-0.45 [-1.32, 0.43]**

Heterogeneity: $Tau^2 = 0.32$; $Chi^2 = 5.59$, df = 1 (P = 0.02); $I^2 = 82\%$
Test for overall effect: Z = 1.00 (P = 0.32)

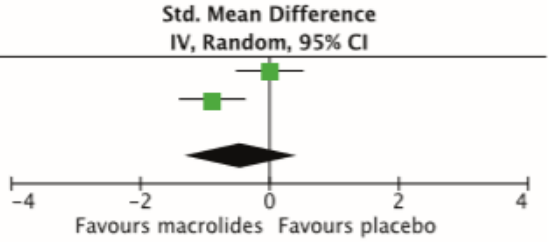
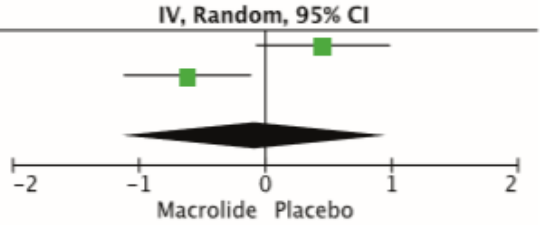


Figure 6.1.2.2. Forest plot of the effect of macrolides versus placebo on SNOT scores in CRS patients.

Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Videler 2011	2	1.34	27	1.48	0.88	29	49.7%	0.46 [-0.08, 0.99]
Wallwork 2006	2.34	1.02	29	2.88	0.71	35	50.3%	-0.62 [-1.12, -0.11]
Total (95% CI)			**56**			**64**	**100.0%**	**-0.08 [-1.14, 0.97]**

Heterogeneity: $Tau^2 = 0.51$; $Chi^2 = 8.24$, 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

STUDY	NUMBER	TIME/DOSE	EFFECT symptoms	Evidence
Ragab, Lund et al 2004 Erythromicin	90	500mgbd 2/52 500mg od 10/52 3 mnths	Sig improvement in sym, QOL, NO, NMCC, endoscopy, ac rhin,, LRT	Ib RT
Wallwork et al 2006 Roxithromycin	64 (CRSsNP)	150 mg daily for 12 weeks	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.	Ib RCT
Fan et al 2014 Clarithromycin	43	250mg/day for 2 weeks or 500mg bd for 1 week, then 250mg bd for 1 week	Sig improvements in QOL, endoscopy	Ib RCT
Varvyanskaya 2014 Clarithromycin	66	250mg/day for 12 or 24 weeks	Sig improvement in SNOT-20, rhinomanometry, NMCC, endoscopy, CT	Ib RCT

Comparator studies of macrolides

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

Study	Methods	Participants	Drug	Outcomes	Results
Hashiba 1997[35]	Single blind	59 CRS	Clarithromycin 400mg twice daily vs. erythromycin 600mg three times daily for 8-12 weeks	Efficacy assessed (symptoms and endoscopic signs) after 2, 4, 8 and 12 weeks.	Clarithromycin was significantly more effective when compared to erythromycin

CRS, chronic rhinosinusitis.

Not all macrolides are equal!

Systematic review and meta-analysis of macrolide safety – key points

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 → good response to macrolides

