Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2019-B-093 Dupilumab

Stand: Juni 2019

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

Dupilumab **[Add-on-Therapie bei schwerer chronischer Rhinosinusitis mit nasaler Polyposis (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	Es liegen keine Beschlüsse vor.
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:	
Dupilumab Dupixent®	Geplantes Anwendungsgebiet laut Beratungsanforderung/Zulassungsantrag: Dupixent ist angezeigt als Add-on-Therapie bei Erwachsenen mit schwerer chronischer Rhinosinusitis mit nasaler Polyposis (CRSwNP), bei denen frühere Therapien mit systemischen Kortikosteroiden und/oder eine Operation versagten oder bei denen eine derartige Therapie aufgrund von Intoleranz oder Kontraindikation nicht geeignet ist. Dupixent ist angezeigt, um die Notwendigkeit einer Operation und die Anwendung von systemischen Kortikosteroiden bei erwachsenen Patienten mit unzureichend kontrollierter, schwerer CRSwNP zu reduzieren. (vorläufige deutsche Übersetzung) *“Dupixent is indicated as an add-on treatment of adults with severe chronic rhinosinusitis with nasal polyposis (CRSwNP) who previously failed or are intolerant or contraindicated to systemic corticosteroids and/or surgery. Dupixent is indicated to reduce the need for surgery and systemic corticosteroid use in adult patients with inadequately controlled severe CRSwNP.”*
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	Erkrankungen der oberen Luftwege – schwere Verlaufsformen von Pollinosis und Rhinitis allergica, nach Versagen intranasal verabreichter Glucocorticoide (DS: c) […]

II. Zugelassene Arzneimittel im Anwendungsgebiet	
(generisch) z.B. Prednison ratiopharm	
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.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2019-B-093 (Dupilumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	11. Juni 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

AMT	appropriate medical therapy
AR	allergic rhinitis
ARS	acute rhinosinusitis
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CRS	chronic rhinosinusitis
CRSsNP	chronic rhinosinusitis without nasal polyps
CRSwNP	chronic rhinosinusitis with nasal polyps
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
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Dupixent ist angezeigt als Add-on-Therapie bei Erwachsenen mit schwerer chronischer Rhinosinusitis mit nasaler Polyposis (CRSwNP), bei denen frühere Therapien mit systemischen Kortikosteroiden und / oder eine Operation versagten oder bei denen eine derartige Therapie aufgrund von Intoleranz oder Kontraindikation nicht geeignet ist.

Dupixent ist angezeigt, um die Notwendigkeit einer Operation und die Anwendung von systemischen Kortikosteroiden bei erwachsenen Patienten mit unzureichend kontrollierter, schwerer CRSwNP zu reduzieren.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *chronische Rhinosinusitis* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 02.05.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, 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.

Die Recherche ergab 402 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 19 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es konnten keine relevanten G-BA Beschlüsse/ IQWiG Berichte identifiziert werden.

3.2 Cochrane Reviews

Head K et al., 2016 [6].

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:

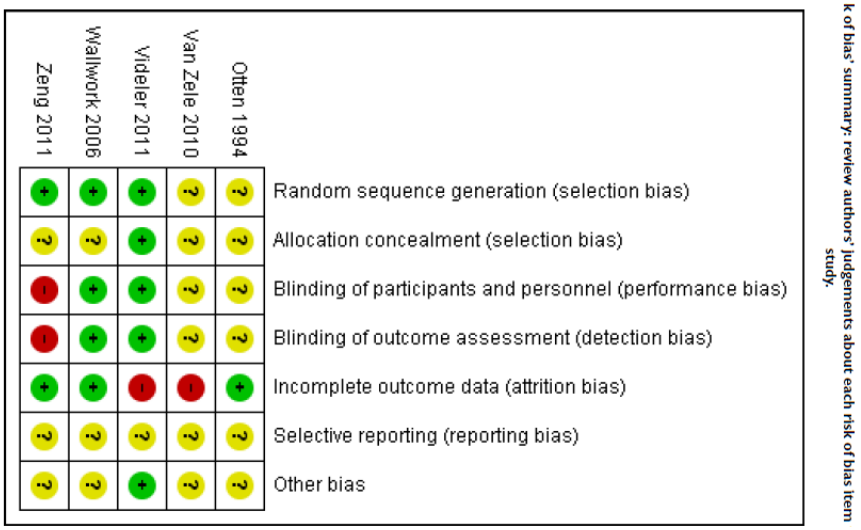
- N=5 RCTs (n=293)

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.

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

Head K et al., 2016 [5].

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

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)

Charakteristika der Population:

- Both the populations and the ’standard’ treatments differed in the two studies
- 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.
- One trial in children (mean age of eight years) without nasal polyps included 48 participants. The trial compared oral corticosteroids (oral methylprednisolone, 1 mg/kg and reduced

progressively over a 15-day treatment course) with placebo in participants who also received a 30-day course of antibiotics.

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.
- We judged the quality of the evidence for oral steroids plus antibiotics for children to be low (further research is very likely to have an important impact on our confidence in the effect estimate and is likely to change the estimate) as the evidence comes from one small trial. The trial did not have a high risk of bias, but it only included children without nasal polyps, who might not have the same results as adults with nasal polyps. The trial did not report results after the end of treatment and the adverse effects of treatment were not well reported.

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.
- Oral steroids as an adjunct to antibiotics
  - One trial in children (mean age of eight years) without nasal polyps included 48 participants. The trial compared oral corticosteroids (oral methylprednisolone, 1 mg/kg and reduced progressively over a 15-day treatment course) with placebo in participants who also received a 30-day course of antibiotics. This study addressed one of the primary outcome measures (disease severity) and one secondary outcome (CT score). For disease severity the four key symptoms used to define chronic rhinosinusitis in children (nasal blockage, nasal discharge, facial pressure, cough) were combined into one score. There was a greater improvement in symptom severity 30 days after the start of treatment in patients who received oral steroids and antibiotics compared with placebo and antibiotics (MD -7.10, 95% CI -9.59 to -4.61; 45 participants; scale 0 to 40). The observed mean difference corresponds to a large effect size. At the same time point there was a difference in CT scan score (MD -2.90, 95% CI -4.91 to -0.89; 45 participants; scale 0 to 24). We assessed the quality of the evidence to be low.
  - 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* or*very 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 [4].

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

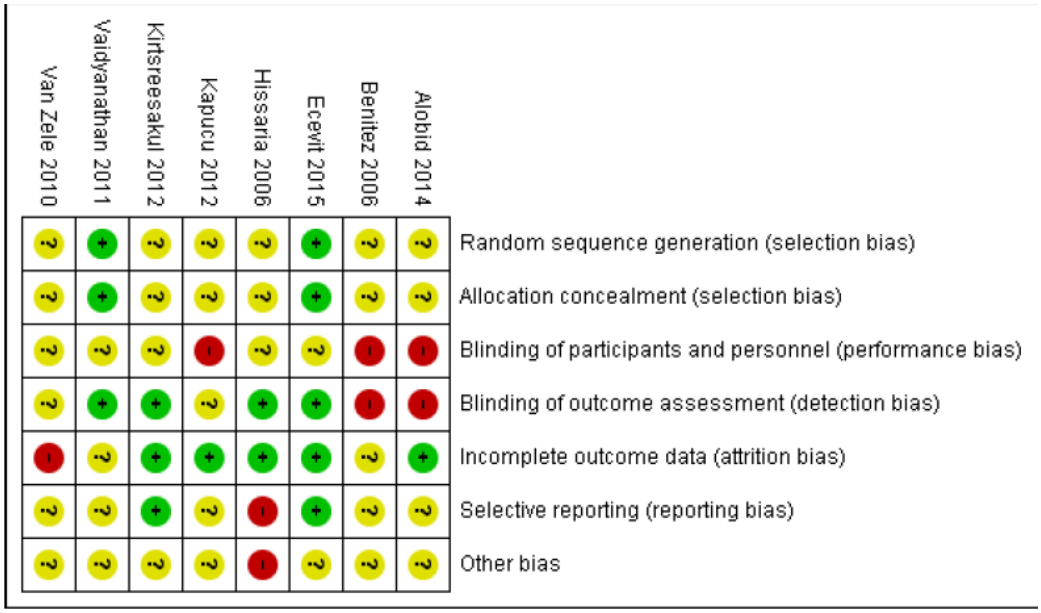
Anzahl eingeschlossener Studien:

- 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 LY 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:

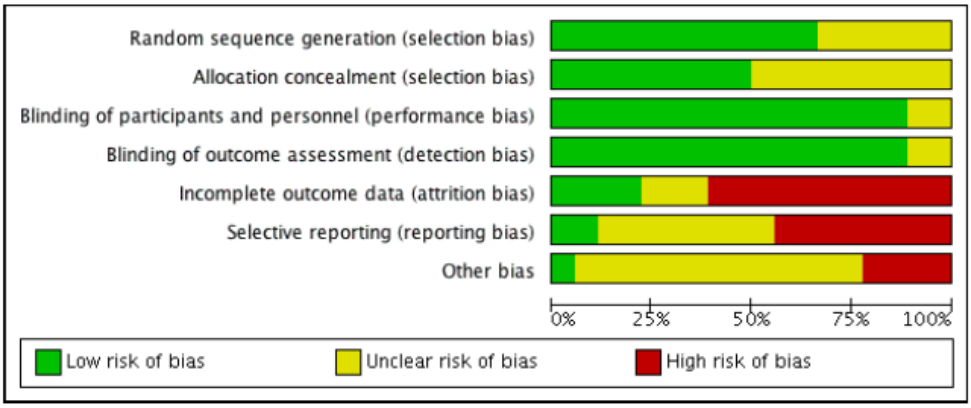
- N=18 (n=2738)

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 LY 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:

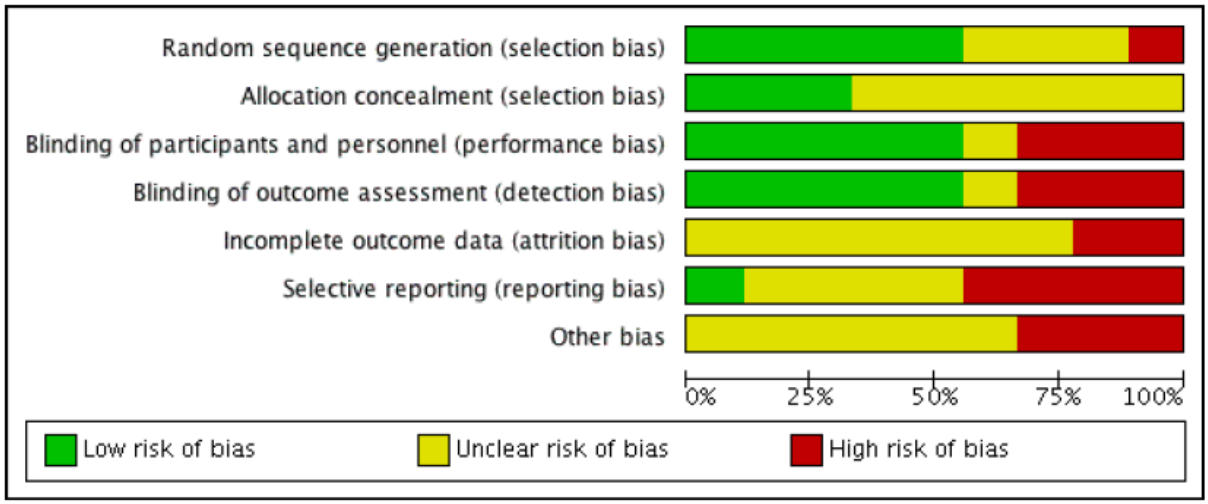
- N=9 (n=911)

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.

Rimmer J et al., 2014 [12].

Surgical versus medical interventions for chronic rhinosinusitis with nasal polyps

Fragestellung

To assess the effectiveness of endonasal/endoscopic surgery versus medical treatment in chronic rhinosinusitis with nasal polyps

Methodik

Population:

- Patients over 16 with bilateral nasal polyps confirmed by direct visualisation (preferably, but not exclusively, with an endoscope).

Intervention:

- Any surgical intervention, including simple polypectomy or more extensive endoscopic sinus surgery

Komparator:

- medical treatment (including placebo)

Endpunkte:

- QoL, Disease severity, Complications, Recurrence rate etc.

