Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: Mepolizumab

Stand: Juli 2020

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Mepolizumab
[Zusatztherapie bei schwerer chronischer Rhinosinusitis mit nasalen Polypen (CRSwNP)]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Tabelle „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	operative Resektion
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse zur frühen Nutzenbewertung nach §35a SGB V: D-505 Dupilumab (Beschluss vom 14.05.2020)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Mepolizumab Nucala®	
Glucokortikoide (topisch)	
Mometasonfuroat (generisch) R01AD09 z.B. Nasonex® Nasenspray	Nasonex ist zur Anwendung bei Erwachsenen und bei Kindern ab 3 Jahren zur symptomatischen Behandlung einer saisonalen allergischen oder perennialen Rhinitis bestimmt. Nasonex Nasenspray ist zur Behandlung einer Polyposis nasi bei Patienten ab 18 Jahren angezeigt
Budesonid R01AD05 (generisch) z.B. Budesonid acis® Nasenspray	Symptomatische Behandlung und Vorbeugung von saisonalem und ganzjährigem allergischen Schnupfen einschließlich Heuschnupfen sowie Nasenpolypen.
Glucokortikoide (systemisch), z.B.	
Prednison H02AB07 (generisch) z.B. Prednison ratiopharm	Erkrankungen der oberen Luftwege – schwere Verlaufsformen von Pollinosis und Rhinitis allergica, nach Versagen intranasal verabreichter Glucocorticoide (DS: c) […]

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Antibiotika, z.B.	
Doxycyclin J01AA02 (generisch)	Doxycyclin ist angezeigt bei Infektionen, die durch Doxycyclin-empfindliche Krankheitserreger verursacht sind (siehe Abschnitt 5.1), insbesondere bei: • Infektionen der Atemwege und des HNO-Bereiches – akute Schube chronischer Bronchitis – **Sinusitis** – Otitis media – Pneumonie durch Mykoplasmen, Rickettsien oder Chlamydien […] Die offiziellen Richtlinien für den angemessenen Gebrauch von antimikrobiellen Wirkstoffen sind bei der Anwendung von Doxycyclin zu berücksichtigen.
Biologika	
Dupilumab D11AH05 Dupixent	Dupixent ist angezeigt als Add-on-Therapie mit intranasalen Kortikosteroiden zur Behandlung von Erwachsenen mit schwerer chronischer Rhinosinusitis mit nasaler Polyposis (CRSwNP), die mit systemischen Kortikosteroiden und/oder chirurgischem Eingriff nicht ausreichend kontrolliert werden kann.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: Mepolizumab

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	9. Juni 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CRS	chronic rhinosinusitis
CRSsNP	Chronic rhinosinusitis without nasal polyps
CRSwNP	Chronic rhinosinusitis with nasal polyps
EPOS	European Position Paper on Rhinosinusitis
ESS	Endoscopic Sinus Surgery
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
ICAR:RS	International Consensus Statement on Allergy and Rhinology: Rhinosinusitis
INCS	Intranasale Kortikosteroide
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LDMs	Low-dose macrolides
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
SMD	Standardisierte Mittelwertdifferenz
SNOT	Sino-Nasal Outcome Test
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Erwachsenen mit schwerer chronischer Rhinosinusitis mit Nasalen Polypen (CRSwNP), die mit einer Therapie aus systemischen Kortikosteroiden und / oder operativem Eingriff nicht ausreichend kontrolliert sind, um den Bedarf an systemischen Kortikosteroiden und operativen Eingriffen zu reduzieren.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Rhinosinusitus durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 18.05.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 433 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 19 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2020 [5].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Dupilumab (neues Anwendungsgebiet: Chronische Rhinosinusitis mit Nasenpolypen)

Anwendungsgebiet

Dupixent ist angezeigt als Add-on-Therapie mit intranasalen Kortikosteroiden zur Behandlung von Erwachsenen mit schwerer chronischer Rhinosinusitis mit nasaler Polyposis (CRSwNP), die mit systemischen Kortikosteroiden und/oder chirurgischem Eingriff nicht ausreichend kontrolliert werden kann.

Zweckmäßige Vergleichstherapie

eine Therapie mit intranasalen Kortikosteroiden (Budesonid oder Mometasonfuroat)

Fazit / Ausmaß des Zusatznutzens

Hinweis auf einen beträchtlichen Zusatznutzen

3.2 Cochrane Reviews

Chong L et al., 2020 [3].

Biologics for chronic rhinosinusitis

Siehe auch die systematischen Reviews von Tsetsos N et al., 2018 [17], Iqbal IZ et al., 2020 [9] und Tsetsos N et al., 2020 [18].

Fragestellung

To assess the effects of biologics for the treatment of chronic rhinosinusitis.

Methodik

Population:

Patients with chronic rhinosinusitis, whether with polyps (CRSwNP) or without polyps (CRSsNP).

Intervention:

anti-IL-4R alpha mAb (dupilumab);

anti-IL-13 (lebrikizumab, tralokinumab);

anti-IL-5 mAb (reslizumab, benralizumab, mepolizumab);

anti-IgE mAb (omalizumab).

In Deutschland ist lediglich Dupilumab für die vorliegende Indikation zugelassen, sodass ausschließlich die Evidenz zu diesem Arzneimittel berücksichtigt wurde.

Komparator:

Placebo or no treatment. Surgery will be an alternative treatment (comparison) when trials in the area become available.

Concurrent treatments: It was expected that most studies would have used intranasal steroids as a concurrent treatment. There was no limitation on the type of pharmacological concurrent treatments used.

Comparison pairs

The following main comparison pairs were proposed in the protocol:

anti-IL-4R@ mAb plus intranasal steroids versus placebo/nomtreatment plus intranasal steroids;

anti-IL-13 plus intranasal steroids versus placebo/no treatment plus intranasal steroids;

anti-IL-5 mAb plus intranasal steroids versus placebo/nomtreatment plus intranasal steroids;

anti-IgE mAb plus intranasal steroids versus placebo/no treatment plus intranasal steroids.

Endpunkte:

Primary

- Health-related quality of life, using validated disease-specific health-related quality of life scores, such as the Sino- Nasal Outcome Test-22 (SNOT-22), Rhinosinusitis Outcome Measures-31 (RSOM-31) and SNOT-20.

- Disease severity, as measured by validated patient-reported symptom score (such as the Chronic Sinusitis Survey (CSS) questionnaire and visual analogue scales). Where this was unavailable, we considered including data measuring the severity of individual symptoms (see below).
- Serious adverse events (SAEs), measured by the number of participants affected.

Secondary

- Avoidance of surgery, measured by the number (proportion) of participants who had, or did not have, surgery for chronic rhinosinusitis symptoms, or who no longer fulfilled the eligibility criteria for surgery.
- Extent of disease as measured by either:
- endoscopic score (depending on population, either nasal polyps size score or other such as Lund Kennedy); and/or
- computerised tomography (CT) scan score (e.g. Lund Mackay with a range of 0 to 24, higher = worse).
- Health-related quality of life, using generic quality of life scores, such as the SF-36, EQ-5D and other well-validated instruments.
- Adverse effects: nasopharyngitis, including sore throat.

Recherche/Suchzeitraum:

Initially

- Cochrane ENT Register (searched via the Cochrane Register of Studies 18 September 2019);
- Cochrane Central Register of Controlled Trials (CENTRAL 2019, Issue 9) (searched via the Cochrane Register of Studies);
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non- Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to 16 September 2019);
- Ovid EMBASE (1974 to 16 September 2019);
- Web of Science (1945 to 16 September 2019);
- ClinicalTrials.gov, www.clinicaltrials.gov (to 18 September 2019);
- WHO International Clinical Trials Registry Platform (ICTRP) (to 18 September 2019);

Living: Systematic Review: As a living systematic review, the Information Specialist will conduct monthly/quarterly searches

Qualitätsbewertung der Studien:

Risk of bias tool (ROB-1) for the orginal version, 'Risk of bias 2.0' tool (ROB-2) for future versions.

sensitivity analysis for risk of bias of included studies: excluding studies with high risk of overall bias for the results, as assessed using the Cochrane ROB-1 and ROB-2 tools

Ergebnisse

Anzahl eingeschlossener Studien:

8 RCTs with 986 participants, 984 had severe chronic rhinosinusitis with nasal polyps

3 studies (784 participants) evaluated dupilumab.

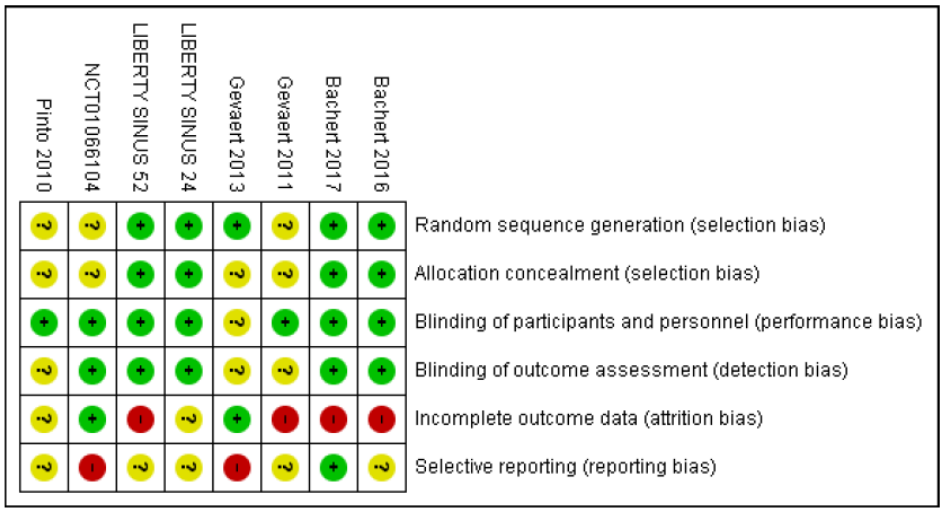
Charakteristika der Population:

Dupilumab versus placebo/no treatment (all receiving intranasal steroids) in patients with nasal polyps

- LIBERTY SINUS 24 (276 participants) gave 300 mg (subcutaneous, SC) dupilumab every two weeks and followed up patients for 24 weeks. Main Diagnosis: bilateral nasal polyps and symptoms of chronic rhinosinusitis despite intranasal corticosteroid therapy before randomisation, Polyp Status 100%
- LIBERTY SINUS 52 (448 participants) randomised patients 1:1:1 into three arms (two dupilumab arms and one placebo arm): 300 mg SC dupilumab every two weeks for 52 weeks, or 300 mg SC dupilumab every two weeks for 24 weeks followed by 300 mg SC dupilumab every four weeks for another 28 weeks. The total period of follow-up was 52 weeks and results were reported for both week 24 and 52. The study had prespecified that some of the data would be pooled across both studies and/or both treatment arms of dupilumab, and did not report the results of the individual trials separately. For the purpose of this review, we combined the results of the different dupilumab arms in the LIBERTY SINUS 52 study,but reported the results of SINUS-52 and SINUS-24 independently by using the data presented in trial registries whenever possible. Main diagnosis: bilateral nasal polyps and symptoms of chronic rhinosinusitis despite intranasal corticosteroid therapy before randomisation; Polyp Status: 100%
- Bachert 2016 (60 participants) gave a 500 mg SC loading dose of dupilumab followed by 300 mg SC weekly for 15 weeks. Main diagnosis: chronic sinusitis with nasal polyps; Previous sinus surgery status: 53.3% had 1 previous surgery for nasal polyps in dupilumab group; 63.3% of placebo group; Previous courses of steroids: excluded if received oral corticosteroids within past 2 months

Qualität der Studien:

Studies with Dupilumab: Liberty Sinus 24, Liberty Sinus 52, Bachert 2016



Studienergebnisse:

- Disease-specific HRQL was measured with the SNOT-22 (score 0 to 110; minimal clinically important difference (MCID) 8.9 points). At 24 weeks, the SNOT-22 score was 19.61 points lower (better) in participants receiving dupilumab (mean difference (MD) -19.61, 95% confidence interval (CI) -22.54 to -16.69; 3 studies; 784 participants; high certainty).

- Symptom severity measured on a 0- to 10-point visual analogue scale (VAS) was 3.00 lower in those receiving dupilumab (95% CI -3.47 to -2.53; 3 studies; 784 participants; moderate certainty).
- The risk of serious adverse events may be lower in the dupilumab group (risk ratio (RR) 0.45, 95% CI 0.28 to 0.75; 3 studies; 782 participants; low certainty).
- The number of participants requiring nasal polyp surgery (actual or planned) during the treatment period is probably lower in those Receiving dupilumab (RR 0.17, 95% CI 0.05 to 0.52; 2 studies; 725 participants; moderate certainty).
- Change in the extent of disease using the Lund Mackay computerised tomography (CT) score (0 to 24, higher = worse) was -7.00 (95% CI -9.61 to -4.39; 3 studies; 784 participants; high certainty), a large effect favouring the dupilumab group.
- The EQ-5D visual analogue scale (0 to 100, higher = better; MCID 8 points) was used to measure change in generic quality of life. The mean difference favouring dupilumab was 8.59 (95% CI 5.31 to 11.86; 2 studies; 706 participants; moderate certainty).
- There may be little or no difference in the risk of nasopharyngiti (RR 0.95, 95% CI 0.72 to 1.25; 3 studies; 783 participants; low certainty).

Fazit der Autoren

In adults with severe chronic rhinosinusitis and nasal polyps, using regular topical nasal steroids, dupilumab improves disease-specific HRQL compared to placebo, and reduces the extent of the disease as measured on a CT scan. It probably also improves symptoms And generic HRQL and there is no evidence of an increased risk of serious adverse events. It may reduce the need for further surgery. There may be little or no difference in the risk of nasopharyngitis.

Kommentare zum Review

Es wurde in den Ergebnissen und dem Fazit der Autoren nur Dupilumab als einzig in Deutschland zugelassene Therapie in der Indikation berücksichtigt. Die beiden systematischen Reviews von Tsetsos N et al., 2018 [17] und Iqbal IZ et al., 2020 [9] befassen sich mit einer vergleichbaren Fragestellung. Allerdings wurden die beiden Studien LIBERTY SINUS 24 und LIBERTY SINUS 52 aufgrund des älteren Suchdatums nicht eingeschlossen.

In Tsetsos N et al., 2018 [17] waren dagegen alle 3 Studien enthalten. Allerdings wurde hier lediglich der Geruchssinn als Endpunkt betrachtet: *All 3 RCTs had very similar study designs and biases, and their perceived homogeneity regarding the primary outcome was corroborated by an I2 value of 0%. The fixed-effects model was used to perform statistical analysis. Objective olfactory outcomes after biologic therapy were measured in the trials using the 40-item UPSIT. The 3 studies were pooled, comprising a total population of 784 patients. The SMD of the pooled studies was 1.22 (95% CI, 1.06 to 1.37). This indicated a robust improvement in olfaction that clearly favored biologic therapy with dupilumab over placebo (p < 0.00001). Subjective rating of loss of smell (score 0-3) was an additional outcome, having been assessed in 2 of the aforementioned studies. The random-effects model was used to perform statistical analysis of the studies (I2 value of 68%). The SMD of the pooled studies was −1.13 (95% CI, −1.42 to −0.84). A significant advantage of dupilumab vs placebo in reducing loss-of-smell score was noted in patients with CRSwNP (p < 0.00001). Overall, dupilumab use led to striking results in olfaction, as the percentage of anosmic patients decreased from 74% to 24% and from 79% to 30% in the SINUS-24 and SINUS- 52 studies, respectively, whereas no change was seen in the placebo groups.*

Head K et al., 2016 [8].