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

- Low serum eosinophilia
- Low tissue eosinophilia

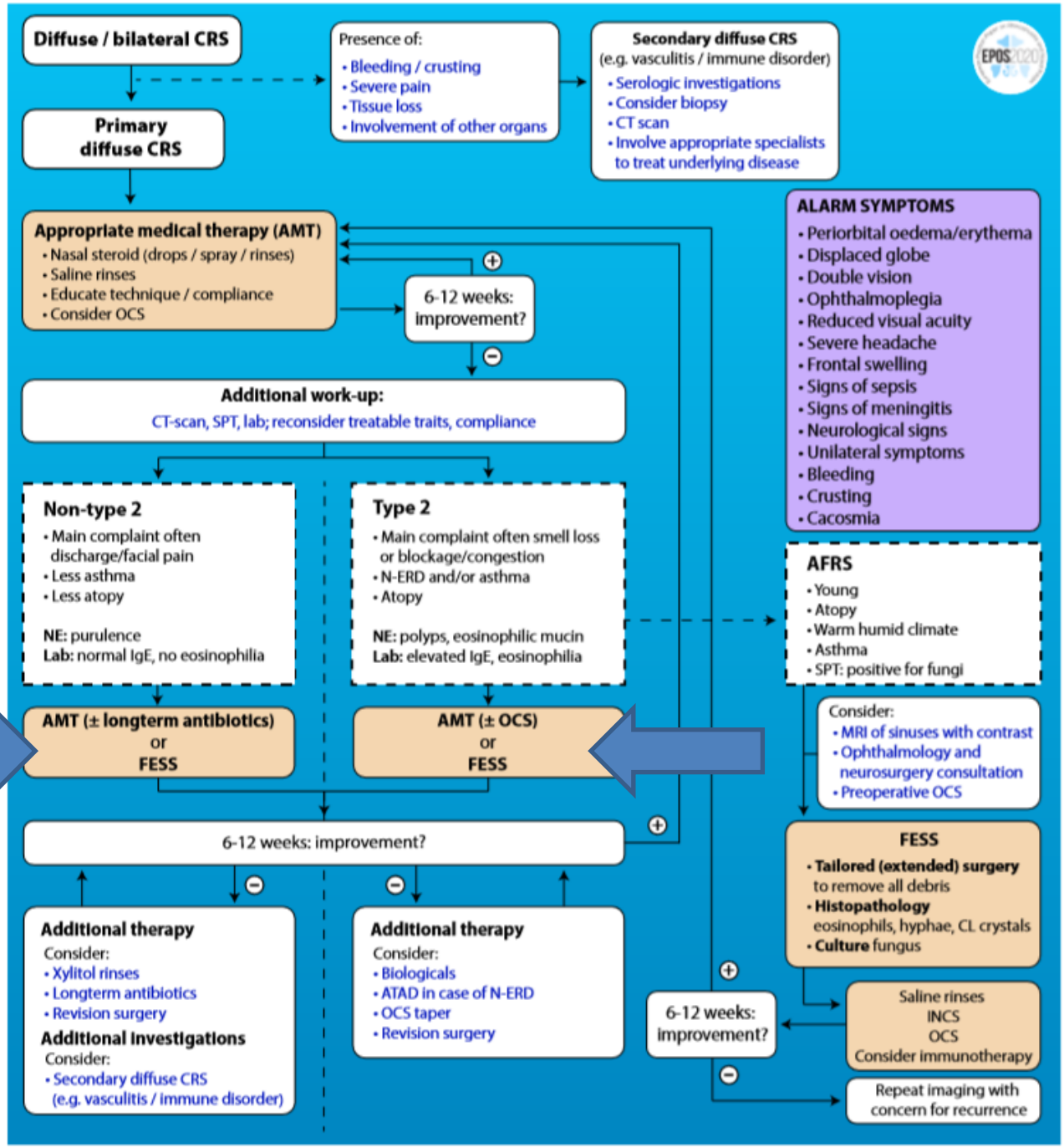
} more reliable & cheaper marker

- 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.



Surgical treatment
Primary ESS

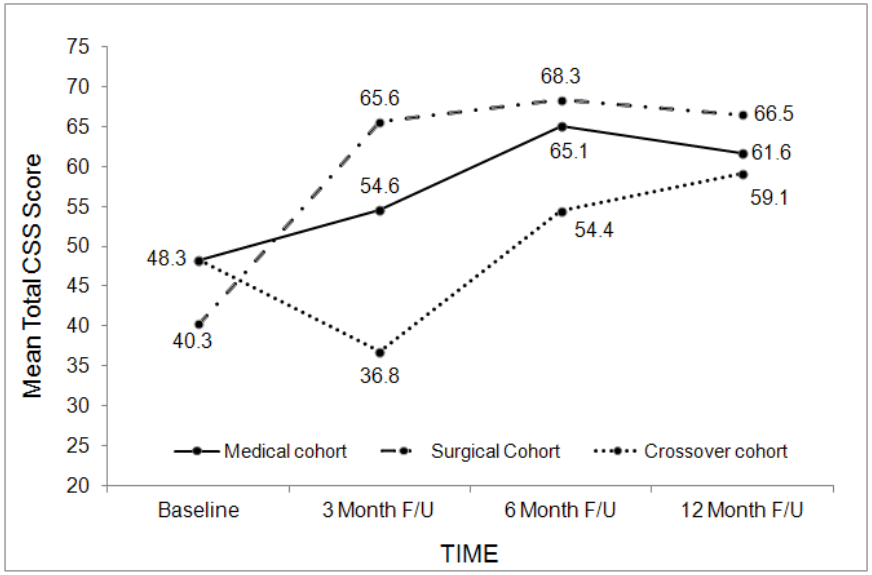
- When to operate – ‘after appropriate medical treatment’ but wide variation in rates of surgery 0.33- 1.8/1000 pop