Recherche/Suchzeitraum:

- August 2015

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions

Ergebnisse

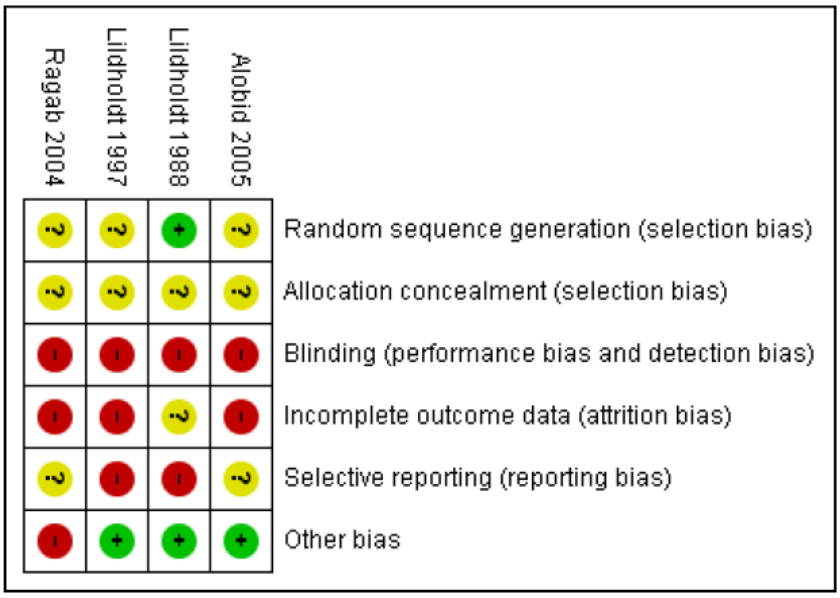
Anzahl eingeschlossener Studien:

- N=4 (n=231)

Charakteristika der Population:

- The studies compared different types of surgery versus various types and doses of systemic and topical steroids and antibiotics.
- Three comparison pairs: **(1)** endoscopic sinus surgery (ESS) versus systemic steroids (one study, n = 109), **(2)** polypectomy versus systemic steroids (two studies, n = 87); **(3)** ESS plus topical steroid versus antibiotics plus high-dose topical steroid (one study, n = 35).
- All participants also received topical steroids but doses and types were the same between the treatment arms of each study, except for the study using antibiotics.

Qualität der Studien:



Studienergebnisse:

Primary outcomes: symptom scores and quality of life scores

There were no important differences between groups in either the patient-reported disease-specific symptomscores or the health-related quality of life scores. Two studies (one comparing ESS plus topical steroid versus antibiotics plus high-dose topical steroid, the other ESS versus systemic steroids) failed to find a difference in generic health-related quality of life scores. The quality of this evidence is low or very low.

Endoscopic scores and other secondary outcomes

Two studies reported endoscopic scores. One study (ESS versus systemic steroids) reported a large, significant effect size in the surgical group, with a mean difference (MD) in score of -1.5 (95% confidence interval (CI) -1.78 to -1.22, n = 95) on a scale of 0 to 3 (0 = no polyposis, 3 = severe polyposis). In the other study (ESS plus topical steroid versus antibiotics plus high-dose topical steroid) no difference was found between the groups (MD 2.3%, 95% CI -17.4% to 12.8%, n = 34). None of the included studies reported recurrence rates. No differences were found for any objective measurements or olfactory tests in those studies in which they were measured.

Complications

Complication rates were not reported in all studies, but rates of up to 21% for medical treatment and 14.3% for surgical treatment are described. Epistaxiswas themost commonly reported complicationwith bothmedical and surgical treatments,with severe complications reported rarely.

Anmerkung/Fazit der Autoren

The evidence relating to the effectiveness of different types of surgery versus medical treatment for adults with chronic rhinosinusitis with nasal polyps is of very low quality. The evidence does not show that one treatment is better than another in terms of patientreported symptom scores and quality of life measurements. The one positive finding from amongst the several studies examining a number of different comparisons must be treated with appropriate caution, in particular when the clinical significance of the measure is uncertain.

As the overall evidence is of very low quality (serious methodological limitations, reporting bias, indirectness and imprecision) and insufficient to draw firm conclusions, further research to investigate this problem, which has significant implications for quality of life and healthcare service usage, is justified.

Sharma R et al., 2014 [15].

Surgical interventions for chronic rhinosinusitis with nasal polyps (Review)

Fragestellung

To assess the effectiveness of simple polyp surgery versus more extensive surgical clearance in chronic rhinosinusitis with nasal polyps.

Methodik

Population:

- patients over 16 with chronic rhinosinusitis with nasal polyps, who have failed a course of medical management and who have not previously undergone any previous surgical intervention for their nasal disease.

Intervention:

- Simple polypectomy

Komparator:

- more extensive surgery

Endpunkte:

- Disease severity, Health-related quality of life, Complications, Recurrence rate etc

Recherche/Suchzeitraum:

- 20 February 2014

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions

Ergebnisse

Anzahl eingeschlossener Studien:

- N=0

Charakteristika der Population:

- Keine

Qualität der Studien:

- Keine

Studienergebnisse:

- keine

Anmerkung/Fazit der Autoren

We are unable to reach any conclusions as to whether isolated nasal polypectomy or more extensive sinus surgery is a superior surgical treatment modality for chronic rhinosinusitis with nasal polyps. There is a need for high-quality randomised controlled trials to assess whether additional sinus surgery confers any benefit when compared to nasal polypectomy performed in isolation.

3.3 Systematische Reviews

Patel Z et al., 2017 [9].

Surgical therapy vs continued medical therapy for medically refractory chronic rhinosinusitis: a systematic review and meta-analysis

Fragestellung

the objective of this review is to use this best available evidence, published over the last decade, to answer our question of whether surgical therapy or continued medical therapy is more effective in treating medically refractory CRS

Methodik

Population:

- Adult CRS patient population (>18 years old)

Intervention:

- Patients who have failed AMT (appropriate medical therapy) who continue to be treated with medical therapy or receive surgical intervention

Komparator:

- k.A.

Endpunkte:

- Primary outcomes:
  - 1. Subjective disease-specific QOL scores;
  - 2. Subjective health utility value QOL scores;
  - 3. Objective validated endoscopic grading scores.
- Secondary outcomes:
  - 1. Objective or subjective measures of “cardinal” sinus symptoms which include facial pain, nasal obstruction, thick discharge or olfactory dysfunction;
  - 2. Missed days due to CRS;
  - 3. Economic impact due to CRS;
  - 4. Reported adverse outcomes due to medical or surgical intervention.

Recherche/Suchzeitraum:

- 2005 to 2016

Qualitätsbewertung der Studien:

- RCTs were evaluated using scheme established by the Cochrane Handbook for Systematic Reviews of Intervention.
- The quality of crossover and cohort studies was assessed using the Newcastle-Ottawa Scale.

Ergebnisse

Anzahl eingeschlossener Studien:

- N=7 (6 Studien für Meta-Analysen)

Charakteristika der Population:

Author	Study design	Quality of study	Demographics	Pertinent outcomes	Pertinent results	Comments
Smith et al.[15] (2011)	Cohort	Moderate	n = 130; MT = 55; ST = 75; age of MT = 51.5 (16.0); age of ST = 44.1 (13.8)	RSDI, CSS, missed work/school days at 6-month follow-up	MT cohort: RSDI total = 14.8 (19.1); CSS total = 11.8 (21.1); missed work/school days = 0.7 (2.3). ST cohort: RSDI total = 24.1 (22.1); CSS total = 27.5 (23.8); missed work/school days = 0.4 (1.1).	50 lost to follow-up; baseline ST group were younger ($p = 0.003$), septal deviation ($p = 0.050$), ASA intolerance ($p = 0.024$); 7 MT crossed over to the ST group
Smith et al.[16] (2013)	Cohort with crossover	Moderate	n = 180; MT = 33; ST = 65; CO = 17; age of MT = 54.2 (16.8); age of ST = 47.4 (13.1); age of CO = 51.9 (14.3)	RSDI, CSS at 12 month follow-up	MT cohort: RSDI total = 12.1 (19.5); CSS total = 13.4 (21.1). ST cohort: RSDI total = 22.3 (24.3); CSS total = 25.5 (24.1). CO cohort: RSDI total = 20.6 (28.6); CSS total = 10.8 (26.8).	Study lost power due to loss of MT patients to the CO cohort; same cohort of patients from Smith, 2011 (therefore NOT included in meta-analysis)
Smith et al.[17] (2014)	Crossover	Moderate	n = 31; age = 45.3 (20–65)	SNOT-22, Lund-Kennedy endoscopic grading, work/school days missed past 90 days with mean follow-up for MT and ST group at 7.1 and 14.6 months, respectively	MT cohort: SNOT-22 = 66.1 (18.4); Lund-Kennedy = 7.7 (2.9); missed work/school days = 6.1 (9.0). ST cohort: SNOT-22 = 16.0 (13.0); Lund-Kennedy = 2.4 (1.7); missed work/school days = 0.2 (0.6).	Significant improvement in SNOT-22, Lund-Kennedy scores, missed days in ST vs MT ($p < 0.001$, $p < 0.001$, $p < 0.001$, respectively)
DeConde et al.[20] (2014)	Cohort	Moderate	n = 280; MT = 58; ST = 222; age of MT = 50.3 (15.0); age of ST = 51.9 (14.6)	B-SIT with minimum 6 month follow-up	Patients with impaired olfaction, B-SIT statistically improves in both MT (2.3 (2.8)) and ST (2.1 (3.0)) with no difference between treatments	Baseline ST group report higher burden disease with SNOT-22 ($p = 0.018$) and RSDI ($p = 0.030$); limited number of patients with impaired olfaction
Luk et al.[19] (2015)	Cohort	Moderate	n = 212; MT = 40; ST = 152; CO = 20; age of MT = 54.1 (13.0); age of ST = 53.3 (14.6); age of CO = 57.0 (15.0)	SF-6D, missed work/school days with 6-month and 12-month follow-up	Mean SF-6D at baseline, 6 months and 12 months follow-up for ST (0.70, 0.79, 0.78, $p < 0.001$), MT (0.76, 0.76, 0.76, $p = 0.967$), CO (0.69, 0.73, 0.75, $p = 0.115$), respectively.	Baseline ST group significantly worse health utility ($p = 0.023$), missed days ($p = 0.009$) compared to MT; do no report data missed work/school days
Rudmik et al.[21] (2015)	Cohort	Moderate[a]	N/A	ICER per QALY	ST: cost $48,838.38; 20.50 QALYs MT: cost $28,948.98; 17.13 QALYs ICER ST vs MT = $5901.05/QALY	Probabilistic sensitivity analysis demonstrate 74% certainty that ST most cost effective if willing to pay $25,000
Scangas et al.[22] (2016)	Cohort	Moderate[a]	N/A	ICER per QALY	ST: cost $42,522.95; 18.53 QALYs MT: cost $29,225.74; 17.57 QALYs ICER ST vs MT = $13,851.26/QALY	Probabilistic sensitivity analysis demonstrate 85% certainty that ST most cost effective if willing to pay $25,000

[a]Used Smith et al.15 study patients to perform cohort-style Markov decision tree.
B-SIT = Brief Smell Identification Test; CO = crossover; CSS = Chronic Sinusitis Survey; ICER = incremental cost effectiveness ratio; MT = medical therapy; QALY = quality-adjusted life-year; RSDI = Rhinosinusitis Disability Index; SF-6D = Short Form-6D; SNOT-22 = 22-item Sino-Nasal Outcome Test; ST = surgical therapy.

Qualität der Studien:

- Moderat (siehe Tabelle)

Studienergebnisse:

Disease-specific QOL scores and Objective endoscopic grading scores

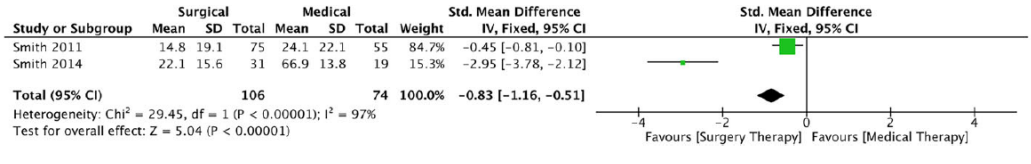


FIGURE 1. Disease-specific quality of life scores. CI = confidence interval; SD = standard deviation.

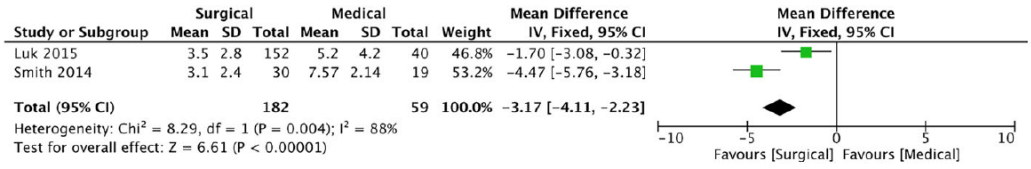


FIGURE 2. Endoscopic grading scores. CI = confidence interval; SD = standard deviation.

Anmerkung/Fazit der Autoren

For patients with CRS who have failed to improve after AMT, outcomes demonstrate that ESS is more effective than continued medical therapy in improving disease specific QOL scores and nasal endoscopy scores. Unpooled data analyzed within our systematic review demonstrates ESS is more effective than continued medical therapy in improving health utility value QOL scores, hyposmia, and cost-effectiveness. Without the reporting of adverse events associated with therapeutic choice in the studies included in this SR, one should use the existing literature on adverse events and clinical judgement in weighing these risks when choosing either medical or surgical therapy

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Pundir V et al., 2016 [10].

Role of corticosteroids in Functional Endoscopic Sinus Surgery - a systematic review and meta-analysis

Fragestellung

The aim of our study was to systematically review the existing evidence on the role of corticosteroids in patients with CRS undergoing FESS. The aim was to determine whether preoperative corticosteroids affect operative parameters; intra-operative corticosteroids reduce surgical pain; and postoperative corticosteroids affect patient's symptom scores, endoscopic appearance and recurrence rates.