Systemic and topical antibiotics for chronic rhinosinusitis

Fragestellung

To assess the effects of systemic and topical antibiotics in people with chronic rhinosinusitis

Methodik

Population:

- Patients with chronic rhinosinusitis, whether with polyps or without polyps

Intervention:

- macrolides (e.g. clarithromycin, erythromycin);
- tetracyclines (e.g. doxycycline);
- beta-lactams (e.g. penicillins/cephalosporins) with/without clavulanic acids;
- quinolones

Komparator:

- placebo or no intervention;
- another class of antibiotics;
- the same type of antibiotic, which is either:
  - given for a different duration;
  - given at a different dose;
- other treatments for chronic rhinosinusitis, including:
  - intranasal corticosteroids;
  - oral/systemic steroids;
  - the same type of antibiotic but given for a different duration;
  - the same type of antibiotic but given at a different dose.

Endpunkte:

- QoL, Disease severity, AEs etc.

Recherche/Suchzeitraum:

- September 2015

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions

Ergebnisse

Anzahl eingeschlossener Studien:

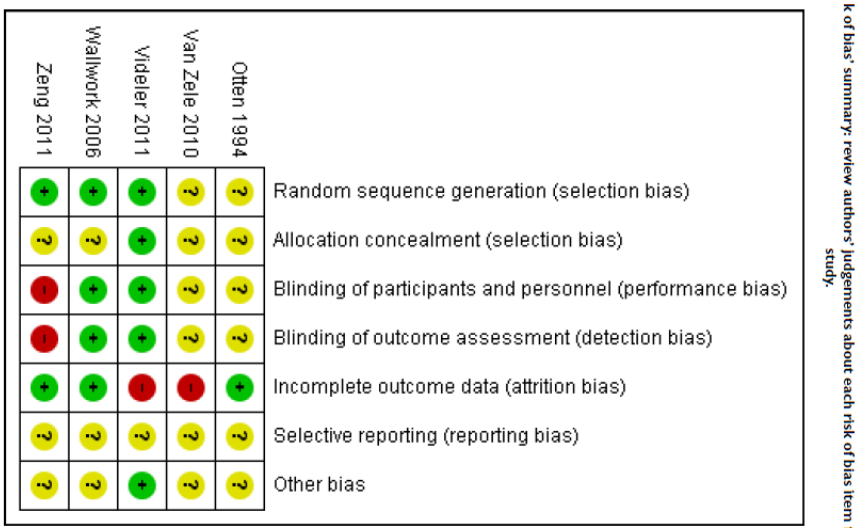
- N=5 RCTs (n=293)

Charakteristika der Population:

- All studies compared systemic antibiotics with placebo or another pharmacological intervention. Four studies recruited only adults and one only children.
- Three used macrolide, one tetracycline and one a cephalosporin-type antibiotic.
- Three recruited only patients with chronic rhinosinusitis without nasal polyps, one recruited patients with chronic rhinosinusitis with nasal polyps and one had a mixed population.
- Three followed up patients for 10 to 12 weeks after treatment had finished.

Qualität der Studien:

- Moderat bis niedrig



Studienergebnisse:

- Three studies compared antibiotics with placebo (176 participants)
  - One study (64 participants, without polyps) reported disease-specific HRQL using the SNOT-20 (0 to 5, 0 = best quality of life). At the end of treatment (three months) the SNOT-20 score was lower in the group receiving macrolide antibiotics than the placebo group (mean difference (MD) -0.54 points, 95% confidence interval (CI) -0.98 to -0.10), corresponding to a moderate effect size favouring antibiotics (moderate quality evidence). Three months after treatment, it is uncertain if there was a difference between groups.
  - One study (33 participants, with polyps) provided information on gastrointestinal disturbances and suspected allergic reaction (rash or skin irritation) after a short course of tetracycline antibiotic compared with placebo.We are very uncertain if antibiotics were associated with an increase in gastrointestinal disturbances (risk ratio (RR) 1.36, 95% CI 0.22 to 8.50) or skin irritation (RR 6.67, 95% CI 0.34 to 128.86) (very low quality evidence).
- Systemic antibiotics plus saline irrigation and intranasal corticosteroids versus placebo plus saline irrigation and intranasal corticosteroids (1 Studie)
  - One study (60 participants, some with and some without polyps) compared a three-month course of macrolide antibiotic with placebo; all participants also used saline irrigation and 70% used intranasal corticosteroids. Disease-specific HRQL was reported using SNOT-22 (0 to 110, 0 = best quality of life). Data were difficult to interpret (highly skewed and baseline imbalances) and it is unclear if there was an important difference at any time point (low quality evidence). To assess patient-reported disease severity participants

rated the effect of treatment on a five-point scale (-2 for “desperately worse” to 2 for “cured”) at the end of treatment (three months). For improvement in symptoms there was no difference between the antibiotics and placebo groups; the RR was 1.50 (95% CI 0.81 to 2.79; very low quality evidence), although there were also slightly more people who felt worse after treatment in the antibiotics group. There was no demonstrable difference in the rate of gastrointestinal disturbances between the groups (RR 1.07, 95% CI 0.16 to 7.10). General HRQL was measured using the SF-36. The authors stated that there was no difference between groups at the end of treatment (12 weeks) or two weeks later.

- Systemic antibiotics versus intranasal corticosteroids (1 Studie)
  - One study (43 participants, without polyps) compared a three-month course of macrolide antibiotic with intranasal corticosteroids. Patient-reported disease severity was assessed using a composite symptom score (0 to 40; 0 = no symptoms). It is very uncertain if there was a difference as patient-reported disease severity was similar between groups (MD -0.32, 95% CI -2.11 to 1.47; low quality evidence).
- Systemic antibiotics versus oral corticosteroids (1 Studie)
  - One study (28 participants, with polyps) compared a short course of tetracycline antibiotic (unclear duration, ~20 days) with a 20-day course of oral corticosteroids. We were unable to extract data on any of the primary efficacy outcomes. It is uncertain if there was a difference ingastrointestinal disturbances (RR 1.00, 95% CI 0.16 to 6.14) or skin irritation (RR 2.00, 95% CI 0.20 to 19.62) as the results for these outcomes were similar between groups (very low quality evidence).

Anmerkung/Fazit der Autoren

We found very little evidence that systemic antibiotics are effective in patients with chronic rhinosinusitis. We did find moderate quality evidence of a modest improvement in disease-specific quality of life in adults with chronic rhinosinusitis without polyps receiving three months of a macrolide antibiotic. The size of improvement was moderate (0.5 points on a five-point scale) and only seen at the end of the three-month treatment; by three months later no difference was found. Despite a general understanding that antibiotics can be associated with adverse effects, including gastrointestinal disturbances, the results in this review were very uncertain because the studies were small and few events were reported.

No RCTs of topical antibiotics met the inclusion criteria.

Head K et al., 2016 [7].

Short-course oral steroids as an adjunct therapy for chronic Rhinosinusitis

Fragestellung

To assess the effects of a short course of oral corticosteroids as an adjunct (’add-on’) therapy in people with chronic rhinosinusitis who are already on standard treatments.

Methodik

Population:

- Patients with chronic rhinosinusitis, whether with polyps or without polyps

(Hinweis: im Folgenden wurden nur Studien an Erwachsenen Personen extrahiert)

Intervention:

- prednisone;
- prednisolone;
- methylprednisolone;
- hydrocortisone;
- cortisone acetate.

Komparator:

- oral steroids plus intranasal corticosteroids versus placebo or no treatment plus intranasal corticosteroids

Endpunkte:

- QoL, Disease severity, AEs etc.

Recherche/Suchzeitraum:

- August 2015

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions

Ergebnisse

Anzahl eingeschlossener Studien:

- N=2 (n=78) (just one trial with adults)

Charakteristika der Population:

- One trial in adults with nasal polyps included 30 participants. All participants used intranasal corticosteroids and were randomised to either short-course oral steroids (oral methylprednisolone, 1 mg/kg and reduced progressively over a 21-day treatment course) or no additional treatment.

Qualität der Studien:

- We judged the quality of the evidence for oral steroids plus intranasal steroids for adults with nasal polyps to be very low (we are very uncertain about the estimate) as the evidence comes from one trial that has a low number of participants. The trial had a high risk of bias due to the way it was conducted. The trial did not report adverse events and did not report results after the end of treatment.

Studienergebnisse:

- Oral steroids as an adjunct to intranasal corticosteroids
  - One trial in adults with nasal polyps included 30 participants. All participants used intranasal corticosteroids and were randomised to either short-course oral steroids (oral methylprednisolone, 1 mg/kg and reduced progressively over a 21-day treatment course) or no additional treatment. None of the primary outcome measures of interest in this review were reported by the study. There may have been an important reduction in the size of the polyps (measured by the nasal polyps score, a secondary outcome measure) in patients receiving oral steroids and intranasal corticosteroids, compared to intranasal

corticosteroids alone (mean difference (MD) -0.46, 95% confidence interval (CI) -0.87 to -0.05; 30 participants; scale 1 to 4) at the end of treatment (21 days). This corresponds to a large effect size, but we are very uncertain about this estimate as we judged the study to be at high risk of bias. Moreover, longer-term data were not available and the other outcomes of interest were not reported.

- There were no data available for the longer term (three months).

Anmerkung/Fazit der Autoren

There might be an improvement in symptom severity, polyps size and condition of the sinuses when assessed using CT scans in patients taking oral corticosteroids when these are used as an adjunct therapy to antibiotics or intranasal corticosteroids, but the quality of the evidence supporting this is low orvery low (we are uncertain about the effect estimate; the true effect may be substantially different from the estimate of the effect). It is unclear whether the benefits of oral corticosteroids as an adjunct therapy are sustained beyond the short follow-up period reported (up to 30 days), as no longer-term data were available.

There were no data in this review about the adverse effects associated with short courses of oral corticosteroids as an adjunct therapy.

More research in this area, particularly research evaluating longer-term outcomes and adverse effects, is required.

Head K et al., 2016 [6].

Short-course oral steroids alone for chronic rhinosinusitis

Fragestellung

To assess the effects of oral corticosteroids compared with placebo/ no intervention or other pharmacological interventions (intranasal corticosteroids, antibiotics, antifungals) for chronic rhinosinusitis.

Methodik

Population:

- Patients with chronic rhinosinusitis, whether with polyps or without polyps

Intervention:

- prednisone;
- prednisolone;
- methylprednisolone;
- hydrocortisone;
- cortisone acetate.

Komparator:

- The main comparators were: placebo or no intervention.
- The main comparison pairs were:
  - oral steroids versus placebo or no treatment;

  - oral steroids followed by intranasal corticosteroids versus placebo or no treatment followed by intranasal corticosteroids.
- Other possible comparison pairs included:
  - oral steroids versus intranasal corticosteroids;
  - oral steroids versus antibiotics;
  - oral steroids versus antifungals.

Endpunkte:

- QoL, Disease severity, AEs etc.

Recherche/Suchzeitraum:

- August 2015

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions

Ergebnisse

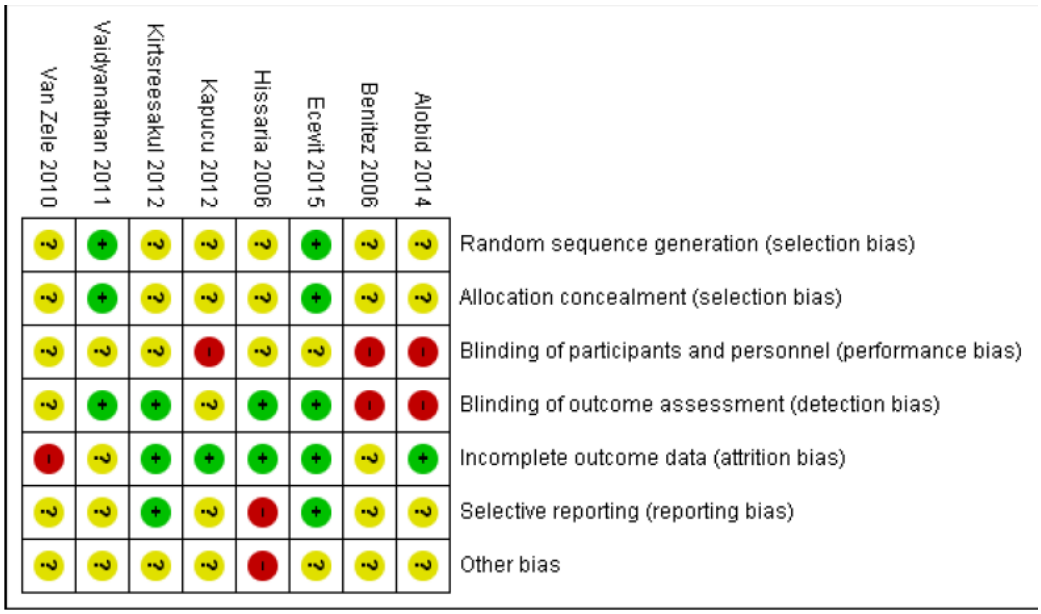
Anzahl eingeschlossener Studien:

- N=8 (474) → which compared oral corticosteroids with placebo or no intervention

Charakteristika der Population:

- All eight included studies are parallel-group, randomised controlled trials
- All trials only recruited adults with chronic rhinosinusitis with nasal polyps.
- There were 474 participants included in the comparison of oral steroids with placebo or no intervention.
- All trials reported outcomes at two to three weeks, at the end of the short-course oral steroid treatment period. Three trials additionally reported outcomes at three to six months.
- Two of these studies prescribed intranasal steroids to patients in both arms of the trial at the end of the oral steroid treatment period.

Qualität der Studien:



Studienergebnisse:

Oral steroids versus placebo or no intervention

- Disease-specific health-related quality of life was reported by one study. This study reported improved quality of life after treatment (two to three weeks) in the group receiving oral steroids compared with the group who received placebo (standardised mean difference (SMD) -1.24, 95% confidence interval (CI) -1.92 to -0.56, 40 participants, modified RSOM-31), which corresponds to a large effect size.We assessed the evidence to be low quality (we are uncertain about the effect estimate; the true effect may be substantially different from the estimate of the effect).
- Disease severity as measured by patient-reported symptom scores was reported by two studies, which allowed the four key symptoms used to define chronic rhinosinusitis (nasal blockage, nasal discharge, facial pressure, hyposmia) to be combined into one score. The results at the end of treatment (two to three weeks) showed an improvement in patients receiving oral steroids compared to placebo, both when presented as a mean final value (SMD -2.84, 95% CI -4.09 to -1.59, 22 participants) and as a change from baseline (SMD -2.28, 95% CI -2.76 to -1.80, 114 participants). These correspond to large effect sizes but we assessed the evidence to be low quality.
- One study (114 participants) followed patients for 10 weeks after the two-week treatment period. All patients in both arms received intranasal steroids at the end of the oral steroid treatment period. The results showed that the initial results after treatment were not sustained (SMD -0.22, 95% CI -0.59 to 0.15, 114 participants, percentage improvement from baseline). This corresponds to a small effect size and we assessed the evidence to be low quality.
- There was an increase in adverse events in people receiving orals steroids compared with placebo for gastrointestinal disturbances (risk ratio (RR) 3.45, 95% CI 1.11 to 10.78; 187 participants; three studies) and insomnia (RR 3.63, 95% CI 1.10 to 11.95; 187 participants; three studies). There was no significant impact of oral steroids on mood disturbances at the dosage used in the included study (risk ratio (RR) 2.50, 95% CI 0.55 to 11.41; 40 participants;

one study). We assessed the evidence to be low quality due to the lack of definitions of the adverse events and the small number of events or sample size, or both).