Medical therapy vs surgery for chronic rhinosinusitis: a prospective, multi-institutional study

Timothy L. Smith, MD, MPH[1], Robert Kern, MD[2], James N. Palmer, MD[3], Rodney Schlosser, MD[4], Rakesh K. Chandra, MD[2], Alexander G. Chiu, MD[5], David Conley, MD[2], Jess C. Mace, MPH[1], Rongwei Fu, PhD[6], James Stankiewicz, MD[7]

International Forum Allergy and Rhinology 2013; 3(1): 4-9

- 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



Improved QOL

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

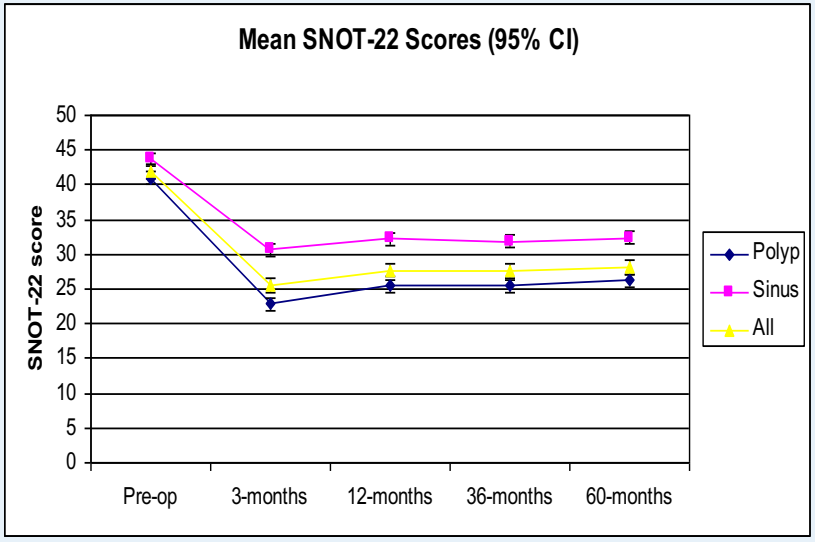
Hopkins, Slack, Lund et al Laryngoscope 2009, 119;2459-2465

- 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

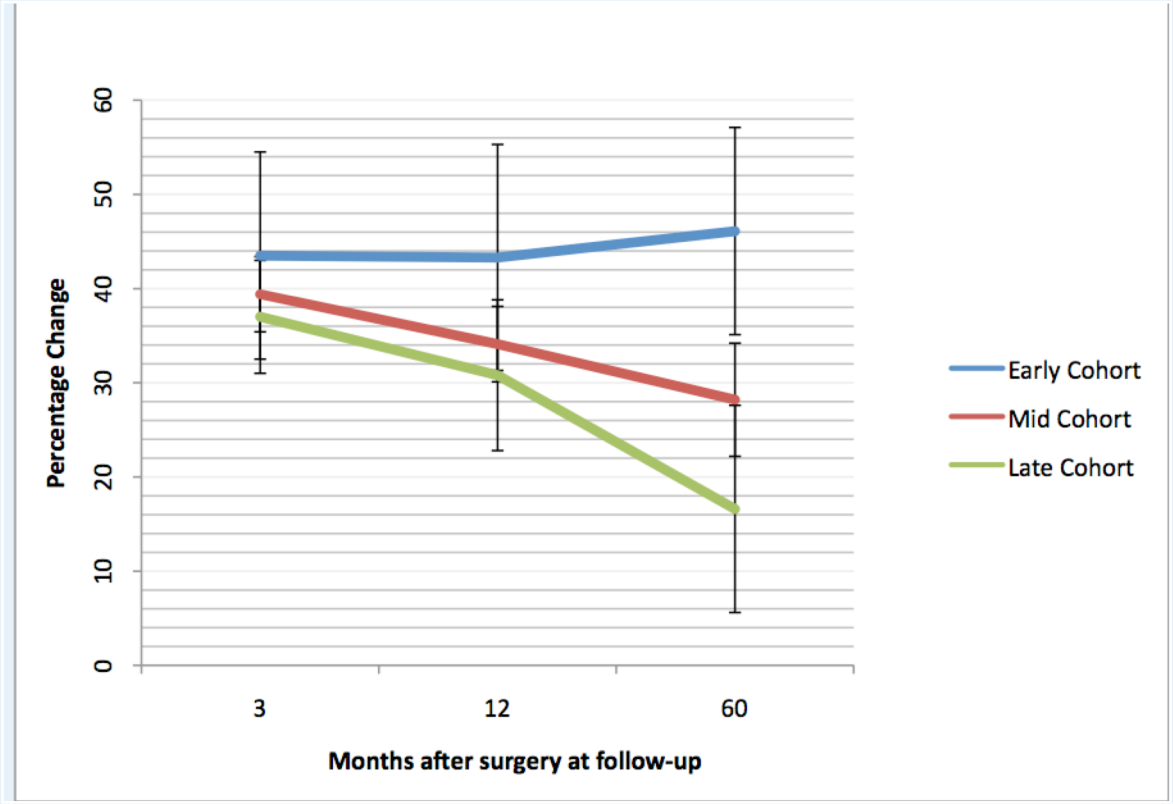
- CRSwNP patients do better than CRSsNP at all time points
- Revision surgery more frequent after less extensive surgery eg endoscopic polypectomy