Methodik

Population:

- participants of any age, who had any co-morbidity including asthma and aspirin sensitivity, allergic or non allergic, followed for any duration and CRS with and without polyps were included

Intervention:

- corticosteroids

Komparator:

- placebo or no corticosteroids

Endpunkte:

- Operative outcomes, anaesthetic related outcomes, post-operative outcomes and risk of recurrence. Operative outcomes included estimated blood loss (EBL), surgical field quality and operative time. Postoperative outcomes included symptoms score (subjective improvement), endoscopic score (objective improvement) and risk of sinusitis.

Recherche/Suchzeitraum:

- last search was 20.09.2014

Qualitätsbewertung der Studien:

- Cochrane 'Risk of bias' tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 18 RCTs (N=1309)

Charakteristika der Population:

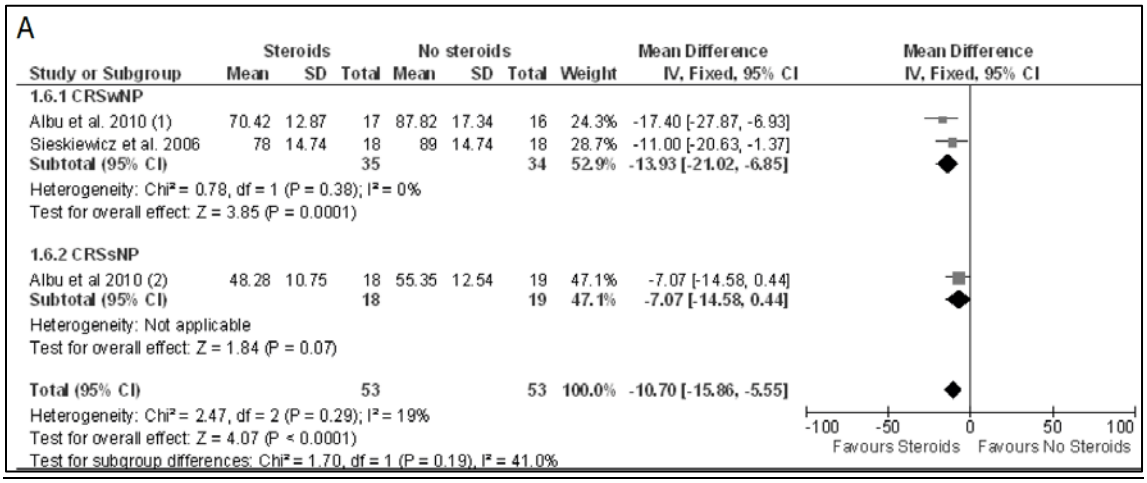
- Four studies had an intrapatient control design in which one side of the nasal cavity was compared with the other side (n=182)
- These studies were included in the meta-analysis and the two groups treated as independent, and then sensitivity analysis was performed excluding these studies to determine the robustness of the results. The remaining 1127 patients were randomised to the steroid group of 607 patients and 520 controls. Sample size per study varied across the trials and ranged from 19 to 162 participants. Use of corticosteroids with FESS was reported for four categories; operative outcomes, anaesthesia related, post-operative outcomes and risk of recurrence. Operative outcomes were reported by three studiesanaesthetic outcomes were reported by one study (58); post-operative outcomes were reported by ten studies and risk of recurrence was reported by six studies
- One RCT reported both on operative and post-operative outcomes, therefore it was included in both categories (55). Albu et al., reported on patients with and without polyps (14); data from this study is included in the meta-analysis as Albu et al. (1) and Albu et al. (2). Albu et al. (1) represent data of patients with CRSwNP and Albu et al. (2) represent data of patients with CRSsNP. In our attempt to get more information about studies with inadequate data, we received no response from the relevant authors

Qualität der Studien:

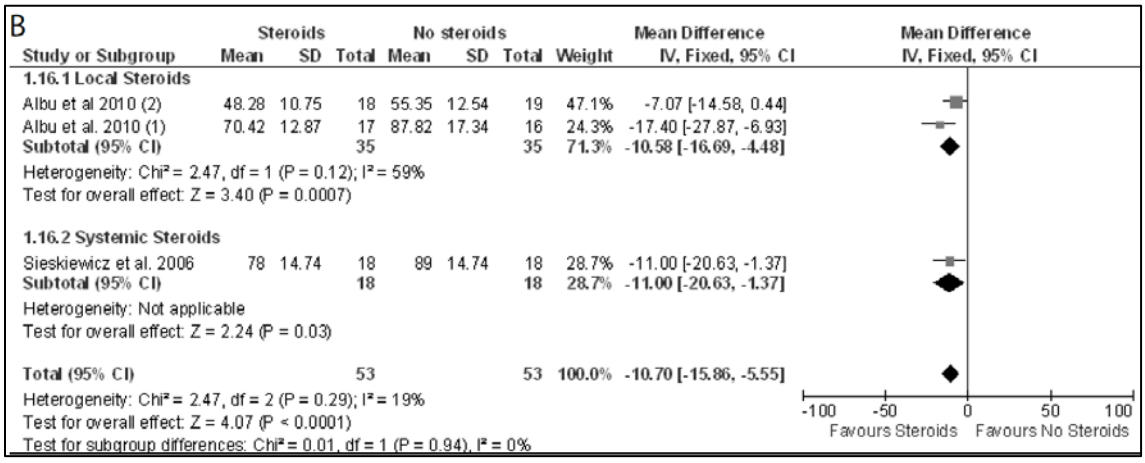
- Generally, included studies had low risk of bias for method of randomisation and blinding, medium risk of bias for incomplete outcome data and selective reporting and unclear risk of bias for allocation concealment.

Studienergebnisse:

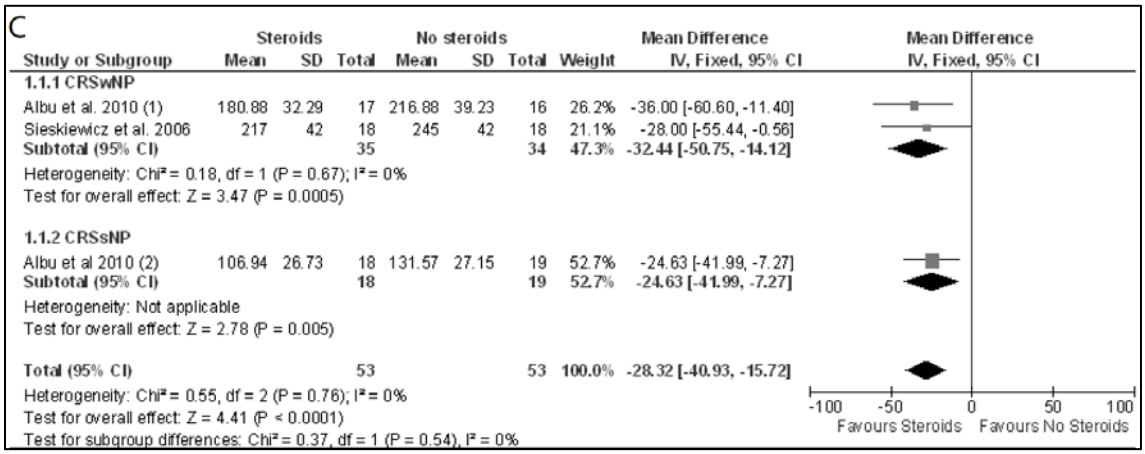
Forest plot A of comparison: Steroids versus No steroids. Outcome: Operative time.



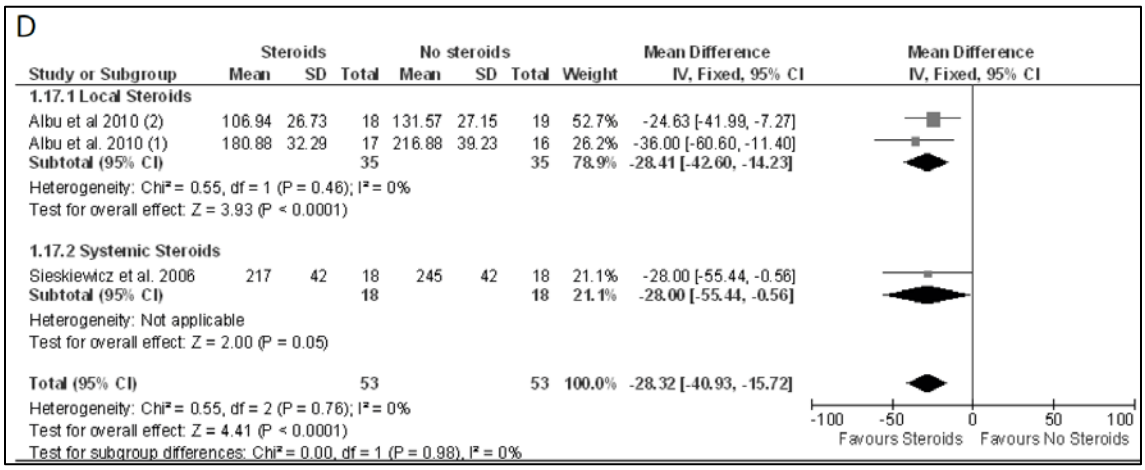
Forest plot B of comparison - Steroids versus No steroids. Outcome: Operative time



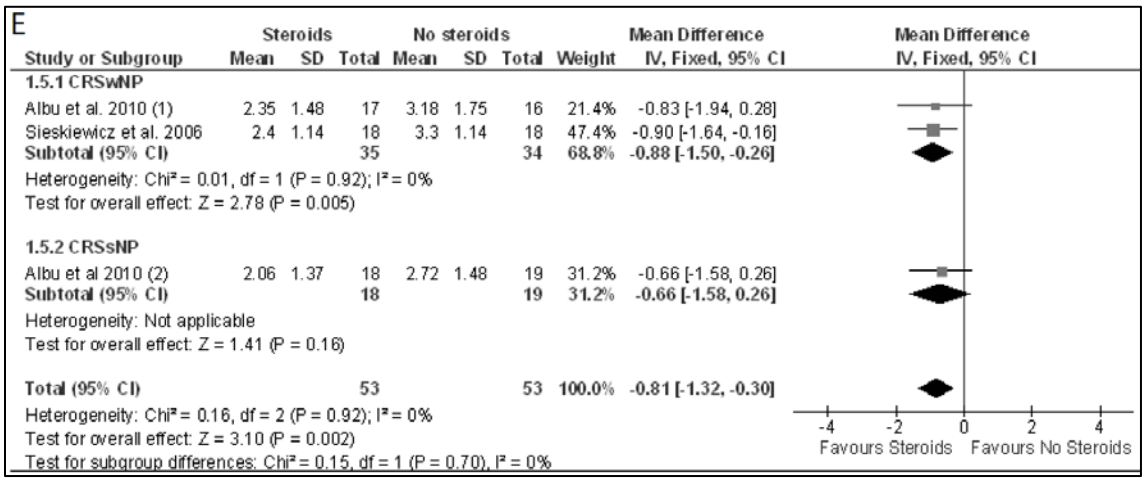
Forest plot C of comparison: Steroids versus No steroids Outcome: Estimated blood loss



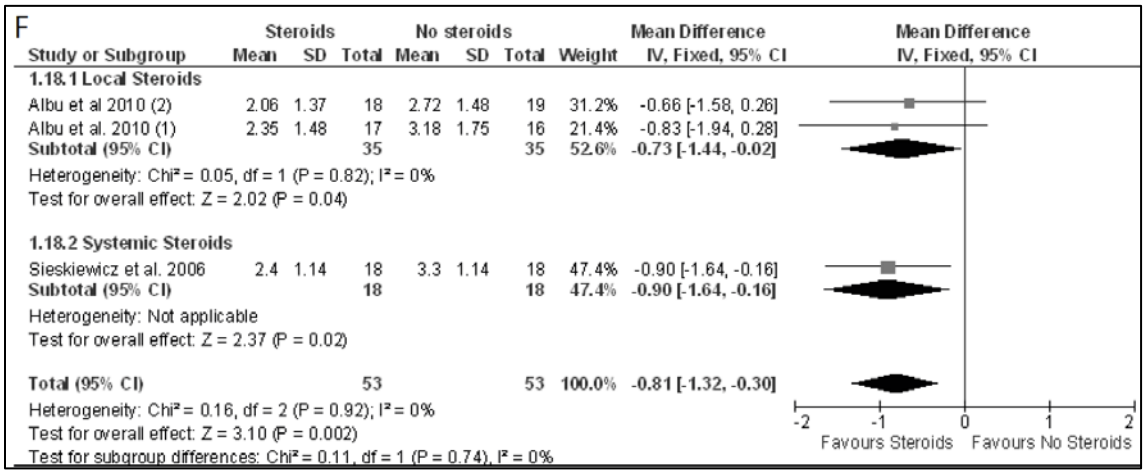
Forest plot D of comparison: Steroids versus No steroids. Outcome: Estimated blood loss