Other comparisons

No studies that compared short-course oral steroids with other treatment for chronic rhinosinusitis met the inclusion criteria.

Anmerkung/Fazit der Autoren

At the end of the treatment course (two to three weeks) there is an improvement in health-related quality of life and symptom severity in patients with chronic rhinosinusitis with nasal polyps taking oral corticosteroids compared with placebo or no treatment. The quality of the evidence supporting this finding is low. At three to six months after the end of the oral steroid treatment period, there is little or no improvement in health-related quality of life or symptom severity for patients taking an initial course of oral steroids compared with placebo or no treatment.

The data on the adverse effects associated with short courses of oral corticosteroids indicate that there may be an increase in insomnia and gastrointestinal disturbances but it is not clear whether there is an increase in mood disturbances. All of the adverse events results are based on low quality evidence.

More research in this area, particularly research evaluating patients with chronic rhinosinusitis without nasal polyps, longer-term outcomes and adverse effects, is required.

There is no evidence for oral steroids compared with other treatments.

Chong L et al., 2016 [2].

Intranasal steroids versus placebo or no intervention for chronic rhinosinusitis (Review)

Fragestellung

To assess the effects of intranasal corticosteroids in people with chronic rhinosinusitis.

Methodik

Population:

Patients with chronic rhinosinusitis, whether with or without polyps

Intervention:

- First-generation intranasal corticosteroids:
  - Beclomethasone dipropionate
  - Triamcinolone acetonide
  - Flunisolide
  - Budesonide
- Second-generation intranasal corticosteroids:
  - Ciclesonide
  - Fluticasone furoate
  - Fluticasone propionate
  - Mometasone furoate

  - Betamethasone sodium phospate
- If other interventions were used, these should have been used in both treatment arms. Allowed co-interventions included:
  - nasal saline irrigation;
  - antibiotics;
  - intermittent nasal decongestants.

Komparator:

- The main comparison pair was:
  - intranasal corticosteroids versus placebo or no intervention.
- Other possible comparison pairs included:
  - intranasal corticosteroids plus co-intervention A versus placebo plus co-intervention A.

Endpunkte:

- QoL, Disease severity, AEs etc.

Recherche/Suchzeitraum:

- August 2015

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions

Ergebnisse

Anzahl eingeschlossener Studien:

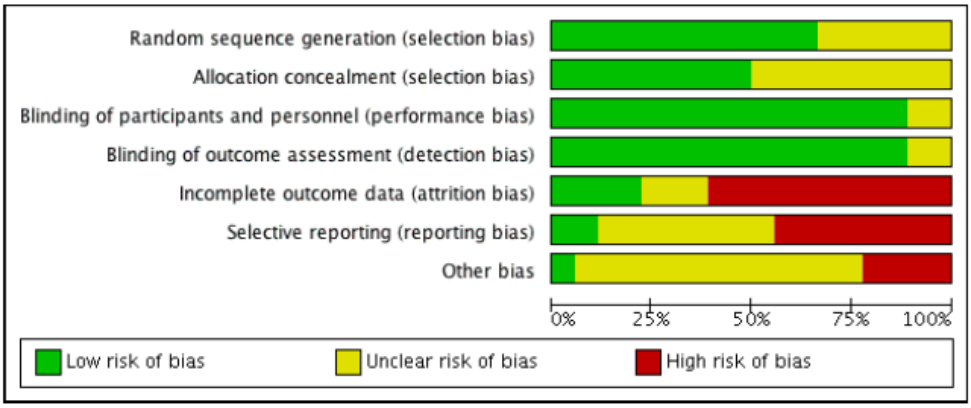
- N=18 (n=2738)

Charakteristika der Population:

- Fourteen studies had participants with nasal polyps and four studies had participants without nasal polyps. Only one study was conducted in children.

Qualität der Studien:

- We included 18 studies in this review. Nine of these had low risk of bias for both selection and blinding (Keith 2000; Lund 2004; Mosges 2011; Parikh 2001; Penttilla 2000; Small 2005; Stjarne 2006; Stjarne 2006a; Zhou 2015). Lang 1983 was only available as an abstract and therefore there was insufficient information to judge the risk of bias formost domains.We didmost of the ratings based solely on the study report(s), as the trials were not registered and no protocols were available.



Studienergebnisse:

Intranasal corticosteroids versus placebo or no intervention

- Only one study (20 adult participants without polyps) measured our primary outcome disease-specific HRQL using the Rhinosinusitis Outcome Measures-31 (RSOM-31). They reported no significant difference (numerical data not available) (very low quality evidence).
- Our second primary outcome, disease severity , was measured using the Chronic Sinusitis Survey in a second study (134 participants without polyps), which found no important difference (mean difference (MD) 2.84, 95% confidence interval (CI) -5.02 to 10.70; scale 0 to 100). Another study (chronic rhinosinusitis with nasal polyps) reported an increased chance of improvement in the intranasal corticosteroids group (RR 2.78, 95% CI 1.76 to 4.40; 109 participants). The quality of the evidence was low.
- Six studies provided data on at least two of the individual symptoms used in the EPOS 2012 criteria to define chronic rhinosinusitis (nasal blockage, rhinorrhoea, loss of sense of smell and facial pain/pressure). When all four symptoms in the EPOS criteria were available on a scale of 0 to 3 (higher = more severe symptoms), the average MD in change from baseline was -0.26 (95% CI -0.37 to -0.15; 243 participants; two studies; low quality evidence). Although there were more studies and participants when only nasal blockage and rhinorrhoea were considered (MD -0.31, 95% CI -0.38 to -0.24; 1702 participants; six studies), the MD was almost identical to when loss of sense of smell was also considered (1345 participants, four studies; moderate quality evidence).
- When considering the results for the individual symptoms, benefit was shown in the intranasal corticosteroids group. The effect size was larger for nasal blockage (MD -0.40, 95% CI -0.52 to -0.29; 1702 participants; six studies) than for rhinorrhoea (MD -0.25, 95% CI -0.33 to -0.17; 1702 participants; six studies) or loss of sense of smell (MD -0.19, 95% CI -0.28 to -0.11; 1345 participants; four studies). There was heterogeneity in the analysis for facial pain/pressure (MD -0.27, 95% CI -0.56 to 0.02; 243 participants; two studies). The quality of the evidence was moderate for nasal blockage, rhinorrhoea and loss of sense of smell, but low for facial pain/ pressure.

- There was an increased risk of epistaxis with intranasal corticosteroids (risk ratio (RR) 2.74, 95% CI 1.88 to 4.00; 2508 participants; 13 studies; high quality evidence).
- Considering our secondary outcome, general HRQL, one study (134 participants without polyps) measured this using the SF-36 and reported a statistically significant benefit only on the general health subscale. The quality of the evidence was very low. It is unclear whether

there is a difference in the risk of local irritation (RR 0.94, 95% CI 0.53 to 1.64; 2124 participants; 11 studies) (low quality evidence).

- None of the studies treated or followed up patients long enough to provide meaningful data on the risk of osteoporosis or stunted growth (children).

Other comparisons

- We identified no other studies that compared intranasal corticosteroids plus co-intervention A versus placebo plus co-intervention A.

Anmerkung/Fazit der Autoren

Most of the evidence available was from studies in patients with chronic rhinosinusitis with nasal polyps. There is little information about quality of life (*very low quality* evidence). For disease severity, there seems to be improvement for all symptoms (*low quality* evidence), a moderate-sized benefit for nasal blockage and a small benefit for rhinorrhoea (*moderate quality* evidence). The risk of epistaxis is increased (*high quality* evidence), but these data included all levels of severity; small streaks of blood may not be a major concern for patients. It is unclear whether there is a difference in the risk of local irritation (*low quality* evidence).

Chong L et al., 2016 [1].

Different types of intranasal steroids for chronic rhinosinusitis

Fragestellung

To assess the relative effects of different types, delivery methods and doses of intranasal corticosteroids.

Methodik

Population:

Patients with chronic rhinosinusitis, whether with or without polyps

Intervention:

- First-generation intranasal corticosteroids:
  - Beclomethasone dipropionate
  - Triamcinolone acetonide
  - Flunisolide
  - Budesonide
- Second-generation intranasal corticosteroids:
  - Ciclesonide
  - Fluticasone furoate
  - Fluticasone propionate
  - Mometasone furoate
  - Betamethasone sodium phospate
- If other interventions were used, these should have been used in both treatment arms. Allowed co-interventions included:

- nasal saline irrigation;
- antibiotics;
- intermittent nasal decongestants.

Komparator:

- The main possible comparison pair was:
  - any first-generation corticosteroid versus any secondgeneration corticosteroid.
- Other possible comparison pairs were:
  - intranasal corticosteroid delivered as spray versus intranasal corticosteroid delivered as drops; and
  - low-dose intranasal corticosteroid versus high-dose intranasal corticosteroid.

Endpunkte:

- QoL, Disease severity, AEs etc.

Recherche/Suchzeitraum:

- August 2015

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions

Ergebnisse

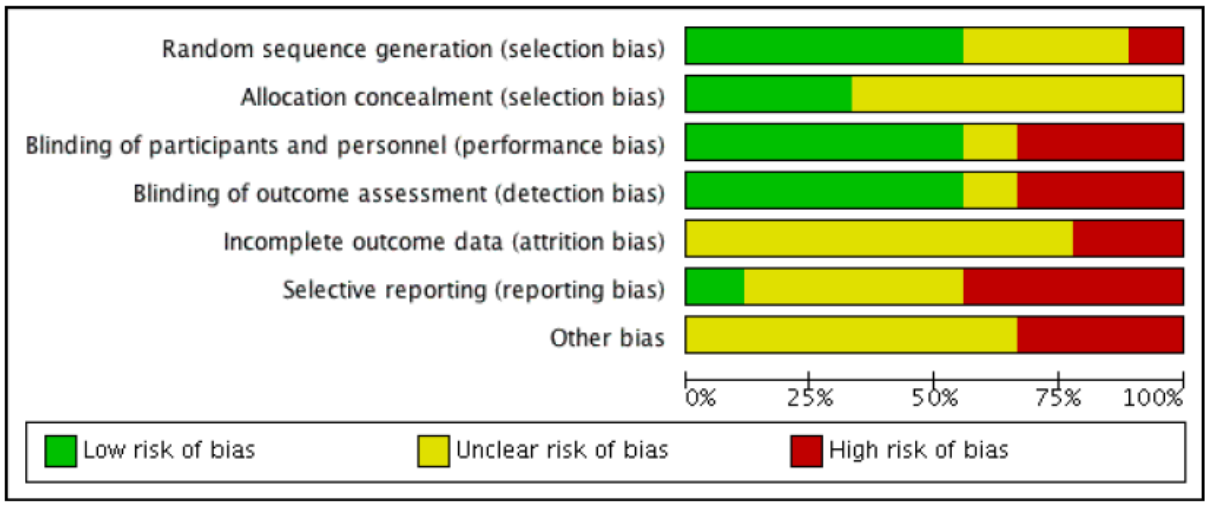
Anzahl eingeschlossener Studien:

- N=9 (n=911)

Charakteristika der Population:

The studies varied in size: some were small, with as few as 20 patients, while others included over 200 participants. Most studies recruited adult patients, but one study only included children. In the majority of the adult studies, most participants were male (72% to 79%). In all of the studies the participants had chronic rhinosinusitis with nasal polyps. The studies either compared different types of steroids (three studies), highdose versus low-dose steroids (five studies), twice daily versus once daily steroids, or different delivery methods (aqueous nasal spray versus aerosol - one study). All of the studies had a placebo group.

Qualität der Studien:



Studienergebnisse:

Fluticasone propionate versus beclomethasone dipropionate

We identified two small studies (56 participants with polyps) that evaluated disease severity and looked at the primary adverse effect: epistaxis, but no other outcomes. We cannot report any numerical data but the study authors reported no difference between the two steroids. The evidence was of very low quality.

Fluticasone propionate versus mometasone furoate

We identified only one study (100 participants with polyps) that evaluated disease severity (nasal symptoms scores), which reported no difference (no numerical data available). The evidence was of very low quality.

High-dose versus low-dose steroids

We included five studies (663 participants with nasal polyps), three using mometasone furoate (400 µg versus 200 µg in adults and older children, 200 µg versus 100 µg in younger children) and two using fluticasone propionate drops (800 µg versus 400 µg). We found low quality evidence relating to disease severity and nasal polyps size, with results from the high-dose and low-dose groups being similar. Although all studies reported more improvement in polyp score in the high-dose group, the significance of this is unclear due to the small size of the improvements.

The primary adverse effect, epistaxis, was more common when higher doses were used (risk ratio (RR) 2.06, 95% confidence interval (CI) 1.20 to 3.54, 637 participants, moderate quality evidence).Most of the studies that contributed data to this outcome used a broad definition of epistaxis, which ranged from frank bleeding to bloody nasal discharge to flecks of blood in the mucus.

Aqueous nasal spray versus aerosol spray

We identified only one poorly reported study (unclear number of participants for comparison of interest, 91 between three treatment arms), in which there were significant baseline differences between the participants in the two groups. We were unable to draw meaningful conclusions from the data.

Anmerkung/Fazit der Autoren

We found insufficient evidence to suggest that one type of intranasal steroid is more effective than another in patients with chronic rhinosinusitis, nor that the effectiveness of a spray differs from an aerosol. We identified no studies that compared drops with spray.

It is unclear if higher doses result in better symptom improvements (low quality evidence), but there was moderate quality evidence of an increased risk of epistaxis as an adverse effect of treatment when higher doses were used. This included all levels of severity of epistaxis and it is likely that the proportion of events that required patients to discontinue usage is low due to the low numbers of withdrawals attributed to it. If epistaxis is limited to streaks of blood in the mucus it may be tolerated by the patient and it may be safe to continue treatment. However, it may be a factor that affects compliance.

There is insufficient evidence to suggest that the different types of corticosteroid molecule or spray versus aerosol have different effects. Lower doses have similar effectiveness but fewer side effects.

Clearly more research in this area is needed, with specific attention given to trial design, disease-specific health-related quality of life outcomes and evaluation of longer-term outcomes and adverse effects.

3.3 Systematische Reviews

Li W et al., 2019 [11].

Efficacy and safety of steroid-impregnated implants following sinus surgery: A meta-analysis

Fragestellung

The purpose of this meta-analysis was to discuss the efficacy and safety of bioabsorbable steroid-impregnated implants following endoscopic sinus surgery (ESS) for chronic rhinosinusitis (CRS) patients.

Methodik

Population:

- patients with CRSsNP, CRSwNP or both

Intervention:

- bioabsorbable steroid-impregnated implants following ESS

Komparator:

- non-steroid-impregnated implants

Endpunkte:

- Lund-Kennedy scores (LKES - assesses sinus outcomes based on the degree of polyps (0 = none, 1 = confined to middle meatus, and 2 = beyond middle meatus), discharge (0 = none, 1 = clear and thin, and 2 = thick and purulent), and edema, scarring, and crusting (for each, 0 = absent, 1 = mild, and 2 = severe))
- Perioperative Sinus Endoscopy (POSE- rates the sinuses individually, specifically assessing the middle turbinate, the middle meatus, the ethmoid cavity, the sphenoid sinus and the frontal recess/sinus.) scores
- Secondary: endoscopy scores of polyp change, significant adhesion, middle turbinate lateralization. For studies that also measured specific safety outcomes, bioabsorbable steroid-impregnated implants safety was also evaluated by documenting all reported adverse events.