BUT

more extensive surgery only demonstrated to be statistically better at 5 years

Percentage change in SNOT-22 according to symptom duration prior to first surgery

Hopkins, Rimmer, Lund Rhinology 2015;53:10-17



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(-)

Figure 1.6.2. EPOS2020 management scheme on diffuse CRS.

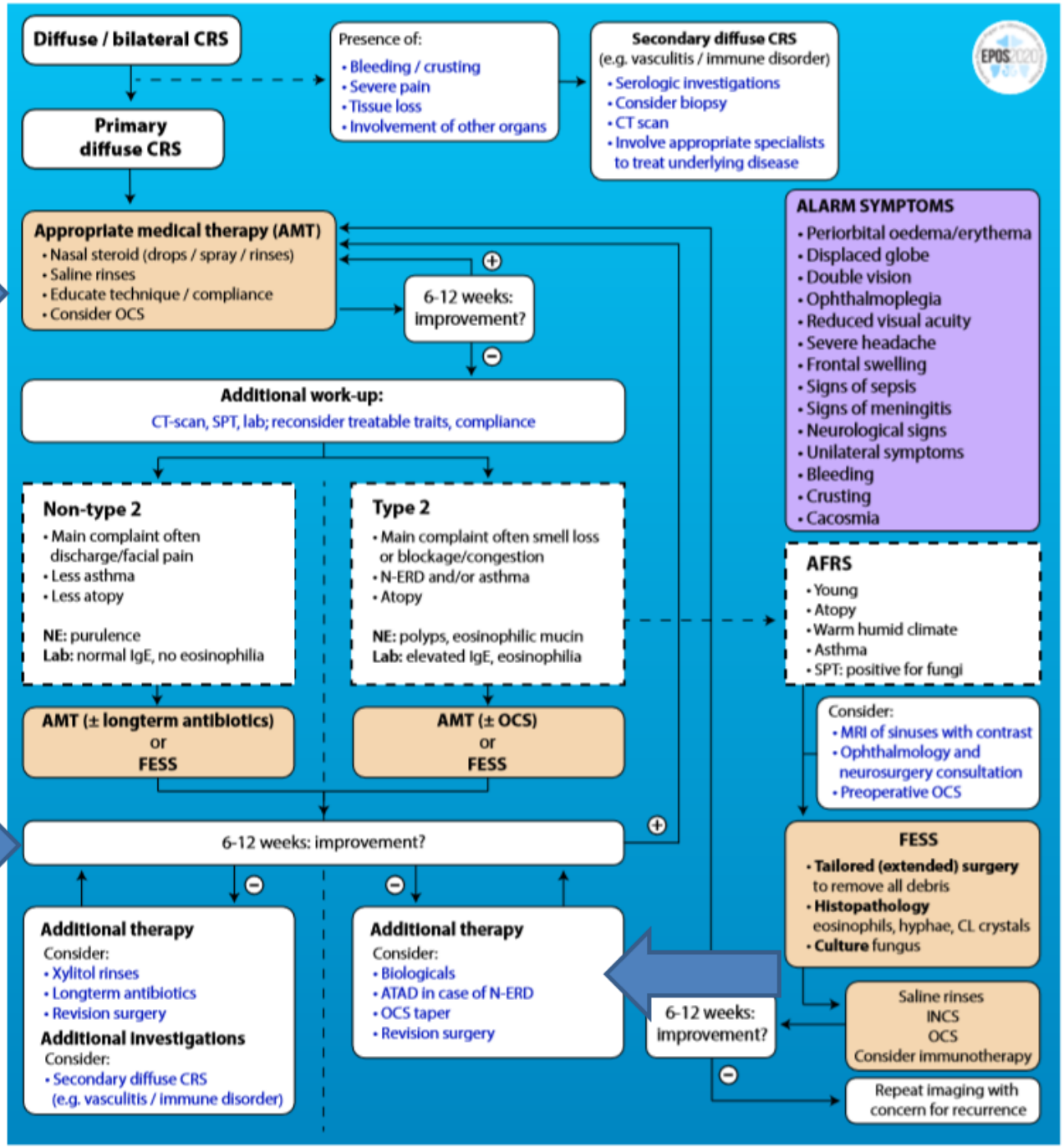
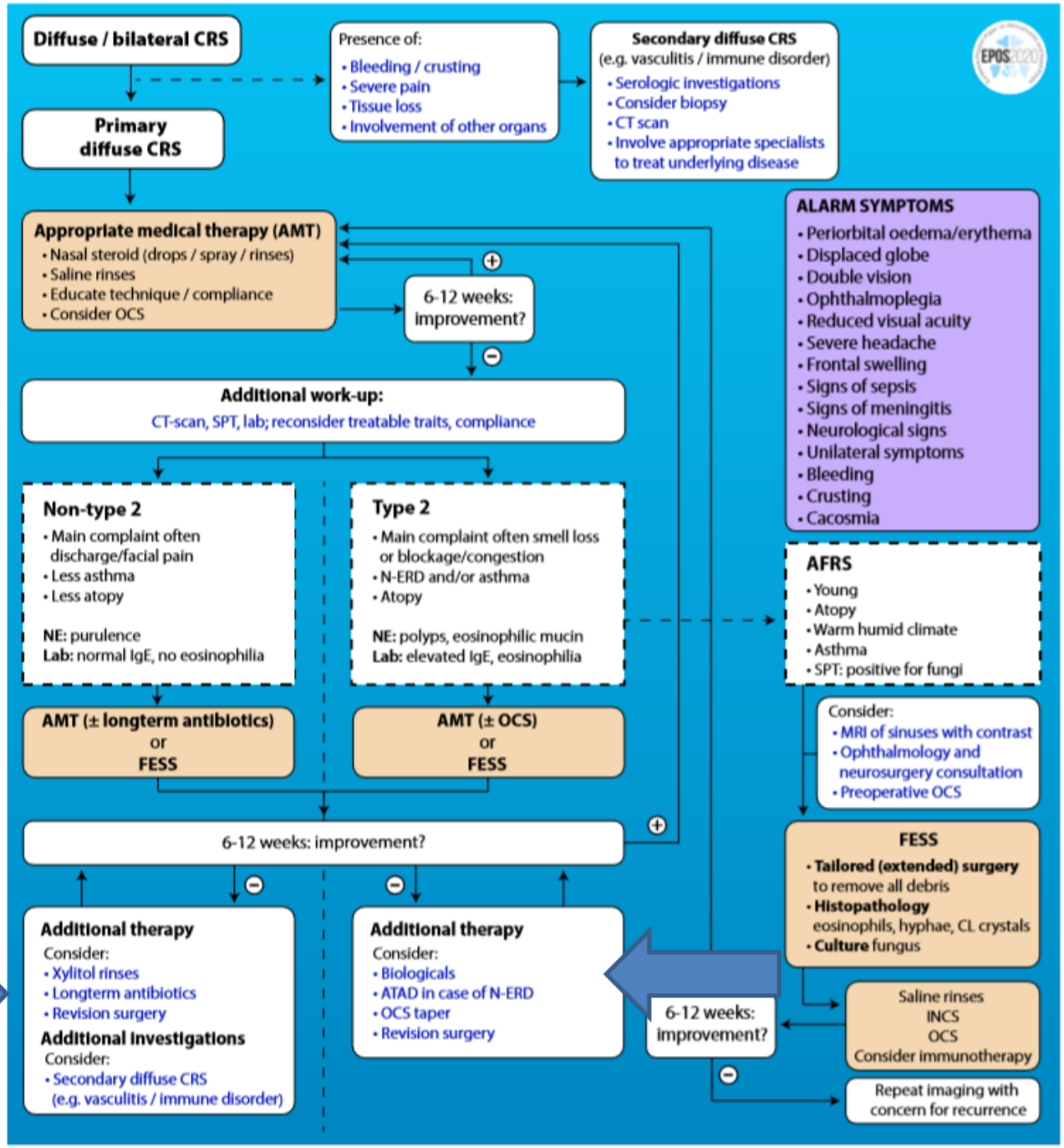
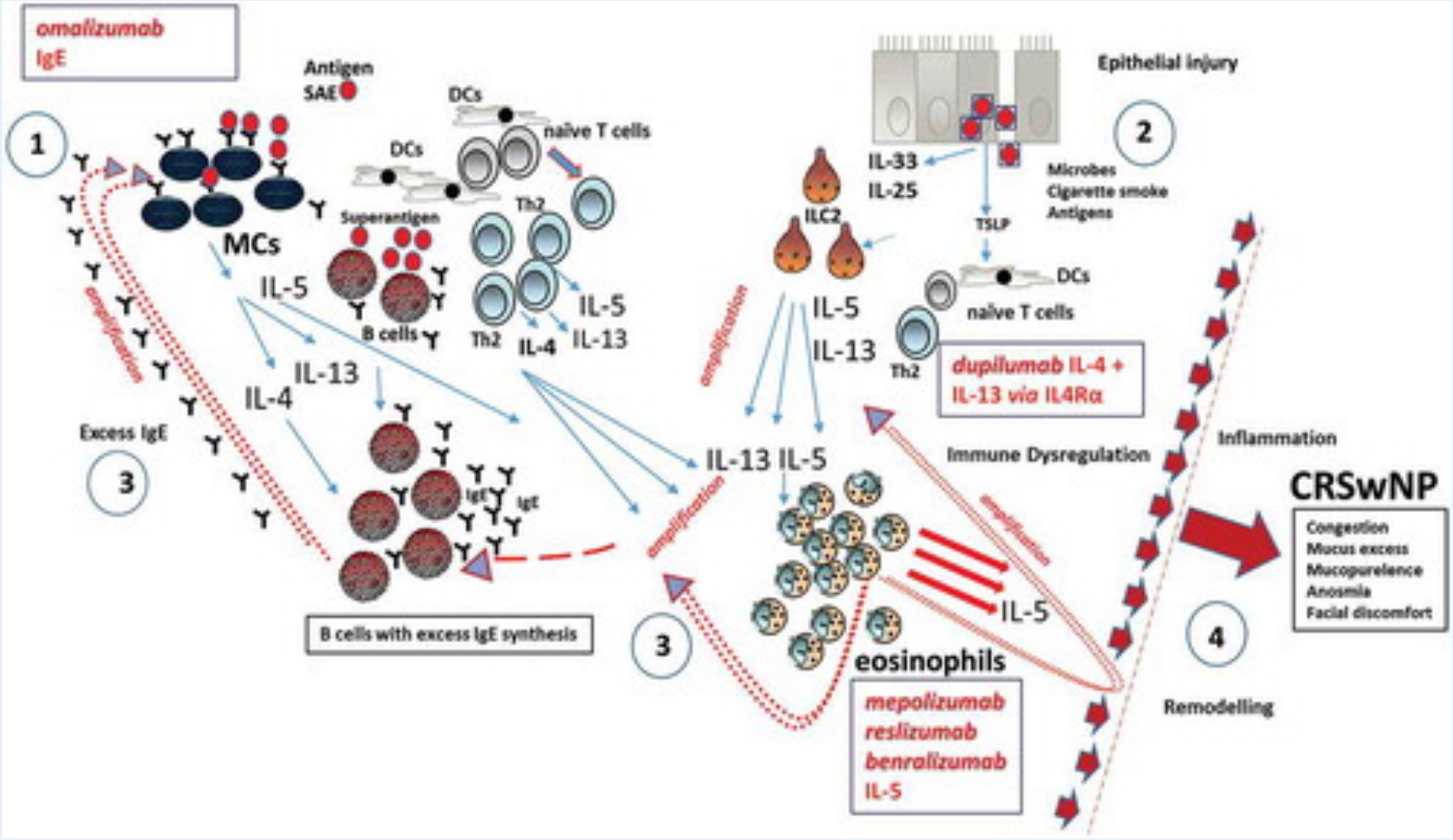


Figure 1.6.2. EPOS2020 management scheme on diffuse CRS.





Potential target areas in pathophysiology of CRS

After Kariyawasam Exp Rev Clin Immunl 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

⟶ revision surgery

	CRSwNP	CRSsNP	All
12 months	3.6%	4.1%	3.7%
36 months	11.8%	10.4%	11.4%
60 months	15.1%	9.5%	13.3%

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