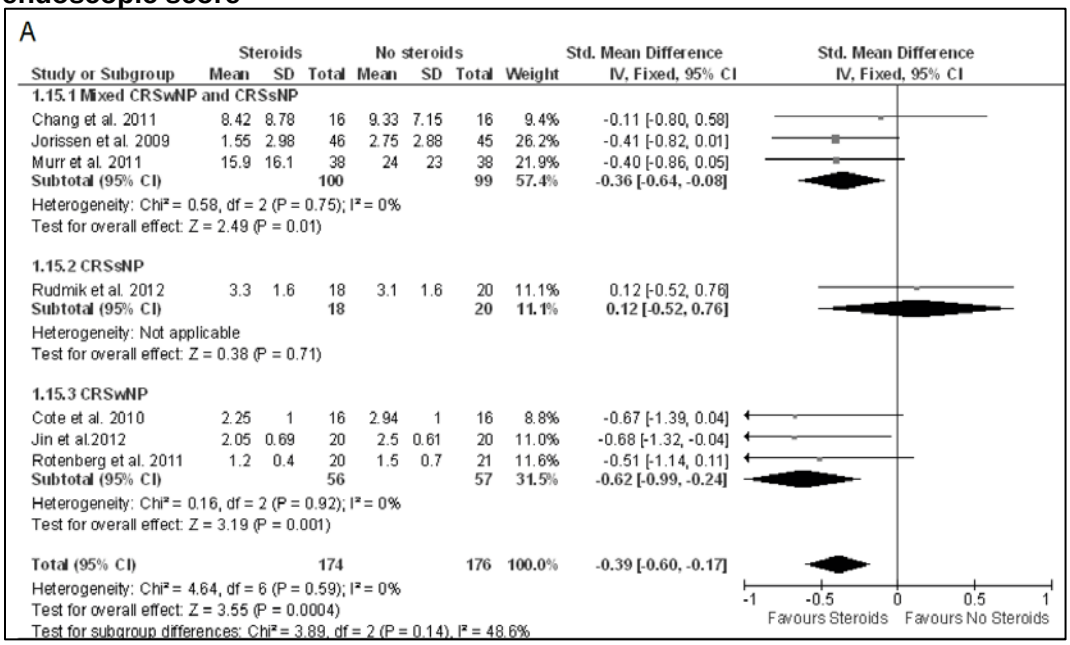
Forest plot E of comparison: Steroids versus No steroids. Outcome: Surgical field quality



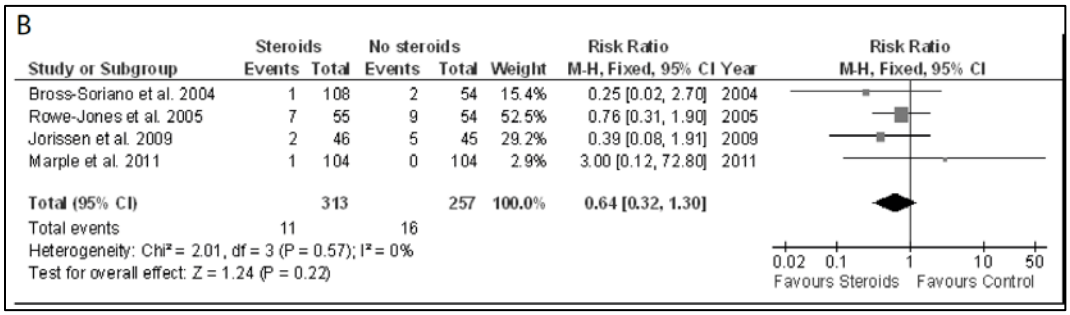
Forest plot F of comparison: Steroids versus No steroids. Outcome: Surgical field quality



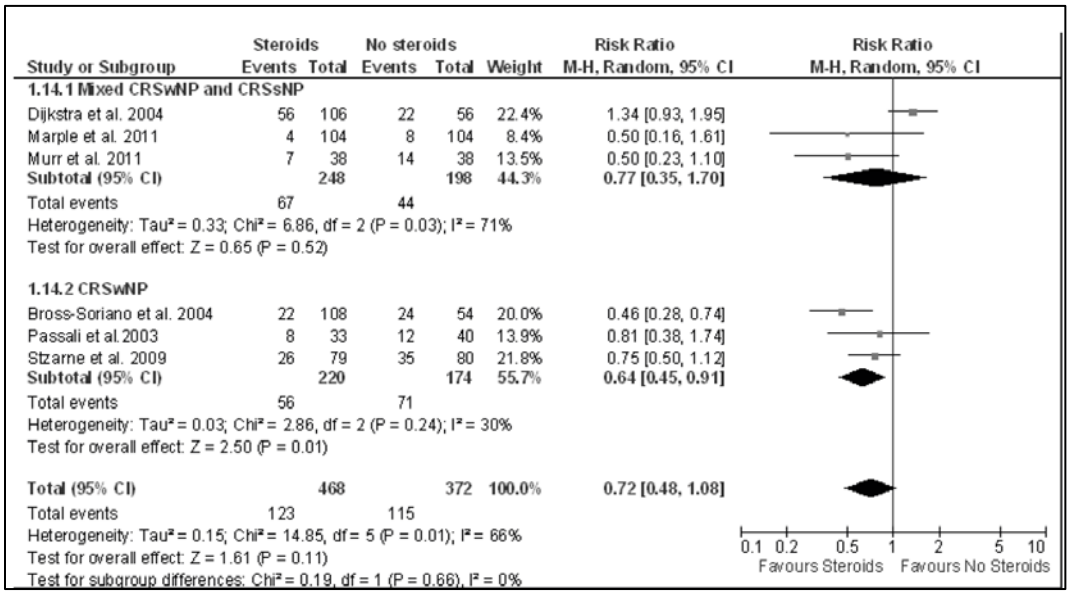
Forest plot A of comparison: Steroids versus No steroids. Outcome: Post operative endoscopic score



Forest plot B of comparison: Steroids versus No steroids. Outcome: 3.4 Risk of infection (Sinusitis)



Forest plot of comparison-Recurrence Risk.



Anmerkung/Fazit der Autoren

Preoperative use of local and/or systemic corticosteroids in FESS, results in significantly reduced blood loss, shorter operative time and improved surgical field quality. Studies are limited on intraoperative use of corticosteroids to reduce post operative pain.

There is no significant benefit seen with the use of postoperative corticosteroids following FESS in improving symptom scores. Corticosteroids improve postoperative endoscopic scores. Risk of recurrence is reduced by postoperative corticosteroids in CRSwNP although this role is unclear in CRSsNP patients. Wellconducted large RCTs are required using, standardised inclusion criteria, specified dose, duration and route of corticosteroids, validated subjective and objective outcome measures, including reporting on long term recurrence rates and complications.

Reychler G et al., 2019 [11].

"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(11). This quality index comprises 27 questions with a total maximum score of 28(12). A grade ranging from “poor” (<14 points) to “excellent” (24–28 points) was assigned to each study evaluated by this quality index(12).

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs (N=263 Patienten)

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 were nebulized 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.

Tsetsos N et al., 2018 [18].

Monoclonal antibodies for the treatment of chronic rhinosinusitis with nasal polyposis: a systematic review*

Fragestellung

The aim of this study is to review all existing evidence concerning the efficacy and safety of monoclonal antibodies used for the treatment of adults with chronic rhinosinusitis with nasal polyposis.

Methodik

Population:

- population comprised adult patients (>18 years old) with CRS with nasal polyposis

Intervention:

- monoclonal antibodies therapy

Komparator:

- placebo or another therapy

Endpunkte:

- change in clinical polyp score, change in quality of life, change in cellular inflammation, change in nasal airflow, change in olfaction and change in Th2 associated biomarkers

Recherche/Suchzeitraum:

- Bis November 2016

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 RCTs (N=256); 142 of them receiving monoclonal antibodies and 114 placebo

Charakteristika der Population:

- Subjects were randomized to receive: anti-IL5 therapy with reslizumab (18) or mepolizumab (20,23) in three studies, anti-IgE therapy with omalizumab in two studies (19,21) and anti-IL-4Rα therapy with dupilumab in the last RCT (22).

Study	Country	Design	Patients (no.)			Study Population	Monoclonal Antibody-(Mechanism of action)	Intervention Protocol	Last visit	Primary Outcome
			Total	TRG	CRG					
Gevaert et al. (2006)	Belgium, Austria	Randomised, double-blind, placebo controlled study	24	16	8	CRSwNP	Reslizumab (anti-IL-5 mAb)	3mg/kg or 1mg/kg or placebo of a single intravenous injection	36w	Safety and pharmacokinetics
Pinto et al. (2010)	USA	Randomised, double-blind, placebo controlled study	14	7	7	CRSwNP or CRSsNP	Omalizumab (anti-IgE mAb)	0,016 mg/kg per IU total serum IgE/ml subcutaneously at enrollement and every 4w for 24w vs placebo	24w	Change in sinus CT opacification
Gevaert et al. (2011)	Belgium	Randomised, double-blind, placebo controlled study	30	20	10	CRSwNP	Mepolizumab (anti-IL-5 mAb)	2 single intravenous inj of 750 mg of mepolizumab or placebo(28 days apart)	48w	Change in TPS
Gevaert et al. (2013)	Belgium	Randomised, double-blind, placebo controlled study	24	16	8	CRSwNP and comorbid asthma	Omalizumab (anti-IgE mAb)	maximum dose of 375mg subcutaneously(every 2w/8inj in total or every m/4inj in total) of omalizumab vs placebo	20w	Change in TPS
Bachert et.al (2016)	USA, Belgium, Spain, Sweden	Randomised, double-blind, placebo controlled study	60	30	30	CRSwNP	Dupilumab (anti-IL-4Rα mAb)	A 600mg loading dose of dupilumab subcutaneously followed by 15 weekly doses of 300 mg plus MFNS 100μg in each nostril twice daily or matched placebo for 16w	16w	Change in TPS
Bachert et.al (2017)	Belgium, Netherlands, United Kingdom	Randomised, double-Blind, placebo controlled study	105	54	51	CRSwNP	Mepolizumab (anti-IL-5 mAb)	A total of six doses (one every 4 weeks) of mepolizumab 750 mg by intravenous infusion or matched placebo plus intranasal steroids(two sprays of 1mg/ml fluticasone propionate daily)	25w	Reduced Need for Surgery

Qualität der Studien:

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Studienergebnisse:

Total Nasal Endoscopic Polyp score

- The reduction in TPS was assessed in all six studies (Table 4). In five of the six studies the use of monoclonal antibodies was proved effective in reducing nasal polyp burden in patients with CRSwNP. In particular, Gevaert et al.(18) showed that the treatment with 1mg/kg of reslizumab managed to improve the TPSs for up to 12 weeks in 5 of 8 patients. Furthermore, half of the subjects who received a single intravenous infusion of 3mg/kg reslizumab presented a reduction in TPS for 4 weeks. A subgroup analysis in the study showed that subjects who responded to reslizumab were found to have elevated nasal IL-5 levels at baseline, compared to the non-responders.
- Gevaert et al. (20) showed that mepolizumab improved significantly the TPSs in 12 of 20 subjects while no change was shown in the placebo group (p=0,028). However, the subgroup analysis in this study showed that no difference for baseline TPSs and local IL-5 levels was found. Similarly, in the Bachert et al.(23) study, mepolizumab caused a significant improvement in the treatment group as compared to control group from week 9 to week 25.
- Concerning omalizumab, Pinto et al.(19) did not manage to show any significant change in TPS in the treatment as compared to placebo group (p<0,58). On the contrary, Gevaert et al.(21) demonstrated that the treatment with omalizumab resulted in significant reduction in TPS compared to placebo (p=0,01 and p=0,99, respectively).

- Finally, in the study of Bachert et al.(22) dupilumab showed a significant improvement in TPS in the treatment group as compared to mometasone sprays alone (p<0,001). The difference was seen at week 4 and continued until the end of the treatment period (week 16). In addition, an improvement of at least 1 point in the polyp score was seen in 70% of the dupilumab plus mometasone group conversely to 20% of the subjects in the placebo plus mometasone group.

CT score

- The change in CT score was evaluated in four of the six included studies (Table 4). Specifically, in three studies the outcome was the improvement in the percentage of sinus opacification in CT images (19,20), in one study it was the Lund-Mackay CT score(21) and in the last one both opacification in CT and the Lund-Mackay CT score were computed for the same purpose (22).
- Pinto et al.(17) showed that omalizumab managed to reduce significantly the inflammation compared to the placebo group. However, the median change of sinus opacification (pre-treatment minus post-treatment) across groups was not statistically significant (p<0,391). On the contrary, Gevaert et al.(19) showed that omalizumab resulted in significant reduction of Lund-Mackay scores on radiologic imaging (p=0,04).
- Mepolizumab was effective in improving CT scores in more than half of the treated subjects as opposed to less than 20% in the placebo group (p=0,06, p=0,024, p=0,049 for the 3 different raters of the study)(20).Finally, in Bachert et al.(22) study a significant improvement from baseline with the use of dupilumab was observed not only in percentage of maxillary sinus opacification (p<0,001) but also in Lund-Mackay total score (p<0,001).