Recherche/Suchzeitraum:

- PubMed, Cochrane, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials in March 2019

Qualitätsbewertung der Studien:

- Risk of Bias Assessment of the RCTs

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs

Charakteristika der Population:

TABLE I.
Study Characteristics of the Included Eight Randomized Controlled Trials.

Study/Year	Design	Sex (M/F)	Mean Age (year)	Nostrils (n)	Type of CRS	Impregnanted Drug (Dose)/Implants	Follow-up (months)
1. Adriaensen/2017	RCT	EG:9/9 CG: 11/7	EG: 50 CG: 45	EG: 18 CG: 18	CRSwNP	EG:FP (40 μg/cm^2)/dressing CG:No/dressing	2
2. Hwang/2018	RCT	EG:17/5 CG: 17/5	EG: 42.05 CG: 42.05	EG: 22 CG: 22	CRSwNP	EG:TS (2 mL, 40 mg/mL)/dressing CG:NS (2 mL)/dressing	2
3. Marple/2012	RCT	EG:60/45 CG: 60/15	EG:46.5 CG:46.5	EG:105 CG:105	CRSwNP CRSsNP	EG:MF (370 μg)/stent CG:No/stent	1
4. Murr/2011	RCT	–	–	EG:38 CG:38	CRSwNP CRSsNP	EG:MF (370 μg)/stent CG:No/stent	2
5. Rudmik/2012	RCT	EG:11/7 CG:9/9	EG:49.9 CG:49.2	EG:18 CG:18	CRSsNP	EG:DM (4 mL, 4 mg/mL) + 4 mL SW/spacer CG:8 mL SW/spacer	3
6. Sow/2018	RCT	–	–	EG:8 CG:8	CRSwNP CRSsNP	EG:HC/dressing CG:NS/dressing	3
7. Xu/2016	RCT	–	–	EG:18 CG:19	CRSwNP	EG:TS (2 mL, 10 mg/mL)/dressing CG:NS (2 mL/dressing	3
8. Zhao/2018	RCT	EG:10/5 CG:10/5	EG:46.53 CG:46.53	EG:15 CG:15	CRSwNP	EG:MF (8 mL)/dressing CG:NS (8 mL)/dressing	3

CG = control group; CRS = chronic rhinosinusitis; CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; DM = dexamethasone; EG = experimental group; F = female; FP = fluticasone propionate; HC = hydrocortisone; M = male; MF = monmetasone furoate; NS = normal saline; RCT = randomized controlled trial; SW = sterile water; TS = triamcinolone solution.

Qualität der Studien:

Risk of Bias Assessment of the RCTs.

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
1. Adriaensen/2017	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
2. Hwang/2018	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
3. Marple/2011	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
4. Murr/2010	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
5. Rudmik/2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
6. Sow/2018	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
7. Xu/2016	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
8. Zhao/2018	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk

RCT = randomized controlled trial.

Studienergebnisse:

- Lund-Kennedy Scores: The pooled results revealed that the experimental group was noted to have a better LKES than the control group; however, there was no significant difference between the experimental group and the control group (WMD − 0.40; 95% CI −1.05, −0.62, P = 0.23). The random-effects model was used due to the high heterogeneity of the effect size (I2 = 62%, P = 0.05).
- Perioperative Sinus Endoscopy Scores: The pooled results indicated that the experimental group had lower Perioperative Sinus Endoscopy (POSE) scores compared with the control group, and there was a significant difference between the two groups (WMD −1.88; 95% CI −2.32 to −1.43, P < 0.00001), without heterogeneity (I2= 44%, P= 0.17).
- Polypoid Change: The pooled results demonstrated a significant difference between the experimental group and the control group (OR −0.16; 95% CI: −0.26 to −0.06; P = 0.002), without heterogeneity (I2 = 0%, P = 0.97).
- Middle Turbinate Lateralization: The pooled results demonstrated a significant difference between the experimental group and the control group (OR 0.28; 95% CI: 0.09 to 0.90; P = 0.03) without heterogeneity (I2 = 0%, P = 0.94)

- Significant Adhesion: The pooled results demonstrated a significant difference between the experimental group and the control group (OR 0.30; 95% CI: 0.12 to 0.73; P = 0.008) without heterogeneity (I2= 0%, P= 0.59).
- Total Serious Adverse Events: We compared the numbers of adverse events, such as postoperative bleeds, frank pus in the sinus, local swelling, and postoperative bleeds in the experimental group with those in the control group, and the pooled results demonstrated no significant difference between experimental group and control group (OR 0.38; 95% CI: 0.07 to 2.03; P = 0.26) without heterogeneity (I2 = 0%, P = 0.76).

Anmerkung/Fazit der Autoren

This meta-analysis of data revealed that bioabsorbable steroid-impregnated implants following ESS are effective in improving the endoscopic appearance of the healing process, and the safety profile appears to be favorable for the treatment of CRS patients.

Kommentare zum Review

In dem Review wurde nicht zwischen Patienten mit CRSsNP und CRSwNP unterschieden. Es ist unklar, wie hoch der Anteil der Personen mit CRSwNP, die dem vorliegenden Anwendungsgebiet entsprechen, ist. Für diese Patientengruppe erfolgten keine separaten Analysen.

Seresirikachorn K et al., 2019 [15].

Factors of success of low-dose macrolides in chronic sinusitis: Systematic review and meta-analysis

Siehe auch Shen S et al., 2018 [16] und Lasso A et al., 2017 [10].

Fragestellung

We hypothesized that the anti-inflammatory and immunomodulatory effects of macrolides at optimal regimens should be effective for specific subgroups. This study aimed to assess the prognostic factors of LDMs therapy that may predict the favorable clinical outcomes by performing a meta-analysis and subgroup analyses.

Methodik

Population:

Patients with CRS 18 years old or older.

Intervention:

Low-dose macrolides (LDMs), LDMs plus standard treatment

Komparator:

Placebo or standard treatment

Endpunkte:

Sino-Nasal Outcome Test (SNOT), symptom score, computed tomography (CT) score, endoscopy score, and gastrointestinal and cardiac adverse effects

Recherche/Suchzeitraum:

MEDLINE and Embase on March 17, 2018

Qualitätsbewertung der Studien:

Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

10 studies were included for qualitative synthesis (8,9,12,15–21), nine studies for quantitative synthesis

8. Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. Laryngoscope 2006;116:189–193.

9. Videler WJ, Badia L, Harvey RJ, et al. Lack of efficacy of long-term, lowdose azithromycin in chronic rhinosinusitis: a randomized controlled trial. Allergy 2011;66:1457–1468.

12. Haxel BR, Clemens M, Karaiskaki N, Dippold U, Kettern L, Mann WJ. Controlled trial for long-term low-dose erythromycin after sinus surgery for chronic rhinosinusitis. Laryngoscope 2015;125:1048–1055.

15. Amali A, Saedi B, Rahavi-Ezabadi S, Ghazavi H, Hassanpoor N. Long-term postoperative azithromycin in patients with chronic rhinosinusitis: a randomized clinical trial. Am J Rhinol Allergy 2015;29:421–424.

16. Deng J, Chen F, Lai Y, et al. Lack of additional effects of long-term, lowdose clarithromycin combined treatment compared with topical steroids alone for chronic rhinosinusitis in China: a randomized, controlled trial. Int Forum Allergy Rhinol 2018;8-14

17. Jiang RS, Wu SH, Tsai CC, Li YH, Liang KL. Efficacy of Chinese herbal medicine compared with a macrolide in the treatment of chronic rhinosinusitis without nasal polyps. Am J Rhinol Allergy 2012;26:293–297.

18. KorkmazH,Ocal B, Tatar EC, et al. Biofilms in chronic rhinosinusitis with polyps: is eradication possible? Eur Arch Otorhinolaryngol. 2014;271:2695–2702.

19. Peric A, Baletic N, Milojevic M, et al. Effects of preoperative clarithromycin administration in patients with nasal polyposis. West Indian Med J 2014; 63:721–727.

20. Varvyanskaya A, Lopatin A. Efficacy of long-term low-dose macrolide therapy in preventing early recurrence of nasal polyps after endoscopic sinus surgery. Int Forum Allergy Rhinol 2014;4:533–541.

21. Zeng M, Long XB, Cui YH, Liu Z. Comparison of efficacy of mometasone furoate versus clarithromycin in the treatment of chronic rhinosinusitis without nasal polyps in Chinese adults. Am J Rhinol Allergy 2011;25:e203–e207.

TABLE I.
Characteristics of Included Studies.

First Author	Year	CRS Subtype	Concurrent ESS	No. of Patients	No. of Macrolides	No. of Control	Macrolides	Dose (mg/d)	Control	Duration of Treatment (wk)
Wallwork	2006	CRSsNP	Without ESS	64	29	35	Roxithromycin	150	Placebo	12
Videler	2011	Mixed (wNP)	Without ESS	60	29	31	Azithromycin	500/7*	Placebo	12
Zeng	2011	CRSsNP	Without ESS	43	22	21	Clarithromycin	250	INCS	12
Jiang	2012	CRSsNP	Without ESS	53	27	26	Erythromycin	500	Herb	8
Peric	2014	CRSwNP	ESS:preoperative	80	40	40	Clarithromycin	500	No macrolide	8
Korkmaz	2014	CRSwNP	Without ESS	44	22	22	Clarithromycin	250†	No macrolide	8
Varvyanskaya	2014	CRSwNP	ESS:postoperative	66	44	22	Clarithromycin	250	No macrolide	24
Amali	2015	Mixed (sNP)	ESS:postoperative	66	22	44	Azithromycin	250	Placebo	12
Haxel	2015	Mixed (wNP)	ESS:postoperative	58	29	29	Erythromycin	250	Placebo	12
Deng	2018	Mixed (wNP)	Without ESS	74	38	36	Clarithromycin	250	No macrolide	12

*Study group received azithromycin 500 mg/d for 3 days during the first week followed by 500 mg/wk for 11 weeks.
†Study group received clarithromycin 1,000 mg/d during the first 2 weeks, followed by 250 mg/d for 6 weeks.
CRS = chronic rhinosinusitis; CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; ESS = endoscopic sinus surgery; Mixed (sNP) = mixed population with predominant without polyps; Mixed (wNP) = mixed population with predominant with polyps; INCS = Intranasal corticosteroids.

Comparisons

- trials compared LDMs therapy versus placebo.[8,9,12,15]
- trials compared LDMs therapy plus standard treatment versus standard treatment.[16,18–20]

- 1 trial LDMs therapy to a standard treatment of intranasal steroid spray.[21]
- One trial was excluded from quantitative synthesis because the LDMs therapywas compared to herbalmedicine, whichwas neither a placebo nor a standard treatment.[17]

Charakteristika der Population:

Ten trials studied 608 participants, 50.3% were male, with the mean age of 43.9 years (nine studies[9,12,15–21]). All patients were adults with CRS: CRSsNP (three trials[8,17,21]), CRSwNP (three trials[18–20]), and mixed subtypes of CRS (a major population of CRSwNP [three trials[9,12,16]] and CRSsNP [one trial[15]]). Two trials measured the serum IgE level at enrollment.[8,12] Both studies had mixed populations of low and high serum IgE.

Qualität der Studien:

The included studies had substantial selection bias for random sequence generation (60% low risk) and allocation concealment (50% low risk). They had modest risks in detection bias (70% low risk), attrition bias (80% low risk), and reporting bias (80% low risk).

Studienergebnisse:

Comparison: LDMs Versus Placebo

- The meta-analysis revealed no difference between the LDMs and placebo in the improvement in 1) the SNOT (SMD = −0.23, 95% CI: −0.69 to 0.24),[8,9,12,15 2)] symptom score (SMD = −0.29, 95% CI: −1.46 to 0.89),[8,12] and endoscopy score (SMD = −0.35, 95% CI: −0.71 to 0.00).[8,12] There was no trial assessing the improvement in CT score. Heterogeneity was substantial for the SNOT (I2 = 68%), symptom score (I2 = 90%). There was no heterogeneity (I2 = 0%) for the endoscopy score.

Comparison: LDMs Plus Standard Treatment Versus Standard Treatment

- The cumulative meta-analysis revealed no difference between the LDMs plus standard treatment and standard treatment in the improvement in [1)] the SNOT (SMD = −0.52, 95% CI: −1.57 to 0.53),[16,18,20 2)] symptomscore (SMD = −0.63, 95% CI: −1.42 to 0.16),16,19,20 3) endoscopy score (SMD = −1.85, 95% CI: −5.59 to 1.88),[16,19,20 and 4)] CT score (SMD = 0.15, 95% CI: −0.25 to 0.54).16,18 Heterogeneity was substantial for the SNOT (I2 = 88%), symptom score (I2 = 85%), endoscopy score (I2 = 98%). There was no heterogeneity (I2 = 0%) for CT score.

Comparison: LDMs Versus Standard Treatment

- There was only one RCT in this comparison. [21] The results showed no difference between LDMs and intranasal steroid spray in the improvement of symptom score (MD = 0.04, 95% CI: −0.56 to 0.64) and endoscopy score (MD = −0.49, 95% CI: −0.10 to 0.12). The SNOT and CT score were not assessed.[21]

Subgroup CRSsNP vs CRSwNP

- When subgroup analysis by CRS subtype was performed, the effects favored LDMs over placebo in the improvement in the SNOT in patients with CRSsNP (SMD = −0.64, 95% CI: −1.01 to −0.27), but not in patients with CRSwNP (SMD = 0.18, 95% CI: −0.19 to 0.55). The subgroup difference was statistically significant (P = .009). Likewise, the effects favored the LDMs over placebo in the improvement in symptom score in patients with CRSsNP (MD =

−0.89, 95% CI: −1.41 to −0.37), but not in patients with CRSwNP (SMD = 0.31, 95% CI: −0.21 to 0.83). The subgroup difference was statistically significant (P = .001). There was no difference between the two subgroups (P = .64) in endoscopy score.

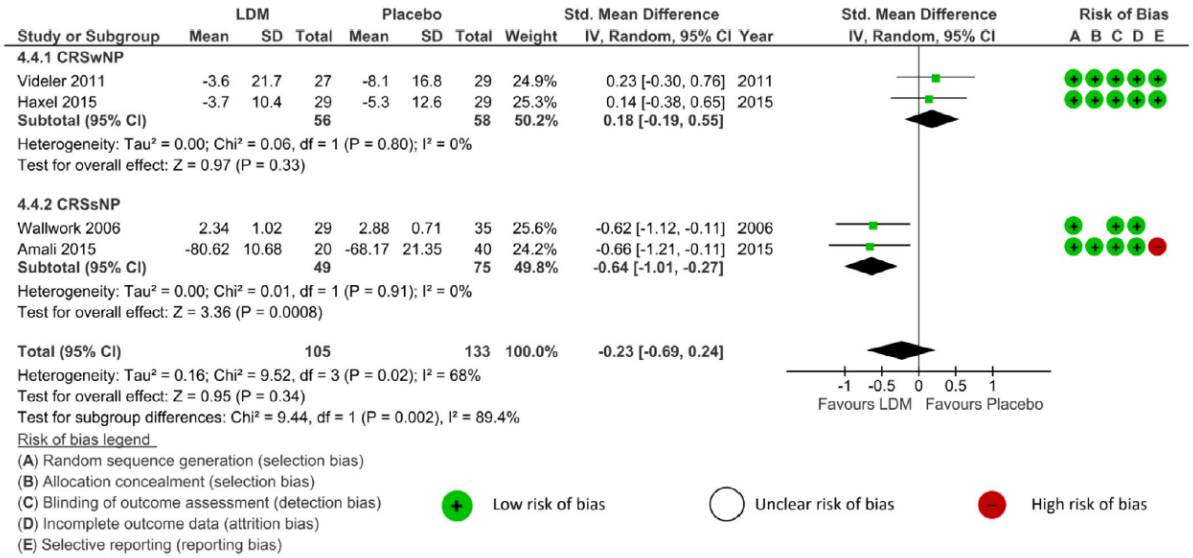


Fig. 2. Improvement in the SNOT at the end of treatment when low-dose macrolides therapy was compared with placebo and subgroup analysis by CRS subtype. CI = confidence interval; CRSsNP = chronic rhinosinusitis without polyps; CRSwNP = chronic rhinosinusitis with polyps; df = degrees of freedom; IV = inverse variance; LDM = low-dose macrolides; Random = random effects; SD = standard deviation; SNOT = Sino-Nasal Outcome Test; Std. mean difference = standardized mean difference. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Advese Events

- There were nine studies that reported gastrointestinal and cardiac adverse effects. LDMs produced greater gastrointestinal adverse effects (5%) when compared to other treatments (1.05%) (risk ratio: 3.52; 95% CI: 1.29 to 9.60). There was no cardiac adverse effect reported in any patients.

Anmerkung/Fazit der Autoren

Although overall beneficial effects were not demonstrated, LDMs with appropriate treatment regimens may provide clinical benefits in disease-specific quality of life, symptoms, endoscopy, and radiology to a specific patientpopulation. The findings from meta-analyses and subgroup analyses suggested that the LDMs should be clinically effective in patients with CRSsNP. When LDMs are administered, a half-dose of macrolides for 24 weeks duration is suggested.

Kommentare zum Review

Lasso A et al., 2017 [10] und Shen S et al., 2018 [16] führten ebenfalls einen SR zum Thema LDMs durch und schlossen dabei RCTs ein, die auch bei Seresirikachorn enthalten waren, jedoch ohne nach dem Satus der Nasenpolypen zu unterscheiden.

Reychler G et al., 2019 [14].

"Clinical efficacy of intranasal drug delivery by nebulization in chronic rhinosinusitis: a systematic review."

Fragestellung

The aim of this systematic review was to summarize the efficacy of intranasal delivery of corticosteroids or antibiotics by nebulization on symptoms, histology, endoscopy scores, clinical outcomes and quality of life in CRS.

Methodik

Population:

- Erwachsene Patienten mit Sinusitis

Intervention:

- Intranasal delivery of corticosteroids or antibiotics by nebulization

Komparator:

- Another way of administration
- Placebo
- No treatment
- Intranasal delivery of another drug by nebulization

Endpunkte:

- Quality of life
- All clinical symptoms
- Endoscopic evaluation (Kupferberg grades, Lund Mackay score…)
- Rhinometry
- Nasal pick inspiratory flow
- Cytology of the nasal cavity

Recherche/Suchzeitraum:

- Bis Mai 2017

Qualitätsbewertung der Studien:

- quality Index developed by Downs and Black for assessing the quality of reporting (10 items), the external validity (3 items), the bias and confounding elements (13 items) and the statistical power (1 item) of all the studies. This quality index comprises 27 questions with a total maximum score of 28. A grade ranging from “poor” (<14 points) to “excellent” (24–28 points) was assigned to each study evaluated by this quality index.

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs (N=263 Patienten)

(13) Bonfils P, Escabasse V, Coste A, et al. Efficacy of tobramycin aerosol in nasal polyposis. Eur Ann Otorhinolaryngol Head Neck Dis 2015;132(3):119-23.

(14) Brown K, Lane J, Silva MP, DeTineo M, Naclerio RM, Baroody FM. A pilot study of the effects of intranasal budesonide delivered by NasoNeb(R) on patients with perennial allergic rhinitis. Int Forum Allergy Rhinol 2014;4(1):43-8.

(15) Dai Q, Duan C, Liu Q, Yu H. Effect of nebulized budesonide on decreasing the recurrence of allergic fungal rhinosinusitis. Am J Otolaryngol 2017.

(16) Desrosiers MY, Salas-Prato M. Treatment of chronic rhinosinusitis refractory to other treatments with topical antibiotic therapy delivered by means of a large-particle nebulizer: results of a controlled trial. Otolaryngol Head Neck Surg 2001;125(3):265- 9.

(17) Reychler G, Colbrant C, Huart C, et al. Effect of three-drug delivery modalities on olfactory function in chronic sinusitis. Laryngoscope 2015;125(3):549-55.

(18) Shikani AH, Kourelis K, Alqudah MA, et al. Multimodality topical therapy for refractory chronic rhinosinusitis: our experience in thirteen patients with and twelve patients without nasal polyps. Clin Otolaryngol 2013;38(3):254-8.

(19) Videler WJ, van Drunen CM, Reitsma JB, Fokkens WJ. Nebulized bacitracin/colimycin: a treatment option in recalcitrant chronic rhinosinusitis with Staphylococcus aureus? A double-blind, randomized, placebo-controlled, cross-over pilot study. Rhinology 2008;46(2):92-8.

(20) Wang C, Lou H, Wang X, et al. Effect of budesonide transnasal nebulization in patients with eosinophilic chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol 2015;135(4):922-9.

Charakteristika der Population:

- Five studies included patients with previous endoscopic surgery (13;15;16;18;19). Naso-sinusal polyps were included in 4 studies (13;17;20;21) but only one study evaluated their sizes (20).
- Nebulization was used alone or compared with oral treatment, nasal spray, nasal irrigation or nasal gel. Nebulized antibiotics have been studied as much as nebulized corticosteroids. Only one study combined both drugs (18).
- Different devices were found in the studies. Six studies used specific nebulizer to target the sinus (14;15;17;20;22) but only 4 out of them performed the administration with a sonic nebulizers (15;17;20;22). Particle size was determined in 3 studies and the mass median aerodynamic diameter varied from 3.2 to 30 µm (19;23).
- The durations of the treatment were heterogeneous, ranging from 7 days to 17 weeks. Regarding the nebulization, the duration of the session was highly variable but often not recorded.

Qualität der Studien:

- The scores obtained by Downs and Black scale ranged from 14 to 23 and the median score was 19.5/28. All studies were classified as “Fair” or “Good” in the quality appraisal.

Studienergebnisse:

Effects on symptoms

- Nebulized corticosteroids showed a higher decrease of the total score of symptoms than saline solution nebulization even if the difference in change was not always significantly different (14;20). The improvement was similar between corticosteroids nebulized and delivered by nasal spray(15).
- Out of the three studies related to the nebulization of antibiotics (13;16;19), symptoms were not improved by the nebulization (13) (16;19).
- Both drugs werenebulized concomitantly in two studies from the same team. An improvement was observed at short and long term with the nebulization and it was mainly related to the presence of polyps (18). The effect disappeared 4 weeks after nasal spray delivery (18).

Effects on histology

- Corticosteroids reduced some inflammatory parameters but only when they are nebulized (20).

- The combination of both nebulized drugs in the same treatment sessions demonstrated an effect only in patients with polyps. This effect was not observed with the nasal spray(18).

Effects on endoscopic evaluation

- The size of polyps decreased with the delivery of corticosteroids by nebulization (15;20). After treatment with budesonide, an intergroup difference was observed in favor of nebulization compared to the administration by spray (15) or placebo (20).
- After tobramycin administration, the endoscopic results improved but they were not different between nebulization and nasal spray (16). In another study, the effect of nebulized aminoglycosides was not different from saline solution nebulization but the patients received oral antibiotics in both groups (19).
- The patients without polyps did not demonstrate a benefit of the treatment when corticosteroids and antibiotics were nebulized concomitantly (18).

Effects on nasal obstruction

- Only nebulized budesonide resulted in increased PNIF even if the change magnitude was not different compared to saline nebulization (14). However, in the same study, no difference in rhinometry improvement was observed between budesonide and saline nebulization (14).
- Saline nebulization was better than tobramycin nebulization on nasal obstruction (16).

Effects on quality of life

- The quality of life of these patients was reduced compared to the general population (19).
- Quality of life was improved by nebulized corticosteroids but it was not different than saline solution nebulization (14).
- No benefit was observed on quality of life after tobramycin nebulization compared to nasal spray delivery or nebulized saline solution (16;19).

Effects on bacteriology

- No study evaluated the effects of corticosteroids on bacteriology. One study evaluated the effect of tobramycin on cultures (13). Efficacy on the initial bacteria was verified with eradication of 47% of strains (13).

Side-effects

- Few side effects were noted in the retrieved studies (13;20). The side-effects were always recovered by an adapted treatment.

Anmerkung/Fazit der Autoren

This systematic review highlighted that based on the present literature nebulization is not better than nasal spray to the delivery of corticosteroids due to the positive results on symptoms, endoscopic appearance and histological outcomes. For antibiotics delivery, the nebulization is not of added value.

Kommentare zum Review

In den Review gingen sowohl Patienten mit CRSsNP als auch CRSwNP ein.

3.4 Leitlinien

Fokkens, W et al., 2020 [4].

European Position Paper on Rhinosinusitis and Nasal Polyps 2020

Zielsetzung/Fragestellung

The core objective of the EPOS2020 guideline is to provide revised, up-to-date and clear evidence-based recommendations and integrated care pathways in ARS and CRS. In summary, the EPOS 2020 guideline will apply to the adult and paediatric patient population with ARS (viral / common cold, post-viral, bacterial), and all forms of CRS.

Methodik

Grundlage der Leitlinie

The European Position Paper on Rhinosinusitis (EPOS 2020) will be the latest in the EPOS series of guidelines on rhinosinusitis The first European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS)was published in 2005, and was soon followed by EPOS 2007

We followed the AGREE II framework

- Repräsentatives Gremium; The guideline development group included all relevant stakeholders including medical specialists of all relevant specialities, microbiologists, primary care physicians, pharmacists and patients were involved.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt (funded by the European Rhinologic Society Journal Rhinology and the Rhinology Foundation);
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert. The EPOS group plans to come with yearly smaller updates on the most relevant changes.
- Delphi rounds to achieve expert consensus

Recherche/Suchzeitraum:

Cochrane Central Register of Controlled Trials (CENTRAL), OVID MEDLINE and OVID EMBASE on 18/02/2019

LoE/GoR

GRADE was used whenever possible

Sonstige methodische Hinweise (Bei Einschränkung der o. g. Kriterien)

- Eine Qualitätsbewetung der Evidenz ist nur auf aggregierter Ebene auf Basis der gesamten Evidenzlage und nicht für jede einzelne Studie dokumentiert.

Management of chronic rhinosinusitis in adults

An important difference compared to EPOS2012 is that we have decided to move away from differentiating between the management of CRSsNP and CRSwNP per se. The understanding of the last decade of endotyping of CRS and the consequences of endotypes for the

management of disease has led to the decision to describe management of CRS based on endotyping and phenotyping. We propose a new clinical classification based on the disease being localized (often unilateral) or diffuse (always bilateral). Both these groups can be further divided into type 2 or nontype 2 disease (Figure 1.2.1.). The major challenge is to find reliable biomarkers that define type 2 inflammation and predict reaction to medication. Unfortunately, recent large studies with monoclonal antibodies directed at type 2 endotypes have not found reliable biomarkers to predict response to treatment. For the moment the combination of phenotype (e.g. CRSwNP, N-ERD), response to treatment (systemic corticosteroids) and possibly also markers like eosinophils, periostin and IgE either in blood or tissue lead us to the best estimation of the endotype and reaction to treatment. This is a rapidly evolving field at the moment and we expect that frequent updates will be necessary.

1.6.2. Management of CRS: an integrated care pathway

For the management of CRS, a full systematic review of the literature has been performed. Many forms of localised CRS in general, either type 2 or non-type 2, are not responsive to medical treatment and need surgery. For that reason, we advise patients with unilateral disease to be referred to secondary care for further diagnosis. Many studies do not make a clear differentiation between CRSsNP and CRSwNP. Very few studies further define CRS phenotypes or endotypes in the disease. CRS research has revealed that patients with a pure or mixed type 2 endotype tend to be more resistant to current therapies, exhibiting a high recurrence rate when compared with pure type 1 or 3 endotypes. For diffuse, bilateral CRS, local corticosteroids and saline remain the mainstay of the treatment. Furthermore, the integrated care pathway (ICP) advises to check treatable traits, to avoid exacerbating factors and advises against the use of antibiotics. In secondary care, nasal endoscopy can confirm disease, point to secondary CRS (e.g. vasculitis) and further differentiate between localized and diffuse disease. In addition, emphasis is put on optimum techniques of medication delivery and compliance. If treatment with nasal steroid and saline is insufficient, an additional work-up with CT scan and endotyping is relevant. Depending on the endotype indication, treatment can be tailored to a more type 2 or nontype 2 profile. International guidelines differ regarding whether long-term antibiotics and oral steroids should be included as part of adequate medical therapy (AMT), reflecting conflicting evidence in the current literature, and concerns with regard to side-effects. There is a lot of debate on the appropriate moment for surgery for CRS. In a recent study for adult patients with uncomplicated CRS, it was agreed that ESS could be appropriately offered when the CT Lund-Mackay score was ≥1 and there had been a minimum trial of at least eight weeks' duration of a topical intranasal corticosteroid plus a short-course of systemic corticosteroid (CRSwNP) or either a short-course of a broad spectrum / culture-directed systemic antibiotic or the use of a prolonged course of systemic low-dose anti-inflammatory antibiotic (CRSsNP) with a post-treatment total SNOT-22 score ≥20. These criteria were considered the minimal threshold, and clearly not all patients who meet the criteria should have surgery, but their application should reduce unnecessary surgery and practice variation. A subsequent study applied these criteria retrospectively to patients recruited to a multicentre cohort study and found that patients where surgery was deemed 'inappropriate' reported significantly less improvement in their quality of life postoperatively. It is important to emphasize that CRS is a chronic disease and ESS a step in the management that is primarily aimed at creating better conditions for local treatment. After surgery continuous appropriate medical treatment is mandatory. If surgery in combination with appropriate medical treatment fails, additional therapy can be considered. Options are the use of aspirin treatment after aspirin

desensitisation (ATAD), longer (tapering) treatment with OCS, long term antibiotics and/or biologicals when indicated.

1.6.3. New treatment options with biologicals (monoclonal antibodies)

The acceptance of dupilumab (anti IL-4Rα) for the treatment of CRSwNP by the US Food and Drug Administration(FDA) and European Medicines Agency (EMA) in 2019 has significantly changed the treatment options in type 2 type CRS and it is expected that other monoclonal antibodies will follow. Until 2019 monoclonal antibodies could only be prescribed in patients with concomitant (severe) asthma. Within the EUFOREA setting, the positioning of biologics in the ICP of CRS with criteria for use and stopping of biologics have been published. The EPOS2020 steering group made some modifications and tightening of these criteria. They concluded that biologicals are indicated in a patient with bilateral polyps, who had had sinus surgery or was not fit for surgery and who had three of the following characteristics: evidence of type 2 disease (tissue eosinopils ≥10/HPF or blood eosinophils ≥250 OR total IgE ≥100), need for at least two courses of systemic corticosteroids or continuous use of systemic corticosteroids (≥2 courses per year OR long term (>3 months) low dose steroids OR contraindication to systemic steroids), significantly impaired quality of life (SNOT-22 ≥40), anosmic on smell test and/or a diagnosis of comorbid asthma needing regular inhaled corticosteroids. The response criteria for biologicals have been taken from the EUFOREA paper, although the EPOS2020 group also discussed whether there was an indication to repeat surgery in patients on biologicals to give them a better starting point. It was decided that we had insufficient data to advise on surgery whilst on biologicals before deciding that they are not effective and that this is a research need.