Quality of Life measures

- SNOT-20, SNOT-22, SF-36 and Rhinosinusitis Outcome Measurement Instrument (RSOM-31) were included in the secondary measures of most of the six studies (Table 4).
- In particular, Pinto et al.(19) showed that although omalizumab appeared to improve SNOT-20 scores significantly in the omalizumab as compared to the placebo group, the net change between the two groups was not statistically significant (p<0,78). Concerning the SF-36, vitality was the only domain in which a statistically significant improvement was observed with the use of omalizumab (p<0,05).
- In Gevaert et al.(21) study, omalizumab appeared to be effective in improving significantly both the SF-36 (physical health) (p=0,02) and sleep and general symptoms of RSOM-31 (p=0,02). Finally, SNOT-22 was improved significantly by the use of both dupilumab(22) and mepolizumab(23) (p<0,001 and p=0,005, respectively)(23).

Nasal airflow (PNIF) and olfaction (UPSIT)

- Change in PNIF was the subject of research in four of the included studies (Table 4). In Pinto et al. study(19), omalizumab was not found to be effective in improving PNIF as the net change across the two groups was not statistically significant (p<0,31). Gevaert et al.(20) reported a reduction in nasal obstraction as patients in the mepolizumab group showed better values from baseline in PNIF as compared to placebo group but the results were not statistically significant (p=0,10). On the contrary, the mean difference between mepolizumab and control group in PNIF values was statisticallly significant (p=0,027, in the second

mepolizumab study(23). At last, Bachert et al.(22) reported a statistically significant mean difference in PNIF for dupilumab group vs placebo (p=0,002).

- Three RCTs studied the effectiveness of monoclonal antibodies in olfaction and the outcome was the change in UPSIT score(19,22,23). Neither omalizumab(19) nor mepolizumab(23) was found to yield a statistically significant benefit concerning UPSIT score (p<0,31 and p=0,233, respectively). On the contrary, dupilumab proved to be effective and lead to a statistically significant improvement as compared to placebo (p<0,001) (22).

Safety and adverse events

- Five RCTs reported a wide variety of adverse events the majority of them were negligible with the most common being upper respiratory tract infections (common cold and nasopharyngitis included). A total number of eight serious adverse events were reported in only two of the included studies none of which was deemed to be associated with the monoclonal antibody therapy

Anmerkung/Fazit der Autoren

Targeting IgE, IL-5 and IL-4/IL-13 cytokine pathways constitutes a novel therapy in patients suffering from CRSwNP. Despite the small number of studies, with their small sample size and several limitations, their results are really encouraging and biologic therapy seems to be safe and well tolerated. However, high-quality trials designed to assess these therapeutic alternatives for this specific subpopulation of patients with CRSwNP refractory to standard treatment are called for.

Yoon H et al., 2018 [19].

Post-operative corticosteroid irrigation for chronic rhinosinusitis after endoscopic sinus surgery: A meta-analysis

Fragestellung

The goal of this study was to perform a systematic review with metaanalysis of the efficacy of steroid nasal irrigation on post-operative management of Chronic rhinosinusitis (CRS) following ESS.

Methodik

Population:

- Patients that underwent ESS

Intervention/ Komparator:

- any kind of steroid, such as budesonide and fluticasone, postoperatively and were compared the effect of steroid irrigation before and after treatment or to amcontrol (nasal saline irrigation alone).

Endpunkte:

- disease-specific QOL questionnaire assessments and endoscopy score, adverse effects

Recherche/Suchzeitraum:

- Bis März 2017

Qualitätsbewertung der Studien:

- Cochrane Risk of bias tool
- Newcastle-Ottawa Scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 12 (N=360)

Charakteristika der Population:

-

Qualität der Studien:

- Regarding the results of bias assessment, the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies → the scores ranged from 5 to 8, which meant that there was adequate selection of patients in included studies.
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Studienergebnisse:

Endoscopic scores after steroid nasal irrigation

- Three studies[4,9,10] assessed the efficacy of steroid nasal irrigation on endoscopic score reduction. Steroid nasal irrigation applied for more than 3 months reduced the endoscopic scores (MD = 4.23; I2 = 0.00%; 95% confidence interval [95% CI]: 3.60, 4.86) significantly compared to pre-treatment values.
- No significant inter-study heterogeneity was detected in this score (I2 < 50%). Given that the important difference in the endoscopic scores between pre-treatment and post-treatment is considered as more than[4,16] and the MD showed the significantly beneficial effects of steroid irrigation

Quality of life after steroid nasal irrigation

Four studies[1,2,9,10] assessed the efficacy of steroid irrigation on QOL. Steroid irrigation that was applied for more than 3 months significantly improved the QOL (MD = 21.92; I2 = 34.69%; [95% CI]: 13.95, 29.89) compared to pre-treatment values.

There was no significant inter-study heterogeneity in this score (I2 < 50%). The significant difference in the QOL from pre-treatment to post-treatment is considered as [8.9.17] The value of the MD demonstrated the significant and beneficial effects of steroid irrigation

Steroid nasal irrigation and control comparison

Three studies[2,6,8] involved a comparison of the reduction in endoscopic scores6,8 and QOL2,6,8 between steroid irrigation treatment and a control. Steroid irrigation did not reduce the endoscopic scores (MD = -0.33; I2 = 0.00%; [95% CI]: -0.67, 0.01) compared to the control group. It also did not improve the QOL (RMD = -3.03; I2 = 0.00%; [95% CI]: -6.64, 0.58) vs the saline alone irrigation.

No significant inter-study heterogeneity (I2 < 50%) was detected for these outcomes. Based on the results, the addition of steroid in the saline irrigation exhibited no significant improvement in endoscopic finding and QOL compared to the saline alone irrigation

Steroid irrigation adverse effects: IOP and HPA axis

The incidence abnormal ACTH (OR = 0.28; [95% CI]: 0.04, 1.84; I2 = 8.7%) was not significantly higher in post-treatment values compared to pre-treatment values.[1,5,8,11] Additionally, there was no difference in cortisol levels between post-treatment values and pre-treatment values (SMD = -0.10; [95%CI]: -0.45,0.24).[8,11,12,18]

Steroid irrigation did not significantly increase the IOP (SMD = -0.02; [95%CI]: -0.29,0.26) compared to pre-treatment values.[5,8,13,18] There was no significant inter-study approximate heterogeneity concerning these measurements (I2 < 50%). Altogether, steroid irrigation may not cause adverse effects, such increased IOP and distorted HPA axis

Anmerkung/Fazit der Autoren

Although steroid irrigation after ESS can efficiently improve sinus inflammation as well as QOL, steroids did not confer any additional benefit over saline alone as post-ESS care for the CRS patient population. However, no adverse effects regarding systemic steroid absorption were found.

3.4 Leitlinien

AWMF 2017 [3].

Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie e.V.

Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin e.V.

Rhinosinusitis, S2k-Leitlinie

Siehe auch: Stuck B et al, 2018 [17], Stuck B et al, 2018 [16]

Leitlinienorganisation/Fragestellung

Ziel dieser Leitlinie ist die Forderung einer qualitativ hochwertigen Versorgung von erwachsenen Patientinnen und Patienten, die sich mit entsprechenden Beschwerden bzw. mit dem Verdacht auf eine entzundliche Erkrankung im Bereich der Nasennebenhohlen (Rhinosinusitis, RS) in arztliche Behandlung begeben.

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:

- Zusätzlich zu den genannten Leitlinien und Positionspapieren wurde zentral eine systematische Literaturrecherche in PubMed (National Library of Medicine) zur Diagnostik und Therapie der RS des Erwachsenen mit einer Begrenzung auf randomisierte Studien und systematische Reviews aus den Jahren 2010-2015 durchgeführt und allen Autoren zur Verfügung gestellt.
- Von den Autoren wurde darüber hinaus zu den jeweiligen Kapiteln eine aktuelle Literaturrecherche nach Originalarbeiten in deutscher oder englischer Sprache aus den letzten 10 Jahren (2005-2015) und nach Reviewartikeln in deutscher oder englischer Sprache aus den letzten 5 Jahren (2010-2015) durchgeführt

LoE

- (soll / soll nicht, sollte / sollte nicht und kann / kann nicht)

GoR

- Empfehlungen mit „soll“ oder „soll nicht“ entsprechen demnach einer starken Empfehlung (erwünschte Effekte überwiegen eindeutig Risiken/Zusatzaufwand oder vice versa), Empfehlungen mit „sollte“ oder „sollte nicht“ einer moderaten Empfehlung (erwünschte Effekte überwiegen vermutlich Risiken/Zusatzaufwand oder vice versa) und „kann“ bzw.

„kann nicht“ einer schwachen Empfehlung (kein ausreichender Anhalt für überwiegenden Nutzen/ Risiko der Intervention).

Sonstige methodische Hinweise

- Diese Leitlinie ist gültig bis 5 Jahre nach Veröffentlichung, spätestens zu diesem Zeitpunkt erfolgt eine inhaltliche Überprüfung und gegebenenfalls eine Aktualisierung. Werden dem Leitlinienkoordinator zwischenzeitlich Erkenntnisse bekannt, die eine Überarbeitung der Leitlinie erfordern, so erfolgt die Aktualisierung bereits früher.
- Die vorliegende Leitlinie ist eine Aktualisierung der im Jahre 2007 erstmals publizierten und im Jahre 2012 aktualisierten S2k-Leitlinie „Rhinosinusitis“ der Deutschen Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie [243, 245] sowie der im Jahre 2008 publizierten Leitlinie „Rhinosinusitis“ der Deutschen Gesellschaft für Allgemeinmedizin und Familienmedizin [244].

Medikamentöse Therapieverfahren

Empfehlungen 1

Welche Rolle spielen medikamentöse Therapieverfahren bei der akuten und der rezidivierenden akuten Rhinosinusitis?

Empfehlungen:	Ergebnis der Abstimmung
■ Dekongestiva können zur symptomatischen Linderung bei ARS verwendet werden. Topische Dekongestiva sollen frei von Benzalkoniumchlorid sein. Dekongestiva sollten nicht länger als 10 Tage angewendet werden.	9/9 starker Konsens
Bei einer ARS und bei einer rez. ARS können Schmerzmittel zur symptomatischen Therapie empfohlen werden.	7/7 starker Konsens
■ Bei einer akuten allergischen und bei der rez. ARS sollten lokale Kortikoid-Anwendungen erfolgen.	4/4 starker Konsens

Dekongestiva:

Sympathomimetika oder Parasympatholytika konnen systemisch und/oder lokal eine vasokonstringierende Wirkung mit vorübergehender Abschwellung der Nasenschleimhaut entfalten und dadurch lt. einiger Studien eine kurzfristige Verminderung von Schmerzen, eine freiere Nasenatmung und eine Erweiterung der Ostien bewirken [13–15, 17]. Andere Studien konnten keine Verbesserungen der Symptome gegenüber Placebo zeigen [18]. Wegen der Gefahr des Rebound-Effektes bzw. der Gefahr der Rhinitis medikamentös empfehlen alle internationalen Leitlinien die Beschränkung der Nutzungsdauer der lokalen Vasokonstringentien (z.B. Xylometazolin bzw. Oxymetazolin 0,05 % oder Ipratropiumbromid 0,03 oder 0,06 %) auf längstens 7 Tage. Eine geringere Gefahr besteht bei niedrigen Dosierungen und bei Vermeidung von Praparationen mit Konservierungsstoffen (z.B. Benzalkoniumchlorid). Anhand der vorliegenden Studien muss von klinisch relevanten Reiz- und Schadigungswirkungen durch Benzalkoniumchlorid (= BKC) in Nasentropfen und Nasensprays ausgegangen werden [4, 12, 19–23]. Da inzwischen auch BKC-freie Praparationen erhältlich sind, wird eine Einschränkung

der Verwendung von BKC empfohlen. Insbesondere Allergiker und Langzeit-Nutzer von Nasensprays sollten diese Substanz meiden.

In einem aktuellen Cochrane Review wird die klinische Evidenz zur Wirksamkeit und Sicherheit von nasalen und systemischen Dekongestiva neu bewertet [5]. Aus dieser Cochrane-Analyse lassen sich keine Unterschiede bezüglich des Sicherheitsprofils zwischen lokal und systemisch applizierten Sympathomimetika feststellen und beiden wird eine gute Verträglichkeit im Rahmen der kurzzeitigen Behandlung der akuten Rhinosinusitis bescheinigt. In 15 Studien mit 1838 Teilnehmern fanden sich jedoch mehr belastbare klinische Daten zur Sicherheit oral applizierter, systemischer Dekongestiva als für die lokale Applikation. Für die lokale Anwendung gilt die Empfehlung zum Gebrauch über max. 10 Tage in möglichst geringer Dosierung und ohne Benzalkoniumchlorid-Zusatz. Im Falle der Ausbildung einer Rhinitis medikamentösen wird eine Entwöhnung, z.B. nach einem Stufenschema unter Verwendung eines topischen Kortikoids, empfohlen [3].

Sekretolytika:

Die chemisch definierten Sekretolytika Acetylcystein und Ambroxol werden zwar haufig unterstutzend neben der Antibiotikagabe bei der ARS eingesetzt, jedoch liegt für den Nutzen dieser Therapie keine Evidenz vor

Steroide:

Mehrere aktuelle Leitlinien [1, 252, 253] empfehlen topische Steroide als generelle Therapieoption bei ARS. Die beiden Ausgangsleitlinien [244, 245] sind dagegen für den hausärztlichen Bereich zurückhaltend. Wegen der Diskrepanz wurde eine erneute Evidenzrecherche durchgeführt.