1.6.4. Conclusion

EPOS2020 provides a full evidence based systematic review of the management of CRS that has been incorporated into an integrated care pathway (Figures 1.6.1. and 1.6.2.). A significant shift in the management of CRS has occurred since EPOS2012. The options of biologicals in the treatment of type 2 CRS will be a paradigm shift in the management of the disease. The exact positioning of this presently very expensive treatment needs to be determined. EPOS2020 further emphasizes the criteria for (revision) surgery in the disease.

Figure 1.6.2. EPOS2020 management scheme on diffuse CRS.

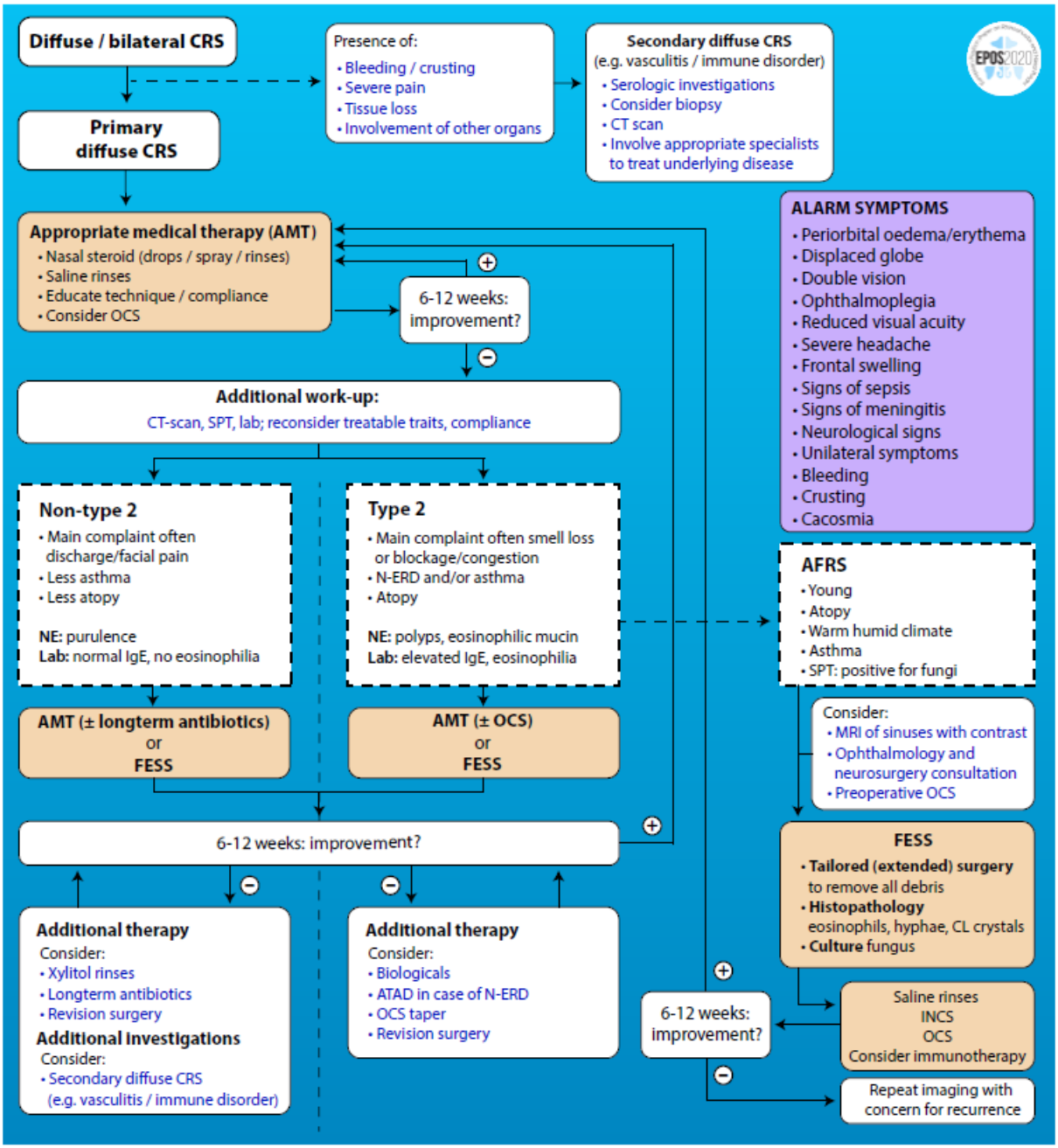
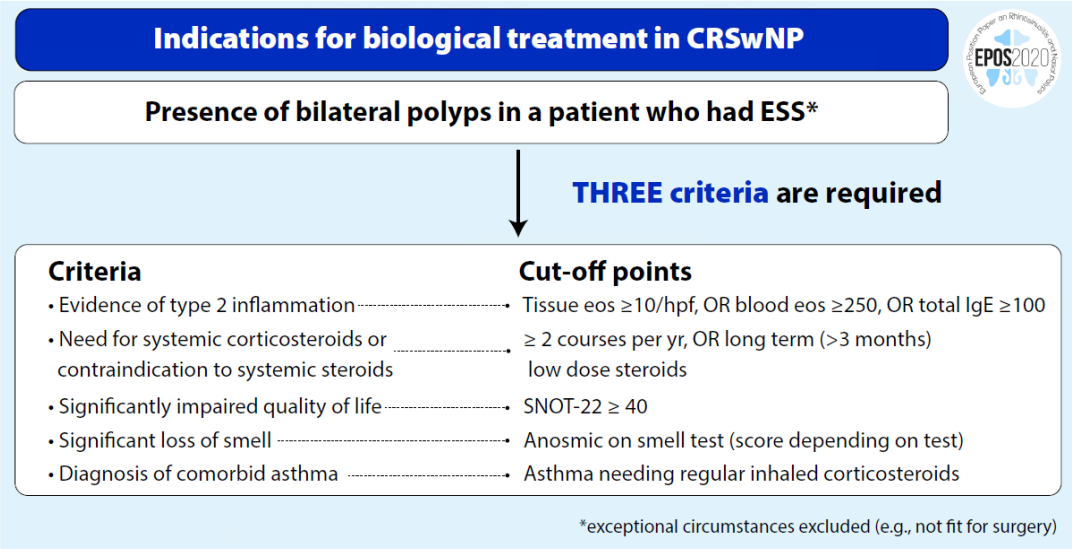


Figure 1.6.3. Indications for biological treatment in CRS.



CRS, chronic rhinosinusitis; CRSwNP: chronic rhinosinusitis with nasal polyps; ESS, endoscopic sinus surgery; hpf: high power field (x400); SNOT-22, sino-nasal outcome test-22.

Table 1.6.1. Treatment evidence and recommendations for adults with chronic rhinosinusitis.

Therapy	Level of evidence	GRADE recommendation
Short term antibiotics for CRS	1b (-)	There are only two small placebo-controlled studies, one in CRS and one in acute exacerbation of CRS. Both show no effect on symptomatology apart from significantly reduced postnasal drip symptom scores at week 2 in the CRS study. Seven studies evaluated two different antibiotics regimes, of which only one was placebo-controlled. One out of seven studies in patients with CRS showed a significant effect on SNOT at 2 and 4 weeks and also one study a significant improvment in symptoms of infection at day 3 to 5 in one antibiotic versus another in a mixed group of patients with CRS and with acute exacerbation. The other 5 studies showed no difference in symptomatology. Only two of these seven studies, both of which were negative, evaluated the effect after one month. The EPOS2020 steering group, is uncertain, due to the very low quality of the evidence, whether or not the use of a short course of antibiotics has an impact on patient outcomes in adults with CRS compared with placebo. Also, due to the very low quality of the evidence, it is uncertain whether or not the use of a short course of antibiotics has an impact on patient outcomes in adults with acute exacerbations of CRS compared with placebo. Gastrointestinal-related adverse events (diarrhoea and anorexia) are frequently reported.
Short term antibiotics for acute exacerbation of CRS	1b (-)	The EPOS2020 steering group, is uncertain, due to the very low quality of the evidence, whether or not the use of a short course of antibiotics has an impact on patient outcomes in adults with acute exacerbations of CRS compared with placebo. Gastrointestinal-related adverse events (diarrhoea and anorexia) are frequently reported.
Longterm antibiotics for CRS	1a (-)	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 for some macrolides. Further studies with larger population sizes are needed and are underway .
Topical antibiotics	1b (-)	Topical antibacterial therapy does not seem to be more effective than placebo in improving symptoms in patients with CRS. However, it may give a clinically non-relevant improvement in symptoms, SNOT-22 and LK endoscopic score compared to oral antibiotics. The EPOS2020 steering group, due to the very low quality of the evidence, is uncertain whether or not the use of topical antibiotic therapy has an impact on patient outcomes in adults with CRS compared with placebo.
Nasal corticosteroids	1a	There is high-quality evidence that long term use of nasal corticosteroids is effective and safe for treating patients with CRS. They have impact on nasal symptoms and quality of life improvement, although the effect on SNOT-22 is smaller than the minimal clinically important difference. The effect size on symptomatology is larger in CRSwNP (SMD -0.93, 95% CI -1.43 to -0.44) than in CRSsNP (SMD -0.30, 95% CI -0.46). The meta-analysis did not show differences between different kinds of nasal corticosteroids. Although in meta-analysis higher dosages and some different delivery methods seem to have a larger effect size on symptomatology, direct comparisons are mostly missing. For CRSwNP, nasal corticosteroids reduce nasal polyp size. When administered after endoscopic sinus surgery, nasal corticosteroids prevent polyp recurrence. Nasal corticosteroids are well tolerated. Most adverse events reported are mild to moderate in severity. Nasal corticosteroids do not affect intraocular pressure or lens opacity. The EPOS2020 steering group advises to use nasal corticosteroids in patients with CRS. Based on the low to very low quality of the evidence for higher dosages or different delivery methods and the paucity of direct comparisons the steering committee cannot advise in favour of higher dosages or certain delivery methods.
Corticosteroid-eluting implants	1a	The placement of corticosteroid-eluting sinus implants in the ethmoid of patients with recurrent polyposis after sinus surgery has a significant but small (0.3 on a 0-3 scale) impact on nasal obstruction but significantly reduces the need for surgery and reduces nasal polyp score. Based on the moderate to high quality of the evidence the steering group considered the use of corticosteroid-eluting sinus implants in the ethmoid an option.
Systemic corticosteroids	1a ,	A short course of systemic corticosteroid, with or without local corticosteroid treatment results in a significant reduction in total symptom score and nasal polyp score. Although the effect on the nasal polyp score remains significant up to three months after the start of treatment by that time there is no longer an effect on the symptom score. The EPOS2020 steering group felt that 1-2 courses of systemic corticosteroids per year can be a useful addition to nasal corticosteroid treatment in patients with partially or uncontrolled disease. A short course of systemic corticosteroid postoperatively does not seem to have an effect on quality of life. Systemic corticosteroids can have significant side effects.
Antihistamines	Ib	There is one study reporting on the effect of antihistamines in partly allergic patients with CRSwNP. Although there was no difference in total symptom score, the days with a symptom score ≤1 was higher in the treated group. The quality of the evidence comparing antihistamines with placebo was very low. There is insufficient evidence to decide on the effect of the regular use of antihistamines in the treatment of patients with CRS.
Anti-leukotrienes	1b (-)	Based on the very low quality of the available evidence, the EPOS2020 steering group is unsure about the potential use of montelukast in CRS and does not recommend its use unless in situations where patients do not tolerate nasal corticosteroids. Also, the quality of the evidence comparing montelukast with nasal corticosteroid is low. Based on the evidence, the steering group does not advise adding montelukast to nasal corticosteroid but studies evaluating the effect of montelukast in patients that failed nasal corticosteroids are missing.
Decongestant	Ib	There is one small study in CRSwNP patients showing a significantly better effect of oxymetazoline combined with MFNS than MFNS alone without inducing rebound swelling. There was no effect of xylometazoline compared to saline in the early postoperative period. This review found a low level of certainty that adding a nasal decongestant to intranasal corticosteroids improves symptomatology in CRS. Although the risk of rebound swelling was not shown in this study, the EPOS2020 steering group suggests in general not to use nasal decongestants in CRS. In situations where the nose is very blocked, the temporary addition of a nasal decongestant to nasal corticosteroid treatment can be considered.

Table 1.6.1. Cont.

Therapy	Level of evidence	GRADE recommendation
Nasal irrigation with saline	Ia	There are a large number of trials evaluating the efficacy of nasal irrigation. However, the quality of the studies is not always very good which makes it difficult to give a strong recommendation. However, the data show: Nasal irrigation with isotonic saline or Ringer's lactate has efficacy in CRS patients. There is insufficient data to show that a large volume is more effective than a nasal spray. The addition of xylitol, sodium hyaluronate, and xyloglucan to nasal saline irrigation may have a positive effect. The addition of baby shampoo, honey, or dexpanthenol as well as higher temperature and higher salt concentration do not confer additional benefit. The steering group advises the use of nasal saline irrigation with isotonic saline or Ringer's lactate with or without the addition of xylitol, sodium hyaluronate, and/or xyloglucan and advises against the use of baby shampoo and hypertonic saline solutions due to side effects.
Aspirin treatment after desensitization (ATAD) with oral aspirin in N-ERD	Ia	Oral ATAD has been shown to be significantly more effective and clinically relevant than placebo in improving QOL (measured with SNOT) and total nasal symptom score in patients with N-ERD. However, the change in SNOT from treating with oral ATAD compared to placebo did not reach the clinically important mean difference. ATAD reduced symptoms after six months compared to placebo. However, ATAD is associated with significant adverse effects, and the risks of not taking the medication strictly on a daily basis puts a burden on patient and caregiver. Based on these data, the EPOS2020 steering group suggests that ATAD can be a treatment for N-ERD patients with CRSwNP whenever there is confidence in the patient's compliance.
Aspirin treatment after desensitization (ATAD) with nasal lysine aspirin in N-ERD	1b (-)	ATAD with lysine aspirin and platelet inhibitors (like Pradugrel) have not been shown to be an effective treatment in CRSwNP patients with N-ERD and are not advised.
Low salicylate diet	Ib	Diets, like low salicylate diet have been shown to improve endoscopic scores and may improve symptoms compared to a normal diet in patients with N-ERD. However, the quality of the evidence at this moment is not enough to draw further conclusions.
Local and systemic antifungal treatments	1a (-)	Local and systemic antifungal treatments do not have a positive effect of QOL, symptoms and signs of disease in patients with CRS. The EPOS2020 steering group advises against the use of anti-mycotics in CRS.
Anti-IgE	Ib	Anti-IgE therapy has been proposed as a promising biologic therapy for CRS. Two RCTs that evaluated anti-IgE monoclonal antibody did not show impact on disease specific QOL but one study did show an effect on the physical domain of SF-36 and AQLQ. One study demonstrated lower symptom scores (change from baseline in anti IgE group) for nasal congestion, anterior rhinorrhoea, loss of sense of smell, wheeze and dyspnoea, a significant reduction of NPS on endoscopic examination, and Lund-MacKay scores on radiologic imaging. Due to the small study population in the existing studies, further studies with larger population sizes are needed and are underway. The available data are insufficient to advise on the use of anti-IgE in CRSwNP at this moment.
Anti-Il-5	Ib	There is only one large sufficiently powered study with Mepolizumab that showed a significant reduction in patients' need for surgery and an improvement in symptoms. Unlike in CRS, there is a significant experience with anti-Il5 in other type 2 driven diseases like asthma that do show a favourable safety profile so far. The EPOS2020 steering group advises use of mepolizumab in patients with CRSwNP fulfilling the criteria for treatment with monoclonal antibodies (when approved).
Anti IL-4/IL-13 (IL-4 receptor α)	Ia	At the moment the only anti-Il-4 treatment studied in CRS is dupilumab. Dupilumab is the only monoclonal antibody that is approved for the treatment of CRSwNP so far. When evaluating all trials with dupilumab, the drug seems to induce conjunctivitis in trials in patients with atopic dermatitis but not in trials with asthma and CRSwNP. No other adverse events have been reported in the literature until now. The EPOS steering group advises to use dupilumab in patients with CRSwNP fulfilling the criteria for treatment with monoclonal antibodies.
Probiotics	1b (-)	Although probiotic therapies show theoretical promise, the two studies performed so far did not show any differences compared to placebo. For this reason, the EPOS2020 steering group advises against the use of probiotics for the treatment of patients with CRS.
Muco-active agents	1b	Data on the effect of muco-active agents in CRS are very limited. The only DBPCT evaluating the addition of S-carboxymethylcysteine to clarithromycin showed a significantly higher percentage of patients with effective response and improved characteristics of nasal discharge at 12 weeks. The EPOS2020 steering group considered the quality of the data insufficient to advise on the use of muco-active agents in the treatment of patients with CRS.
Herbal treatment	1b	Of five RCTs evaluating herbal treatment, a large DBPCT, using tablets, showed overall no effect, although a post-hoc sensitivity analysis, showed a significant benefit in major symptom score at 12 weeks of treatment over placebo in patients with a diagnosis of CRS for >1 year and a baseline MSS >9 (out of max 15). Of the four studies evaluating different local herbal treatment, three showed a favourable effect. However, not all studies were blinded and the quality of the studies was variable. The treatment does not show significantly more adverse events than placebo. The quality of the evidence for the local treatment is low. Based on the available data, the EPOS2020 group cannot advise on the use of herbal medicine in CRS.
Acupuncture and traditional Chinese medicine	1b (-)	There is no evidence that traditional Chinese medicine or acupuncture is more effective than placebo in the treatment of CRS. The safety of Chinese medicine is unclear because most of the papers are not (easily) accessible. Minor and serious adverse events can occur during the use of acupuncture and related modalities, contrary to the common impression that acupuncture is harmless. For this reason, the EPOS2020 steering group advises against the use of traditional Chinese medicine or acupuncture.

Table 1.6.1. Cont.

Therapy	Level of evidence	GRADE recommendation
Oral verapamil	1b	A very small pilot study showed significant improvement in QOL (SNOT-22), polyp score (VAS), and CT scan (LM-score) of oral verapamil over placebo. (Potential) side effects limited the dosage. The quality of the evidence for oral verapamil is very low. Based on the potential side effects the EPOS2020 steering group advises against the use of oral verapamil.
Nasal furosemide	1b	A recent DBPCT study showed significantly reduced QOL (SNOT-22) scores and polyp score (VAS), and significantly more patients with an NPS of 0 in the furosemide nasal spray treated group versus placebo. There was no indication of a difference in adverse events between topical furosemide and placebo. However, the quality of the evidence is very low. The EPOS2020 steering group cannot advise on the use of nasal furosemide.
Capsaicin	1b	Capsaicin showed a significant decrease in nasal obstruction and nasal polyp score in two small studies, however data on other symptoms like rhinorrhea and smell are either non-significant or unreported. The quality of the evidence is low and the EPOS steering group concludes that capsaicin may be an option in treatment of CRS in patients with CRSwNP but that larger studies are needed.
Proton-pump inhibitors	1b (-)	Proton-pump inhibitors have been shown in one study to be not effective. Moreover, long term use of proton pump inhibitors has been associated with increased risk of cardiovascular disease. The EPOS2020 steering group therefore does advise against the use of proton pump inhibitors in the treatment of CRS.
Bacterial lysate	1b	There is one DBPCT from 1989 comparing the bacterial lysate Broncho-Vaxom to placebo in a large group of CRS patients resulting in a significant decrease in purulent nasal discharge and headache over the full six month period compared to placebo and reduced opacification of the sinus X-ray. Based on this limited evidence, the EPOS2020 steering group cannot advise on the use of Broncho-Vaxom in the treatment of CRS.
Phototherapy	1b (-)	We identified two trials with opposing findings. The quality of the evidence for the use of phototherapy in patients with CRS is very low. Based on the evidence, the EPOS2020 steering group cannot make a recommendation on the use of phototherapy in patients with CRS.
Filgastrim (r-met-HuG-CSF)	1b (-)	There is one study evaluating Filgastrim compared to placebo in CRS. There was no significant difference in effect on QOL between the two groups. Based on the evidence, the EPOS2020 steering group cannot make a recommendation on the use of Filgastrim in patients with CRS.
Collodial silver nasal spray	1b (-)	One very small study did not find differences between nasal colloidal silver spray and placebo. Based on the evidence, the EPOS2020 steering group cannot make a recommendation on the use of collodial silver nasal spray in patients with CRS.

ATAD, Aspirin treatment after desensitisation ; CI, confidence interval; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; DBPCT, double blind placebo controlled trial; LK, Lund Kennedy; MFNS, mometasone fuorate nasal spray; MSS, major symptom score; N-ERD, NSAID-exacerbated respiratory disease; NPS, nasal polyp score; QOL, quality of life; RCT, randomised controlled trial; SNOT-22, sino-nasal outcome test-22; SMD, standard mean difference.

Referenzen aus Leitlinien
Siehe Leitlinie

Orlandi R et al., 2016 [12].

International Consensus Statement on Allergy and Rhinology: Rhinosinusitis Executive Summary

Siehe auch: Orlandi R et al., 2016 [13].

Leitlinienorganisation/Fragestellung

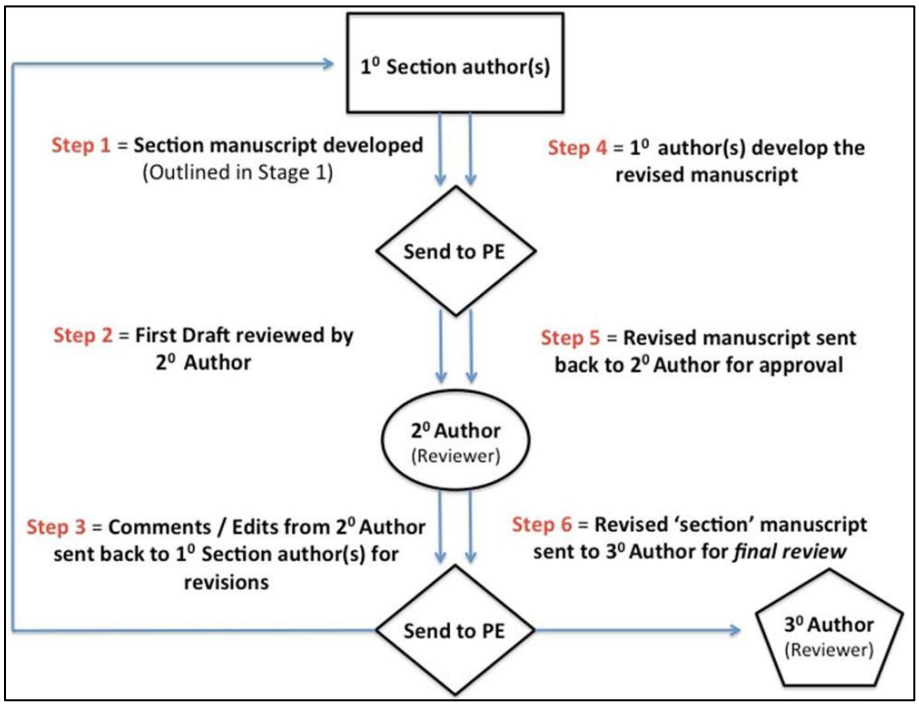
In an effort to both consolidate and critically appraise this information, rhinologic experts from around the world have produced the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR:RS)

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;

- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.



Recherche/Suchzeitraum:

- To provide the content for each topic, a systematic review of the literature for each topic using Ovid MEDLINE(1947 to July 2014), EMBASE (1974 to July 2014), and Cochrane Review databases was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standardized guidelines

LoE/ GoR

Grade	Research quality
A	Well-designed RCTs
B	RCTs with minor limitations; overwhelming consistent evidence from observational studies
C	Observational studies (case control and cohort design)
D	Expert opinion; case reports; reasoning from first principles

TABLE II-2. AAP-defined strategy for recommendation development[6]

Evidence quality	Preponderance of benefit over harm	Balance of benefit and harm	Preponderance of harm over benefit
A. Well-designed RCTs	Strong recommendation	Option	Strong recommendation against
B. RCTs with minor limitations; overwhelmingly consistent evidence from observational studies	Recommendation	Option	Strong recommendation against
C. Observational studies (case control and cohort design)	Recommendation	Option	Recommendation against
D. Expert opinion, case reports, reasoning from first principles	Option	No recommendation	Recommendation against

AAP = American Academy of Pediatrics.

Evidence-Based Rhinosinusitis Management Recommendations – Chronic Rhinosinusitis

TABLE III-4. Summary of recommendations for CRSsNP management

Intervention	LOE	Benefit	Harm	Cost	Benefit-harm assessment	Policy level
Saline irrigation	A	Improved symptomatic, radiologic, and endoscopic outcomes	Local irritation, nasal burning, headaches, and ear discomfort	Minimal	Preponderance of benefit over harm	Recommended
Topical corticosteroids (standard delivery)	A	Improved symptoms and endoscopic appearance	Epistaxis, headache	Low to moderate	Benefits outweigh harm	Recommended
Topical corticosteroids (nonstandard delivery)	B-C	Improvement in symptoms and endoscopic appearance	Epistaxis, nasal irritation, possible systemic absorption	Moderate to high, depending on method	Varies by method	Irrigation, mucosal atomization, and maxillary sinus tube are options. YAMIK catheter is recommended against
Oral corticosteroids	N/A					Insufficient evidence for a recommendation
Antibiotics: oral nonmacrolide	N/A					Insufficient evidence for a recommendation
Antibiotics: oral macrolide	B	Reduction in endoscopy scores and some symptoms	Significant potential for medication interactions. Rare adverse events	Low	Benefits appear to outweigh harm	Option
Antibiotics: intravenous	C	Possible symptom improvement	Thrombophlebitis, neutropenia, sepsis, deep vein thrombosis, elevated liver enzymes, drug adverse events, rash, bleeding	High	Risks outweigh benefits	Recommendation against
Antibiotics: topical	B	None demonstrated in randomized trials	Local irritation, possible systemic absorption	Moderate to high	Harm outweighs benefits	Recommended against
Antifungals: topical	A	None demonstrated in randomized trials	Local irritation (rare)	Moderate	Harm outweighs benefits	Recommended against
Surfactants, Manuka honey, xylitol	N/A					Insufficient evidence for a recommendation
Colloidal silver	N/A		Significant safety concerns			Recommended against

CRSsNP = chronic rhinosinusitis without nasal polyps; LOE = level of evidence; N/A = not applicable.

Saline Irrigation: *Given the preponderance of benefit in combination with an aggregate grade A of evidence, this therapy is strongly recommended. It is important to recognize that it is often implemented as an adjunct to other topical therapy strategies. Isotonic and hypertonic saline*

irrigations appear to provide similar subjective outcomes and high-volume saline irrigation appears to be superior to low-volume nasal saline spray techniques.

- Aggregate Grade of Evidence: A (Level 1a: 1 study; Level 1b: 6 studies; Level 2a: 1 study; Level 2b: 4 studies).
- Benefit: Improved QoL, symptoms, and endoscopic,and radiologic outcomes.Well tolerated. No risk of systemic adverse effects. Low cost.
- Harm: Local irritation, nasal burning, headaches, and ear pain/congestion. Low risk of infection from contamination.
- Benefits-Harm Assessment: Preponderance of benefit over harm.
- Value Judgments: Important to use nasal saline irrigation as an adjunct to other topical therapy strategies. Higher-volume (>200 mL) irrigations appear to be superior to low-volume nasal sprays, but further trials are required.
- Policy Level: Recommend.
- Intervention: High-volume (>200 mL) nasal saline irrigations are recommended as an adjunct to other medical therapies for CRS.

Topical Corticosteroids–Standard Delivery (Sprays): *INCS has excellent support in the literature for its use in CRS, with evidence of benefit and low risk of harm. For CRSwNP, the evidence is strong as well:*

- Aggregate Grade of Evidence: A (Level 1b: 36 studies; Level 2b: 4 studies).
- Benefit: Improved symptoms, endoscopic appearances, polyp size, and QoL, objective tests of olfaction, and airway and polyp recurrence.
- Harm: Epistaxis, nasal irritation, headache.
- Benefits-Harm Assessment: Benefit outweighs harm.
- Value Judgments: None.
- Policy Level: Recommended.
- Intervention: Topical nasal corticosteroids (sprays or drops) are recommended for CRSwNP before or after sinus surgery.

Topical Corticosteroids–Nonstandard Delivery: *Topical corticosteroids may be delivered via irrigation, atomization devices, through tubes in the maxillary sinus (MAST tubes), or through catheters (eg, YAMIK).*

For CRSwNP, the evidence is stronger but the risk of systemic absorption cannot be entirely excluded based on current knowledge:

- Aggregate Grade of Evidence: B (Level 1b:1 study; Level 4: 5studies).
- Benefit: Overall not possible to statistically confirm therapeutic improvement on present evidence.
- Harm: No evidence of adrenal suppression but cannot be excluded with non-standardized delivery and dosage regimes.
- Benefits-Harm Assessment: Off label use, likely negligible side effects compared with oral corticosteroids.
- Value Judgments: Only one level 1B study so insufficient data at present.
- Policy Level: Option.

- Intervention: Nonstandard delivery of topical corticosteroids is an option in CRSwNP, mainly after sinus surgery.

Oral Corticosteroids: *The data on oral corticosteroids differs considerably depending on whether polyps are present. No published studies exist to determine the benefit of oral corticosteroids alone in CRSsNP, other than one study addressing olfaction. Given the potential risks of systemic corticosteroids, clearer evidence addressing the use of corticosteroids in CRSsNP patients is crucial to balance these risks. There are no current studies evaluating the benefit of oral corticosteroids in the perioperative period, representing a large gap in evidence and a potential area for future study. Due to the lack of clear evidence on the benefits of oral corticosteroids in CRSsNP, no recommendation can be made.*

For CRSwNP, *the data support the infrequent use of oral corticosteroids. The long-term efficacy of an oral corticosteroid taper, followed by maintenance with INCS is likely 8 to 12 weeks. Practitionersmust be aware of the relative benefits vs. risks when developing treatment plans with their patients.*

- Aggregate Grade of Evidence: A (Level 1b: 5 studies; Level 3: 2 studies; Level 4: 11 studies).
- Benefit: Significant short-term improvements in subjective and objective measures in CRSwNP patients. Duration of improvement may last 8 to 12 weeks in conjunction with INCS use.
- Harm: More GI symptoms in corticosteroid group, no severe reactions reported. Transient adrenal suppression, insomnia, and increased bone turnover. All established corticosteroid risks exist, particularly with prolonged treatment.
- Benefits-Harm Assessment: Preponderance of benefit to harm in small, short-term follow-up and with use less than once every 2 years.
- Value Judgments: Significant improvements in subjective and objective measures based on high quality data, low risk and low cost. Risks of oral corticosteroids outweigh benefits relative to surgery with use more than once every 2 years.
- Policy Level: Recommendation.
- Intervention: Oral corticosteroids are recommended in the short-term management of CRSwNP. Longer-term or frequent use of corticosteroids for CRSwNP is not supported by the literature and carries an increased risk of harm to the patient.