Topische Steroide bei ARS:

Für durch Röntgen oder Endoskopie nachgewiesene ARS von mehr als 1 Woche Dauer ziehen die Autoren eines aktuellen Cochrane-Reports [2] die Schlussfolgerung, dass eine Therapie mit Kortikoid-Spray als Mono- oder Co-Therapie mit Antibiotika mäßige Effektivität bezüglich symptomatischer Besserung biete. Die vier eingeschlossenen Studien wurden allerdings an Kliniksambulanzen durchgeführt [6, 9–11] bzw. untersuchten Patienten mit rezidivierender oder allergischer RS [9–11]. Die Ergebnisse sind deswegen auf die primärmedizinischen Verhältnisse nicht übertragbar. Die Einschlusskriterien eines zweiten systematischen Reviews [7] beziehen ebenfalls neben unkomplizierter ARS vorwiegend die Studien mit rez. ARS bzw. das Klientel von Kliniksambulanzen ein [6, 8–11, 39].

Die einzige im rein hausärztlichen Setting durchgeführte RCT an 240 Erwachsenen mit unkomplizierter ARS fand keine Vorteile für die Verwendung intranasaler Steroide [39]. Die Diagnose wurde dabei rein klinisch gestellt: mindestens 3 Symptome und 1 Befund bei weniger als einer Woche Krankheitsdauer.

Orale Steroid-Medikation bei ARS:

Ein Cochrane Review [40] fand keinen positiven Effekt einer Steroidmedikation bei Erwachsenen mit nur klinisch diagnostizierter akuter Sinusitis im hausärztlichen Bereich [36, 38]. Die meisten Studien stammen aus HNO-Ambulanzen und zusätzlicher radiologischer Diagnosestellung [37, 41, 45]. Dort zeigte sich (in Kombination mit Antibiotikagabe und bei erheblichem Risiko für Bias) eine NNT von 7 für Symptomlinderung bzw. für kurzfristige Schmerzlinderung. Die Steroid-Dosierungen lagen bei 24-80mg Prednisolon für 3 bis 7 Tage bzw. 1mg Betamethason täglich für 5 Tage.

Topische Steroide bei der rez. ARS:

Ein systematisches Review [46] fand drei relevante Studien, die allerdings alle CRS und rez. ARS zusammen untersuchten. Insgesamt wird dort die Evidenzlage wegen des Risikos für Bias als nur mäßig gut eingeschätzt.

Die multizentrische Studie von Meltzer [8] schloss Kinder ab 12 Jahren mit rez. ARS ein und wurde u.a. an zahlreichen Allergiker-Ambulanzen durchgeführt. Die Studie von Qvarnberg [44] untersuchte 40 Patienten mit chronischer oder rezidivierender RS, die zu einer operativen Versorgung überwiesen wurden. Die methodisch beste und für die Fragestellung relevanteste Studie von Dolor [10] umfasste insgesamt 95 erwachsene Patienten mit rez. ARS (79%) oder CRS (21%); die Hälfte wurden in der Primärebene bzw. an HNO-Ambulanzen behandelt. Eine Behandlung mit einmal täglich 200µg Fluticason intranasal für drei Wochen zusätzlich zu 10 Tagen Behandlung mit Cefuroxim führte zu einer subjektiven Besserung nach im Median 6 Tagen gegenüber 9,5 Tagen unter Placebo.

Antihistaminika:

Bei bekannter allergischer Disposition (Anamnese, positiver kutaner Allergietest, Nachweis von spezifischem IgE) konnte bei Patienten mit einer ARS der Niesreiz und die Nasenobstruktion durch 10mg/d Loratadin gelindert werden [42]. Ein Behandlungsversuch ist auch denkbar mit topischen H1-Blockern (=Antihistaminika) [27, 35, 43].

Schmerzmittel:

Bei der ARS wird lediglich bei bestehenden Schmerzen und nicht als abschwellende Maßnahme die Einnahme von Analgetika / Antiphlogistika empfohlen. Wegen der stärker entzündungshemmenden Wirkung ist ASS und Ibuprofen vor Paracetamol in dieser Indikation zu empfehlen, wegen der besseren Magenverträglichkeit bzw. falls im Behandlungsverlauf eine operative Intervention geplant ist oder notwendig wird, Ibuprofen vor ASS. Es liegen hierzu keine Studien bei RS vor, eine Behandlung sollte je nach Effekt erfolgen.

Sonstige:

Weder in Bezug auf die Gabe von Zink noch auf die Gabe von Vitamin C liegen klinische Studien zur Wirksamkeit bei ARS vor, daher kann eine Anwendung derzeit nicht empfohlen werden.

Empfehlungen 2

Welche Rolle spielen medikamentöse Therapieverfahren bei der **chronischen Rhinosinusitis**?

Empfehlungen:	Ergebnis der Abstimmung
■ Dekongestiva sollten bei der CRS aufgrund der Gefahr der Entstehung einer Rhinitis medicamentosa nicht angewendet werden.	7/7 starker Konsens
■ Topische Kortikosteroide sollten zur Therapie der CRSsNP und insbesondere der CRScNP zur Anwendung kommen.	6/6 starker Konsens
■ Die Therapie mit systemischen Kortikosteroiden kann in Einzelfällen erwogen werden.	7/7 starker Konsens
■ Ausgewählte Biologika können bei Versagen etablierter Therapieformen im Einzelfall bei CRScNP eingesetzt werden.	6/6 starker Konsens

Empfehlung:	Ergebnis der Abstimmung
Eine adaptive Desaktivierungsbehandlung sollte bei Patienten mit gesichertem NERD-Syndrom und einer CRScNP bei Auftreten einer Rezidiv-Polyposis durchgeführt werden.	7/7 starker Konsens

Dekongestiva

- Die Verbreitung des Einsatzes von Dekongestiva durch HNO-Ärzte ist gemäß Umfragen eher gering [28]. Dabei erscheint das Risiko, die rezeptfrei verfügbaren Dekongestiva dauerhaft bei CRS oder einer chronischen Nasenatmungsbehinderung anderer Genese zu verwenden, deutlich erhöht: von 895 Patienten mit chronischer mittelgradiger bis schwerer Rhinitis verwendeten 49% abschwellende intranasale Mittel seit mehr als einem Jahr. Ausgeprägte nasale Blockade, langes Leiden, Schlafstorungen, Ubergewicht und die Aufforderung zu geringerem Konsum verstärkten den übertriebenen Gebrauch von Dekongestiva [26].
- Neben Dekongestiva aus Adrenalin-Derivaten werden neuerdings Capsaicin haltige Sprays versucht – mit langanhaltender antiphlogistischer Wirkung bei der chronischen (nichtallergischen) Rhinitis [24], dies allerdings noch mit unbekanntem Verbreitungsgrad.

Sekretolytika

- Bisher wurde die Studienlage fur die Anwendung von Sekretolytika bei der chronischen Sinusitis als nicht ausreichend belegt angesehen [244, 245, 252]. Daher erfolgte eine dezidierte Literatursuche. Dabei zeigten sich in den letzten 5 Jahren folgende neue Studien: In einer prospektiven Pilotstudie zeigte das Mukolytikum Erdosteine alleine eine stärkere Verbesserung der Symptomatik als Erdosteine mit einem topischen Glukokortikoid bei Patienten mit CRScNP [25]. Alternativ ist hier ein partieller Antagonismus der gut belegten Wirkung von Glukokortikoiden ein Erklärungsansatz. Aufgrund der geringen Anzahl von Studien, deren Gute und der niedrigen eingeschlossenen Patientenanzahl können Mukolytika nicht sicher die Symptomatik einer CRS bessern, die Anwendung kann aber in bestimmten Subgruppen als Therapieoption angewendet werden. Dabei ist die Studienlage weitgehend auf den HNO-ärztlichen Bereich begrenzt.

Glukokortikosteroide

- Die Anwendung von topischen Glukokortikosteroiden gilt als die Erstlinientherapie der CRS [1, 244, 245, 252]. Sie gilt für alle Versorgungsebenen. Entsprechend werden sie auch häufig gemas Umfragen zur Therapie der CRS verordnet (z.B. von Allergologen in 74,6%) [29]. Bislang untersuchten insgesamt 25 randomisierte Studien den Effekt von Glukokortikoiden bei CRS [308]. So konnte in einer Placebo-kontrollierten Studie bei Patienten mit CRS unter Anwendung von Mometason-Fuorat insbesondere eine Besserung der nasalen Sekretion und der Nasenatmungsbehinderung im Vergleich zu Placebo nachgewiesen werden [33]. Ein aktueller Cochrane Review identifizierte 18 Studien zum Einschluss in eine qualitative, sowie 13 in eine quantitative Analyse zur Untersuchung der Wirksamkeit von intranasalen, topischen Glukokortikoiden bei CRS [34]. In der weiteren Analyse verringert sich die Studienanzahl so weit, dass nur noch eine Studie [32] mit Patienten mit CRSsNP im Hinblick auf die Wirkung auf die Lebensqualität untersucht wurde. Entsprechend verzichtet der Cochrane Review auf eine separate Darstellung der Ergebnisse an Patienten mit CRScNP und CRSsNP. Er weist eine Besserung der subjektiven Symptomatik, speziell der Nasenatmung, Rhinorrhoe, Riechstörung und von Kopf-/Gesichtsschmerz nach [34]. Dabei erscheinen die ersten drei Symptome starker verbessert, bzw. die Besserung mit hoherer

Datenqualität nachgewiesen. Die Effektstarke wird als moderat angegeben. Die Datenlage ist fur topische Glukokortikoide bei CRScNP relativ klar: Sie fuhren zu einer Besserung der subjektiven Symptomatik, eine Verringerung der Grose der nasalen Polypen sowie eine Senkung der Rezidivhäufigkeit von Polypen nach Nasennebenhöhlenoperationen [257]. Ihre Wirkung (hier: Fluticason 400 µg 2x /die) im Hinblick auf das Riechvermögen kann aber durch eine NNH-OP noch gesteigert werden [30]. Auch eine Besserung der subjektiven Lebensqualität wurde berichtet [31]. Ein aktueller Cochrane Review zum Vergleich verschiedener topischer Glukokortikoide konnte keine Überlegenheit von Fluticason versus Mometason oder Beclomethason im Hinblick auf Wirksamkeit oder Nebenwirkungen feststellen [154]. Eine höhere Dosierung scheint möglicherweise die Lebensqualität mehr zu verbessern, allerdings auf Kosten einer größeren Häufigkeit einer Epistaxis. Die systemische Anwendung von Glukokortikoiden kann allein oral oder zusätzlich zur topischen Therapie erfolgen.

- Die alleinige, orale Gabe von Glukokortikoiden uber zwei oder drei Wochen bei CRScNP bessert gemäß eines aktuellen Cochrane Reports [155] die subjektive Sinusitis-spezifische Lebensqualität und die Schwere der Erkrankung gemessen anhand der Ausprägung der Symptome. Die Größe der Polypen verringert sich im Rahmen der oralen Therapie [257] mit einer größeren Effektstarke als durch die topische Therapie alleine [155]. Diese Wirkung war 10 [153] bzw. 26 Wochen [151] nach Therapie nur noch in verringertem Ausmaß nachweisbar, so dass aufgrund der Heterogenität der Daten die Autoren darauf hinweisen, dass der Therapieeffekt zu diesem Zeitpunkt nicht mehr sicher nachgewiesen werden kann. Die orale Gabe verursacht dagegen wahrscheinlich mehr gastrointestinale Nebenwirkungen (risk ratio RR) 3,45; 95% Konfidenzintervall 1,11 – 10,78; 187 Teilnehmer und Schlafstörungen (RR 3,63; 95% Konfidenzintervall 1,10 – 11,95; 187 Teilnehmer [152, 153, 156] im Vergleich zu Placebo. Ein erhöhtes Risikoprofil für Stimmungsänderungen konnte nicht nachgewiesen werden.
- Eine zusätzliche systemische (orale) Glukokortikoid-Gabe bessert die Grose nasaler Polypen starker als die topische Gabe allein [160]. Dies wurde in einem aktuellen Cochrane Review bestätigt [161]. Bei allerdings nur einer Studie (N=30), die den additiven Effekt von oralen Glukokortikoiden zur topischen Therapie bei Erwachsenen untersucht hat [160], besteht aufgrund der als sehr gering eingestuften Datenqualität und fehlender Daten zur Beeinflussung der subjektiven Lebensqualität der Studienteilnehmer die Notwendigkeit zur Durchführung weiterer spezifisch geplanter Studien. Neben der Standardtherapie von topischen Glukokortikoiden als Nasenspray oder –tropfen ist auch die Zugabe der Glukokortikoide zur Nasenspülung eine Therapieoption, wenn auch derzeit unter den Bedingungen eines Off-label-Gebrauchs [307] oder als Inhalation. Ein aktueller Cochrane Review [154] identifizierte nur eine Studie, die die Applikation von Budesonid als Nasenspray mit der als Inhalation verglich [159]. Bei Besserung von Symptomatik und Polypengrose in beiden Therapiegruppen wurden deutliche methodische Mangel der Studie aufgedeckt und daher die beobachtete stärkere Besserung in der Inhalationsgruppe bei gleicher Nebenwirkungsrate sehr kritisch und zurückhaltend interpretiert. Weitere Untersuchungen verwendeten neuartige Applikationsmodi, die insgesamt die Wirksamkeit der Glukokortikoide bestatigen [142, 143, 150, 157, 158]. So kann das Glukokortikoid auch als Inhalation/Verneblung appliziert werden und bewirkt effektiv eine verringerte Polypengrose im Vergleich zu Placebo mit Besserung der Symptomatik [157]. Beim Vergleich

verschiedener Applikationsmodi besserten orale und inhalative Gabe eines Glukokortikoids das Riechvermogen mehr als die Applikation als Nasenspray bei CRS [158]. Systemische Effekte einer Budesonid-haltigen Spülung oder Inhalationstherapie konnten nicht nachgewiesen werden (N=20) [142]. Der Effekt fur die CRSsNP ist weniger klar als bei CRScNP [308]. Dennoch wurden auch hier Empfehlungen zugunsten einer topischen Therapie mit Glukokortikoiden ausgesprochen [1, 141, 244, 245, 252]. Dabei berichtete eine Meta-Analyse eine erhöhte Wirksamkeit topischer Steroide in der postoperativen Situation und bei Anwendung von Applikationsarten, die die Nasennebenhohlen erreichen [139].

- Die systemische Gabe von Glukokortikoiden bei CRSsNP ist weniger untersucht und erreicht daher ein geringes Evidenzniveau [140]. Ein Cochrane Review zur alleinigen systemischen Gabe von Glukokortikoiden bei CRSsNP [155] konnte keine randomisierten, kontrollierten Studien zu dieser Fragestellung identifizieren und auswerten und verzichtet daher auf eine Unterscheidung CRScNP/CRSsNP. Der bereits angesprochene Cochrane Review zur topischen Therapie [34] schloss von vier Studien mit CRSsNP [32, 33, 144, 148] zur weiteren Analyse ein. Er kritisiert die kleineren Fallzahlen und die schlechtere Datenqualitat. Bei Patienten mit CRSsNP (N=20) zeigte sich die Anwendung von Fluticason mittels neuartigem Applikationssystem im Vergleich zu Placebo überlegen: Es besserte sich die Lebensqualität und der Endoskopiescore sowie die Nasenatmung (gemessen mittels peak nasal inspiratory flow) [144].
- Die Anwendung topischer Glukokortikoide fuhrt zu dem vermehrten Auftreten einer Epistaxis (Relatives Risiko 2,74; 95% Konfidenzintervall 1,88-4; 2508 Teilnehmer, 13 Studien) [34]. In wie weit andere lokale oder systemische Nebenwirkungen durch topische Glukokortikoide begünstigt sind, bleibt gemäß der Cochrane Analyse unklar. Ursache sind dabei sowohl fehlende Daten wie auch geringe Datenqualität bei sehr heterogener Qualität der Erfassung von
- Nebenwirkungen. Glukokortikoide sind bei CRScNP, aber auch bei CRSsNP als Standardtherapie anzusehen. Dabei bestehen die besten Daten zur Wirksamkeit als Applikation als Nasenspray.

Antihistaminika

- In 11% der klinischen Studien zur CRS zahlten Antihistaminika zur maximalen medikamentösen Therapie in Kombination mit anderen Medikamenten [149]. Dennoch ist die Datenlage im Rahmen von Studien sehr begrenzt [147]. Zur Behandlung der CRS erscheint die Verschreibung von Antihistaminika möglich, vor allem bei Vorliegen einer allergischen Ko-Morbiditat.

Leukotrienantagonisten

- Eine Literatursuche zu klinischen Studien der letzten 5 Jahre zur Anwendung von Leukotrienantagonisten bei CRS wies auf zwei Übersichtsarbeiten hin, die die Therapieoptionen kritisch würdigten [145, 146]. In diesen wurden Patienten mit CRS (N=24) postoperativ doppelt-blind randomisiert Placebo-kontrolliert mit 10 mg Montelukast therapiert [177] und ein positiver Effekt bei allerdings Verwendung von nicht-validierten Lebensqualitätsinstrumenten nachgewiesen [257]. Ebenfalls postoperativ ergab bei CRScNP der Vergleich von Montelukast mit einem topischen Glukokortikoid (Mometason) in einer randomisierten Studie eine grosere Rezidivrate der Polypen (48% vs. 20%) bei Behandlung mit dem Leukotrienantagonisten. Eine weitere prospektive randomisierte Untersuchung verglich orale und topische Glukokortikoidgabe mit und ohne Anwendung von Montelukast [178]. Im Gegensatz zu den ubrigen Studien waren hier Patienten mit CRScNP

ohne operative Intervention eingeschlossen. Eine Besserung der Lebensqualität zeigte sich nach 8, nicht mehr aber nach 12 Wochen durch den Zusatz von Montelukast. Leukotrienantagonisten scheinen im Vergleich zu Placebo einen positiven Effekt zu haben. Bei Anwendung von topischen Steroiden ist dieser Effekt auf einen Gewinn an Lebensqualität begrenzt.

Biologika

- Anti IgE-Antikorper (Omalizumab) Omalizumab ist ein Anti-IgE Antikörper, der zur Behandlung eines schweren allergischen Asthmas zugelassen ist, welches sich mit der üblichen stadiengerechten Kombination aus Kortison und Beta-2-Sympathomimetika nicht kontrollieren lasst. Vorausgesetzt wird eine nachgewiesene Allergie auf ganzjährig bedeutsame Inhalationsallergene bei deutlich reduzierter Lungenfunktion (Einsekundenkapazitat weniger als 80%). Im Rahmen der Entwicklung dieses Medikamentes wurde als günstige Nebenwirkung auch eine Verkleinerung der nasalen Polypen bei CRScNP beschrieben [176].
- Im Rahmen einer prospektiven, Placebo-kontrollierten Studie [174] zeigte sich wahrend einer sechsmonatigen Therapie eine tendenzielle, aber nicht-signifikante Besserung des subjektiven Befindens. Kritisiert wurde dabei der Einschluss von Patienten mit CRSsNP in diese Studie [241]. Die klinische Wirksamkeit von Omalizumab wurde mit signifikant verringerter Polypengrose nach 8 Wochen Therapiedauer belegt [175], gleichzeitig bessert sich der CT-Befund und das subjektive Befinden. Wegen der weiteren Größenabnahme nach 16 Wochen Therapie sollte diese langfristig, nach derzeitigem Kenntnisstand ggf. unbefristet erfolgen. Damit ist die Wirksamkeit dieser Therapieform prinzipiell belegt.
- Anti IL-5-Antikorper (Mepolizumab, Reslizumab): Nach intravenoser Applikation bewirkte die systemische Anwendung eines Anti-IL5-Antikorper eine deutliche Reduktion der Polypengrose Das Ansprechen konnte basierend auf dem IL-5 Spiegel im Nasensekret vorhergesagt werden [179]. Die Therapie zeigte ein Ansprechen bei in etwa 50% der nicht selektionierten Patienten mit Polyposis; ein hoher IL-5 Spiegel im Nasensekret schien die therapeutische Antwort vorherzusagen und fiel unter der Verumtherapie auch deutlich ab [179]. Weiterhin steht Mepolizumab als IL-5 Antikorper zur Therapie zur Verfügung. In einer randomisierten, doppelt-verblindeten Untersuchung erhielten 30 Patienten 2 Injektionen Mepolizumab (750 mg, N=20) im zeitlichen Abstand von 4 Wochen oder Placebo (N=10). Es zeigten 12 von 20 Mepolizumab erhaltende Patienten eine signifikante Verkleinerung der Polypen und eine Besserung des CT-Befundes [183]. Damit ist die Wirksamkeit dieser Therapieform prinzipiell belegt.

Topische antimykotische Therapie

- Die Anwendung von antimykotischen Therapien ist gering verbreitet [28], da trotz vier randomisierter Studien kein dauerhafter positiver Effekt einer topischen antimykotischen Therapie bei CRS nachgewiesen werden konnte, der den von NaCl-Nasenspülungen übersteigt [182, 184, 308]. Lediglich kurzfristig – nach 2 Wochen Therapie – und temporar begrenzt, zeigte sich ein signifikanter Unterschied [180]. Dabei wurde eine fehlende Wirkung auch beim postoperativen Situs nachgewiesen [181]. Entsprechend kann diese Therapie nicht empfohlen
- werden [307]. In einer kontrollierten Studie mit Vergleich verschiedener antimykotischer Therapien zeigte sich Fluconazol als Nasenspray oder Spulung Itraconazol oder einer Kontrollgruppe gegenuber uberlegen bei Patienten, die die Kriterien einer allergischen Pilzsinusitis mit postoperativem Situs erfullten [173].

Sonstiges:

Einen Einfluss der Körperposition konnte bei zusätzlicher, sechs-wöchiger Anwendung einer deutlich vorgebeugten Kopfposition (Quadrupede Head Position) zur maximalen medikamentösen Therapie mit Glukokortikosteroid, Antibiotikum, Antihistaminikum und standardisiertem Myrthol nachgewiesen. Prospektiv, randomisiert, doppelt-blind zeigte sich eine Besserung der Lebensqualität und des CT-Befundes signifikant überlegen bei der Anwendung der Therapie in dieser Kopfposition zweimal täglich für 20 min (N=106) [165].

Empfehlungen 3

In welchen Fällen und mit welchen Substanzen sollte eine akute oder eine rezidivierende akute Rhinosinusitis antibiotisch therapiert werden?

Antibiotische Therapie

Allgemeine Empfehlung:	Ergebnis der Abstimmung
Bei einer ARS bzw. einer akuten Exazerbation einer rez. ARS sollten in der Regel keine Antibiotika gegeben werden (starker Konsens, 7/7).	7/7 starker Konsens
1. Eine antibiotische Therapie bei ARS oder einer akuten Exazerbation einer rez. ARS: ■ sollte erwogen werden bei Patienten mit besonderen Risikofaktoren, insbesondere chronisch entzündlicher Lungenerkrankung, Immundefizienz bzw. Immunsuppression oder ■ sollte erfolgen bei Hinweisen auf Komplikationen, wie starke Kopfschmerzen, Gesichtsschwellungen, Lethargie	7/7 starker Konsens
2. Eine antibiotische Therapie kann empfohlen werden bei ARS oder einer akuten Exazerbation einer rez. ARS und starken bzw. sehr starken Schmerzen plus erhöhten Entzündungswerten (CRP über 10 mg/l oder BSG über 10mm/h bei Männern bzw. über 20mm/h bei Frauen).	7/7 starker Konsens
3. Eine antibiotische Therapie kann erwogen werden bei ARS oder einer akuten Exazerbation einer rez. ARS (erhöhte Wahrscheinlichkeit einer bakteriellen Ursache) mit: ■ starken Beschwerden und/oder ■ Verstärkung der Beschwerden im Lauf der Erkrankung, und/oder ■ Fieber > 38,5 °C	7/7 starker Konsens

Empfehlung zur Auswahl des Antibiotikums :	Ergebnis der Abstimmung
Nach Abwägung von Wirkungen und Nebenwirkungen kann bei der ARS oder einer akuten Exazerbation einer rez. ARS mit einer Therapiedauer 5-10 Tage die folgende Antibiotikaauswahl empfohlen werden (Abweichungen von den angegebenen Dosierungen können erforderlich werden: 1. Wahl: Amoxicillin 3 x 500mg/d bzw. Cephalosporin (Cefuroxim 2 x 250mg/d) 2. Wahl: Makrolide z.B. Azithromycin 500mg/d oder Amoxicillin + Clavulansäure oder Doxycyclin oder Co-Trimoxazol (ggf. andere Antibiotika entsprechend regionalen Resistenzmustern)	7/7 starker Konsens

Empfehlungen:	Ergebnis der Abstimmung
■ Bei CRSsNP sollte der längerdauernde Einsatz von Clarithromycin bei Versagen der Standardtherapie erwogen werden. Im Einzelfall kann zur Besserung des Befundes Erythromycin bzw. zur passager begrenzten Besserung der Lebensqualität Roxithromycin eingesetzt werden. Azithromycin sollte nicht angewandt werden.	7/7 starker Konsens
■ Bei CRScNP kann im Falle einer Rezidiv-Polyposis eine längerdauernde Therapie mit Doxycyclin erwogen werden.	7/7 starker Konsens
■ Die Anwendung von Erythromycin, Azithromycin und Roxithromycin kann nicht empfohlen werden bei CRScNP.	7/7 starker Konsens
■ Die topische Anwendung von Antibiotika bei Patienten mit CRS sollte nicht erfolgen.	7/7 starker Konsens

Empfehlungen:	Ergebnis der Abstimmung
■ Bei Versagen einer konservativen Therapie sollte eine operative Therapie erwogen werden (starker Konsens, 6/6)	6/6 starker Konsens
■ Im Einzelfall kann auch eine primäre operative Therapie sinnvoll sein.	5/5 starker Konsens

- Für den Therapiebeginn sollte ein gezielt enges Wirkspektrum gegen die wahrscheinlichsten Erreger gewählt werden [253]. In den oben genannten erfolgreichen Studien bei ARS wurde 3 x 500 mg/d Amoxicillin oder 2-3 x 1330 mg/d Penicillin für 7-10 Tage [95, 216] oder Azithromycin 1x 500 mg/d für 3 Tage [111] verwendet.
- Vergleichende Studien und Metaanalysen zu unterschiedlicher Dosierung, Therapiedauer oder Wirkstoffen erbrachten fast durchgängig eine Gleichwertigkeit aller antibiotischen Substanzen [93, 94, 97, 271, 275, 276]. Auffällig hierbei ist, dass in Deutschland häufig mit vergleichsweise hohen Dosierungen gearbeitet wird.
- Antibiotika führen in einer sorgfältig selektierten Klientel (z.B. Schmerz + Entzündungsparameter) zu einer Verkürzung der durchschnittlichen Krankheitsdauer um mindestens 3 Tage (NNT = 4,5) [98]. In Langzeituntersuchungen der therapeutischen RCT's ließen sich bisher keine günstigen Effekte einer Antibiotikatherapie auf die Rezidivquote oder Komplikationsrate nachweisen [271, 275]. Auch in retrospektiven Studien ergaben sich keine Belege dafür, dass eine antibiotische Behandlung einer ARS schwere Komplikationen oder die Entwicklung einer CRS verhindern kann [102, 103].
- Die Häufigkeit leichterer Nebenwirkungen von Antibiotika (insbesondere Störungen im Magen-Darmtrakt) lag in den meisten neueren Studien um 15-20 % über der von Placebo [98] (+15%) [95] (+20%) [271] (+17%) [267] (+19%)]. Mittelstarke Nebenwirkungen, die einen Therapieabbruch notwendig machten, traten in durchschnittlich 2-3 % der Antibiotikatherapien
- auf [93]. In einem systematischen Review zur Frage des Nutzens einer antibiotischen Therapie konnten keine Belege für Unterschiede zwischen ARS und akut rez. ARS gefunden werden [101]. Entsprechend sollte daher jede Episode einer rez. ARS wie eine ARS behandelt werden.