Oral Nonmacrolide Antibiotics for ≤ 3 Weeks: *The lack of rigorous clinical studies and the combination of AECRS and CRS in most studies precludes the ability to make recommendations regarding the use of nonmacrolide antibiotics for less than 3 weeks in CRSsNP.*

For CRSwNP, despite the widespread use of antibiotics, there is again a paucity of evidence for their efficacy. Antibiotics have a number of potential harms so that their use in CRSwNP in a nonacute exacerbation should be discouraged.

- Aggregate Grade of Evidence: B (1 Level 1b study; 1 Level 4 study).
- Benefit: Reduction in polyp size with doxycycline; but no change in patient-reported outcomes; lack of placebo in erdosteine trial makes it impossible to determine a benefit for this therapy.
- Harm: GI upset and potential for resistance and for anaphlyaxis.

- Benefits-Harm Assessment: Harm outweighs demonstrated benefits.
- Value Judgments: Unclear/limited benefits with significant harm and potentially significant cost.
- Policy Level: Recommendation against.
- Intervention: Nonmacrolide antibiotics (<3 week course) should not be prescribed for CRSwNP in nonacute clinical situations.

Oral Nonmacrolide Antibiotics for ≥ 3 Weeks: *With only 1 study in the literature and only 38% of the patient population showing improvement in the extended treatment duration, recommendation of nonmacrolide oral antibiotics for longer than 3 weeks in treatment of CRSsNP is limited by lack of appropriate evidence.*

For CRSwNP, no studies examining the use of nonmacrolide antibiotics for longer than 3 weeks have been published. Therefore, no evidence-based recommendations can be made regarding this practice.

Oral Macrolide Antibiotics: *For CRSwNP, the picture is similar. Limited data from 1 RCT as well as lower-level evidence demonstrate some benefit, particularly following ESS. Existing studies have utilized different drugs, dosages, and durations of therapy.*

- Aggregate Grade of Evidence: B (Level 1b: 2 studies; Level 2b: 5 studies; Level 3b: 1 study; Level 4: 1 study).
- Benefit: Macrolides appear to reduce polyp burden in post-ESS patients and improve CRS symptoms.
- Harm: Significant potential for medication interactions. Rare mild adverse events, particularly potential for severe cardiovascular complications.
- Cost: Low.
- Benefits-Harm Assessment: Benefits appear to outweigh harm, though data are limited.
- Value Judgments: Limited data to determine benefitharm balance. Optimal drug, dosage, and duration of therapy are not known.
- Policy Level: Option.
- Intervention: In CRSwNP, macrolides may be beneficial in setting following ESS to decrease recurrence of polyps.

Intravenous Antibiotics: The high preponderance of adverse events noted in the literature in the treatment of CRS with IV antibiotics makes it difficult to recommend. Associated costs of line placement and the treatment of the potential adverse events preclude it from being a cost effective option in the uncomplicated CRS patient. However, for the subset of patients with CRS complications or extrasinus manifestations of CRS, the benefits of treatment may outweigh the cost and risk of possible adverse events.

- Aggregate Grade of Evidence: C (Level 4: 3 studies).
- Benefit: Possible improvement in patient-reported symptoms in cohort and case-controlled studies.
- Harm: Thrombophlebitis, neutropenia, sepsis, deep vein thrombosis, elevated liver enzymes, drug adverse events, rash, bleeding.
- Benefits-Harm Assessment: Risk of harm over the possible benefits noted.

- Value Judgments: Risk of adverse events and cost of treatment greatly outweighs possible benefit for routine use in CRS.
- Policy Level: Recommendation against.
- Intervention: Intravenous antibiotics should not be used for routine cases of CRS. For patients with complications or extrasinus manifestations of CRS, the benefits of treatment may outweigh the cost and risk of possible adverse events.

Topical Antibiotics: Existing evidence of topical antibiotics in CRS fails to consistently demonstrate benefits. Their routine use cannot be recommended. Some case series have reported effectiveness, particularly in recalcitrant cases of CRS, suggesting there may be a role in unusual cases.

- Aggregate Grade of Evidence: B (Level 1b: 4 studies; Level 2a: 6 studies; Level 4: 4 studies).
- Benefit: RCTs failed to show any benefit from the use of topical antibiotic irrigations.
- Harm: Nasal congestion, irritation, epistaxis. Theoretical possibility of systemic absorption with topical aminoglycosides. Possibility of developing bacterial resistance.
- Benefits-Harm Assessment: Relative harm over benefit.
- Value Judgments: Topical therapy may be a preferable alternative to IV therapy for infections caused by organisms resistant to oral antibiotics.
- Pollicy Level: Recommendation against.
- Intervention: Topical antibiotics are not recommended for CRS.

Evidence-Based Rhinosinusitis Management Recommendations – Surgery for Chronic Rhinosinusitis

Definition of Appropriate Medical Therapy Prior to ESS: The evidence for what should constitute appropriate medical therapy prior to surgical intervention is very much lacking. Recommendations are given based on available evidence, but the grade of evidence is D, leading to weak strength of recommendation.

- Aggregate Grade of Evidence: D.
- Benefit: Symptomatic improvement and avoidance of risks of surgical intervention.
- Harm: Risks of corticosteroids, gastrointestinal side effects of antimicrobials, risk of cardiovascular toxicity with macrolide antibiotics, potential for increasing antibiotic resistance.
- Benefits-Harm Assessment: Differ for particular therapy and clinical scenario.
- Value Judgments: Perceived lower risk of antibiotic treatment vs. risks of surgery, although recent evidence has shown a low breakeven threshold for surgery vs. oral corticosteroids. Additional evidence is needed in assessing antibiotic vs surgery benefitharm balance. Clearly, patient preference plays a large role in the decision to continue medical therapy or to proceed with surgery.
- Policy level: Recommendation.
- Intervention:

- **For CRSwNP:** Appropriate medical therapy prior to surgical intervention should include a trial of INCS, saline irrigations, and a single short course of oral corticosteroids. Antibiotics are an option.
- **Length of Appropriate Medical Therapy Prior to ESS:** There are no direct studies on this topic and recommendations are inferred from studies on individual therapies. There are multiple RCTs evaluating the benefits of INCS in CRS. Studies where treatment duration is less than or equal to 3 weeks show no benefit over placebo, whereas studies of 4weeks or more consistently favor INCS.

- Aggregate Grade of Evidence: D.
- Benefit: Symptomatic improvement and avoidance of risks of surgical intervention.
- Harm: Risks of corticosteroids, gastrointestinal side effects of antimicrobials, risk of cardiovascular toxicity with macrolide antibiotics, potential of increasing antibiotic resistance.
- Value Judgements: Low risk of treatment and delay of surgery vs risks of surgery considered in recommending a 3-week to 4-week trial.
- Policy Level: Recommendation
- Intervention: A trial of 3 to 4 weeks of AMT should be considered as the minimum.

Referenzen aus Leitlinien
Siehe Guideline

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 1 of 12, May 2020) am 13.05.2020

#	Suchfrage
1	[mh sinusitis]
2	[mh rhinitis]
3	[mh “nasal polyps”]
4	#1 OR #2 OR #3
5	(rhinosinusitis OR nasosinusitis OR pansinusitis OR ethmoiditis OR sphenoiditis OR kartagener*):ti,ab,kw
6	((inflamm* OR maxilla* OR frontal*) AND sinus*):ti,ab,kw
7	((nose* OR nasal* OR nasi OR intranasal* OR paranasal* OR rhinosin* OR rhinitis OR sinus* OR sinonasal*) AND (papilloma* OR polyp OR polyps OR polyposis)):ti,ab,kw
8	#5 OR #6 OR #7
9	#4 OR #8
10	#9 with Cochrane Library publication date from May 2015 to May 2020

Systematic Reviews in Medline (PubMed) am 13.05.2020

#	Suchfrage
1	sinusitis[mh]
2	rhinitis[mh]
3	paranasal sinus diseases[mh:noexp]
4	#1 OR #2 OR #3
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6	(inflamm*[tiab] OR maxilla*[tiab] OR frontal*[tiab]) AND sinus*[tiab]
7	#5 OR #6
8	#4 OR #7
9	nasal polyps[mh]
10	nose[mh]
11	nose diseases[mh]
12	(nose*[tiab] OR nasal*[tiab] OR nasi[tiab] OR intranasal*[tiab] OR paranasal*[tiab] OR rhinosin*[tiab] OR rhinitis[tiab] OR sinus*[tiab] OR sinonasal*[tiab])
13	#10 OR #11 OR #12
14	polyps[mh]
15	(papilloma*[tiab] OR polyp[tiab] OR polyps[tiab] OR polyposis[tiab])
16	#14 OR #15
17	#13 AND #16

18	#9 OR #17
19	chronic disease[mh]
20	recurrence[mh]
21	chronic[tiab] OR persis*[tiab] OR recurrent*[tiab]
22	#19 OR #20 OR #21
23	(#8 OR #18) AND #22
24	CRSwNP[tiab] OR CRSwp[tiab]
25	#23 OR #24
26	(#25) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
27	((#26) AND ("2015/05/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
28	(#23) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 13.05.2020

#	Suchfrage
1	sinusitis[mh]
2	rhinitis[mh]
3	paranasal sinus diseases[mh:noexp]
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6	(inflamm*[tiab] OR maxilla*[tiab] OR frontal*[tiab]) AND sinus*[tiab]
7	#5 OR #6
8	#4 OR #7
9	nasal polyps[mh]
10	nose[mh]
11	nose diseases[mh]
12	(nose*[tiab] OR nasal*[tiab] OR nasi[tiab] OR intranasal*[tiab] OR paranasal*[tiab] OR rhinosin*[tiab] OR rhinitis[tiab] OR sinus*[tiab] OR sinonasal*[tiab])
13	#10 OR #11 OR #12
14	polyps[mh]
15	(papilloma*[tiab] OR polyp[tiab] OR polyps[tiab] OR polyposis[tiab])
16	#14 OR #15
17	#13 AND #16
18	#9 OR #17
19	#8 OR #18
20	CRSwNP[tiab] OR CRSwp[tiab]
21	#19 OR #20
20	(#19) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
21	(((#20) AND ("2015/05/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
22	(#21) NOT (retracted publication [pt] OR retraction of publication [pt])

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Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Kontaktdaten

Deutsche Gesellschaft für Allgemein- und Familienmedizin

Was ist der Behandlungsstandard in der Behandlung " Erwachsenen mit schwerer chronischer Rhinosinusitis mit Nasalen Polypen (CRSwNP), die mit einer Therapie aus systemischen Kortikosteroiden und / oder operativem Eingriff nicht ausreichend kontrolliert sind**"? Unterscheidet sich der Behandlungsstandard in der Situation** „Unzureichende Therapie nach erfolgtem operativem Eingriff"**?**

Die Therapie der chronischen Rhinosinusitis mit Polyposis nasi (CRScNP oder synonym auch CRSwNP) besteht nach der aktuellen Leitlinie „Rhinosinusitis" aus einer Reihe konservativer Basis-Maßnahmen. Die Empfehlungen der Leitlinie zu diesen Basismaßnahmen lauten wie folgt:

- eine nasale Anwendung von Salzlösungen z. B. als hochvolumige (≥150 ml), iso- bis leicht hypertone Spülung sollte für die symptomatische Therapie der CRS zum Einsatz kommen.
- Topische Kortikosteroide sollten zur Therapie der CRSsNP und insbesondere der CRScNP zur Anwendung kommen.

Die Leitlinie sieht in ausgewählten Fällen weitere Behandlungsmöglichkeiten vor, die jedoch nicht Behandlungsstandard sind. Die Empfehlungen hierzu lauten wie folgt:

- Die Therapie mit systemischen Kortikosteroiden kann in Einzelfällen erwogen werden.
- Ausgewählte Biologika können bei Versagen etablierter Therapieformen im Einzelfall bei CRScNP eingesetzt werden.
- Bei CRScNP kann im Falle einer Rezidiv-Polyposis eine längerdauernde Therapie mit Doxycyclin erwogen werden.

Die operative Therapie steht in der Regel als Therapieoption bei Versagen der konservativen Maßnahmen zur Verfügung. Standard ist hierbei entsprechend die operative Behandlung bei therapieresistenter chronischer Rhinosinusitis. Die Empfehlungen der Leitlinie hierzu lauten wie folgt:

- Bei Versagen einer konservativen Therapie sollte eine operative Therapie erwogen werden
- Im Einzelfall kann auch eine primäre operative Therapie sinnvoll sein.

Entsprechend werden systemische Steroide oder operative Maßnahmen in der Regel nur bei Patienten zur Anwendung gebracht, bei denen die bisher gültigen Behandlungsstandards nicht erfolgreich gewesen

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sind. Für Patienten, die weder durch topische/systemische Kortikosteroide, noch durch operative Maßnahmen ausreichend kontrolliert sind, existiert daher derzeit kein Behandlungsstandard, der über die Fortführung der Basismaßnahmen hinausgeht, sofern kein Analgetika-Intoleranz-Syndrom vorliegt (siehe nachfolgende Frage).

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „Erwachsenen mit schwerer chronischer Rhinosinusitis mit Nasalen Polypen (CRSwNP), die mit einer Therapie aus systemischen Kortikosteroiden und / oder operativem Eingriff nicht ausreichend kontrolliert sind**“, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Bei Patienten mit therapierefraktärer oder rezidivierter Polyposis nasi kann ein sogenanntes Analgetika-Intoleranz-Syndrom ursächlich sein. Bei diesem Krankheitsbild besteht eine Überempfindlichkeit gegenüber der Arzneimittel-Gruppe der nicht-steroidalen Antirheumatika (daher auch Synonym „Aspirin-Intoleranz“). Es wird daher die Abklärung auf ein solches Analgetika-Intoleranz-Syndrom bei Patienten mit therapieresistenter oder rezidivierter Polyposis nasi empfohlen, diese beinhaltet eine gezielte Anamnese und im Verdachtsfall eine weitergehende Diagnostik (z.B. Provokations-Testung). In den Fällen, in denen ein Analgetika-Intoleranz-Syndrom nachgewiesen wurde, besteht prinzipiell die weitere therapeutische Möglichkeit der adaptiven Desaktivierung. Bei der adaptiven Desaktivierung wird, in der Regel unter stationären Bedingungen, mit langsam aufsteigenden Dosierungen von Acetylsalicylsäure (ASS) eine Toleranz (Refrakterität) gegenüber nicht-steroidalen Antirheumatika induziert. Anschließend ist eine regelmäßige Einnahme einer niedrigen Dosierung von ASS erforderlich. Durch diese adaptive Desaktivierung können eine Reduktion der Entzündung bzw. des Polypenwachstums und eine Verlängerung der Intervalle zwischen den notwendigen Revisionsoperationen erreicht werden.

(hier ergänzen – sofern verfügbar – auf welcher (Daten-)Grundlage basiert die Einschätzung; ggf. beifügen der zitierten Quellen)

S2k-Leitlinie Rhinosinusitis (AWMF-Register-Nr. 017/049 und 053-012)