Empfehlungen 4

In welchen Fällen und mit welchen Substanzen sollte eine chronische Rhinosinusitis antibiotisch therapiert werden?

Empfehlungen:	Ergebnis der Abstimmung
■ Bei CRSsNP sollte der längerdauernde Einsatz von Clarithromycin bei Versagen der Standardtherapie erwogen werden. Im Einzelfall kann zur Besserung des Befundes Erythromycin bzw. zur passager begrenzten Besserung der Lebensqualität Roxithromycin eingesetzt werden. Azithromycin sollte nicht angewandt werden.	7/7 starker Konsens
■ Bei CRScNP kann im Falle einer Rezidiv-Polyposis eine längerdauernde Therapie mit Doxycyclin erwogen werden.	7/7 starker Konsens
■ Die Anwendung von Erythromycin, Azithromycin und Roxithromycin kann nicht empfohlen werden bei CRScNP.	7/7 starker Konsens
■ Die topische Anwendung von Antibiotika bei Patienten mit CRS sollte nicht erfolgen.	7/7 starker Konsens

Systemische Antibiotika:

Erythromycin

Postoperative Einnahme von Erythromycin (250 mg/die) über 3 Monate zeigte im Vergleich zu Placebo allenfalls bei Patienten mit CRSsNP eine Tendenz zur Besserung des endoskopischen Befundes [100].

Azithromycin

Eine prospektive, Placebo-kontrollierte Studie untersuchte die Wirksamkeit von Azithromycin in Patienten mit CRS. Dabei wurde eine inhomogene Patientengruppe (92% voroperiert, 58% mit Revisionsoperation; N=60) rekrutiert [131]. 500 mg Azithromycin für 3 Tage gefolgt von 500 mg/Woche für 11 Wochen zeigte zusätzlich zur NaCl-Nasendusche und topischen Kortikoid keine subjektive Besserung der Lebensqualität, der Symptomatik oder eine erhöhte Nebenwirkungsrate [131], auch nach Analyse unter Cochrane-Standards [99].

Clarithromycin

Die Anwendung von Clarithromycin ist als Antibiotikum bei der CRS bereits relativ weit verbreitet [28]. Für Clarithromycin (500 mg/die für 2 Wochen, danach 250 mg/die für 6 Wochen) zusätzlich zur Anwendung eines topischen Steroids ist eine Verringerung der Häufigkeit von Biofilmen, nicht jedoch der Symptome oder des CT-Befundes bei allerdings geringer eingeschlossener

Patientenanzahl (N=19) nachgewiesen [368]. Die Wirksamkeit auf Biofilme konnte für Patienten mit CRSsNP bestätigt werden (N=32) [347], ein zusätzlicher Nutzen topischer Steroide in dieser Hinsicht aber nicht. Ein Vergleich der Dosis von 250 mg gegenüber 500 mg/die Clarithromycin bei CRSsNP belegte Vorteile für eine höhere Dosis in ihrer klinischen Wirksamkeit [132]. Die Wirksamkeit von Clarithromycin (200 mg/die) ließ sich bei Erwachsenen durch gleichzeitige Einnahme von Carboxymethylcystein (Carbocystein) (1500 mg/die) noch steigern: sowohl die Rate der Ansprecher (64,2 vs. 45,6%), wie auch das Ausmaß der anterioren und posterioren nasalen Sekretion besserte sich mehr, als bei der alleinigen Einnahme von Clarithromycin bei einer großen eingeschlossenen Patientenanzahl (N=425) [130]. Dabei zeigten sich nach 12 Wochen die klinischen Symptome einer Schleimhautrötung bei 67,1% versus 63,6% der behandelten Pati enten gebessert oder geheilt. Auch fur die Symptome Schleimhautschwellung (75,9% versus 66,0%), die Menge des Nasensekrets (72,3% versus 62,7%), die Art des Nasensekret (91,9% versus 86,6%) und das post-nasale Sekret (86,2% versus 70,3%) zeigte sich eine hohere Besserungsrate fur die Kombination von Clarithromycin mit Carboxymethylcystein (Carbocystein).

In chinesischen Patienten zeigte Clarithromycin eine effektive Besserung sowohl bei CRScNP (N=17) als auch CRSsNP (N=33) in einer offenen Anwendungsstudie [128]. Allerdings war die Besserung bei CRSsNP starker ausgeprägt und zwar sowohl im Befinden, als auch in der Besserung des Befundes. In chinesischen Patienten mit CRsNP wurde Mometason im Vergleich zu Clarithromycin untersucht (N=43). Dabei zeigten beide Therapiegruppen einen vergleichbaren therapeutischen Effekt [129]. Im Vergleich von Antibiotika (Clarithromycin) mit topischen Glukokortikoid bei chinesischen Patienten mit CRSsNP zeigte sich eine geringe Überlegenheit des Antibiotikums in endoskopischen Scores, aber nicht der Lebensqualität, Symptomatik oder der Nebenwirkungen bei Auswertung nach Cochrane Standards [99].

Roxithromycin

Ein Cochrane Report untersuchte den Effekt systemischer Antibiotika auf die CRS, schloss aufgrund der Datenqualitat aber nur eine Studie (N=64) ein. Darin wurde Roxithromycin 150 mg/ die Placebo-kontrolliert fur 3 Monate angewendet und bewirkte eine passagere Besserung der Symptomatik, basierend auf dem SNOT-20 Score [133]. Dieser Effekt konnte aber nach 6

Monaten nicht mehr bestätigt werden [137]. Head et al. bestätigen dies bei Auswertung nach Cochrane Standards und verweist auch auf einen gering gebesserten endoskopischen Befund (ausgedruckt als Summenwert) [99].

Doxycyclin

Orales Doxycyclin (eingenommen fur 3 Wochen, an Tag 1 200 mg, danach 100 mg/die) konnte bei Patienten mit CRScNP im Vergleich zu Placebo signifikant die Polypengrose reduzieren [156]. Die Wirkung war ähnlich ausgeprägt im Vergleich zu Glukokortikoiden und war fur die Zeit 2-12 Wochen nach Therapiebeginn nachweisbar. Auch die subjektive Lebensqualität besserte sich. Entsprechend wurde eine längere, 3-monatige Einnahme empfohlen [257]. Seitens des Cochrane Reviews wurde die Studie deutlich kritisiert. So wurden Aussagen zum Effekt auf die krankheitsspezifische Lebensqualität aufgrund der Datenqualität nicht abgeleitet. Eine Haufung von gastrointestinalen Nebenwirkungen konnte für Anwendung von Doxycyclin bei CRScNP [156] nicht nachgewiesen werden.

Topische Antibiotika

Der aktuelle Cochrane Review identifizierte keine Studien zur Auswertung in eine Analyse mit topischer Anwendung von Antibiotika [99]. Dabei liegen durchaus randomisierte Studien vor: Trotz zweier randomisierter Studien [308] liegt derzeit jedoch ungenügende Evidenz vor, um einen positiven Effekt topischer Antibiotika bei CRS zu bestätigen [307]. Dies betrifft sowohl Antibiotika als Zugabe zur Nasenspülung, wie auch solche, die mittels Verneblung (Auswertung von vier Studien [138] appliziert werden, wie z. B. Bacitracin/Colimycin [136, 307]. Fur vernebelte Antibiotika wurden allerdings ein geringes Nebenwirkungspotential berichtet [138]. Die Anwendung von Mupirocin-Nasenspulungen bei Staph. aureus positiver, postoperativer Infektion (N=25) war in 88,9% effektiv in der Eradikation des Staph. aureus (im Vergleich zu 0% bei NaCl-Nasenspülung) [134]. Dieser positive Effekt war aber zeitlich limitiert und 2-6 Monate spater nicht mehr nachweisbar. In einer Kohortenstudie zeigte sich zudem eine Besserung des endoskopischen Befundes bei Staph. aureus positiver CRS [135]. Bei Nachweis einer klinischen Infektion in der postoperativen Phase scheint eine topische Anwendung von Antibiotika als Alternative zur systemischen Gabe möglich. Allerdings ist die Aussagekraft trotz einer großen Kohorte (N=321) eingeschränkt aufgrund der geringen Häufigkeiten von akuten Exazerbationen in der postoperativen Phase [127]. Patienten mit CF (N=27) mit lokalem Nachweis von Staphylokokken oder Pseudomonas profitierten von der Zugabe von Tobramycin zu Hyaluronsaure bei topischer Anwendung fur 14 Tage (randomisierte, doppel-blinde Studie) [119]. Dabei besserten sich der endoskopische Befund und das Befinden durch die Therapie. Zusammenfassend besitzt eine topische antibiotische Therapie einen Stellenwert nur in speziellen Patientengruppen und sollte vornehmlich wissenschaftlich begleitet werden, auch aufgrund des Risikos einer Resistenzentwicklung. Die Indikation ergibt sich bei Versagen der Standardtherapie mit Kortikoiden bzw. relevanten Kontraindikationen dieser.

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Rosenfeld RM et al., 2015 [13].

American Academy of Otolaryngology—Head and Neck Surgery Foundation

Clinical Practice Guideline (Update): Adult Sinusitis

Siehe auch: Rosenfeld RM et al., 2015 [14]

Leitlinienorganisation/Fragestellung

This update of a 2007 guideline from the American Academy of Otolaryngology—Head and Neck Surgery Foundation provides evidence-based recommendations to manage adult rhinosinusitis, defined as symptomatic inflammation of the paranasal sinuses and nasal cavity

The purpose of this multidisciplinary guideline is to identify quality improvement opportunities in managing adult rhinosinusitis and to create explicit and actionable recommendations to implement these opportunities in clinical practice.

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:

- original MEDLINE search was updated from December 2006 to March 2014

LoE

Grade	Treatment	Diagnosis	Prognosis
A	Systematic review[b] of randomized trials	Systematic review[b] of cross-sectional studies with consistently applied reference standard and blinding	Systematic review[b] of inception cohort studies[c]
B	Randomized trials or observational studies with dramatic effects or highly consistent evidence	Cross-sectional studies with consistently applied reference standard and blinding	Inception cohort studies[c]
C	Nonrandomized or historically controlled studies, including case-control and observational studies	Nonconsecutive studies, case-control studies, or studies with poor, nonindependent, or inconsistently applied reference standards	Cohort study, control arm of a randomized trial, case series, or case-control studies; poor quality prognostic cohort study
D	Case reports, mechanism-based reasoning, or reasoning from first principles		
X	Exceptional situations where validating studies cannot be performed and there is a clear preponderance of benefit over harm		

[a]American Academy of Otolaryngology—Head and Neck Surgery Foundation guideline development manual.[32]
[b]A systematic review may be downgraded to level B because of study limitations, heterogeneity, or imprecision.
[c]A group of individuals identified for subsequent study at an early, uniform point in the course of the specified health condition or before the condition develops.

GoR

Table 1. Strength of Action Terms in Guideline Statements and Implied Levels of Obligation.

Strength	Definition	Implied Obligation
Strong Recommendation	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or, in the case of a strong negative recommendation, that the harms clearly exceed the benefits) and that the quality of the supporting evidence is high (Grade A or B).[a] In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation	A recommendation means the benefits exceed the harms (or, in the case of a negative recommendation, that the harms exceed the benefits), but the quality of evidence is not as high (Grade B or C).[a] In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Option	An option means that either the quality of evidence is suspect (Grade D)[a] or that well-done studies (Grade A, B, or C)[a] show little clear advantage to one approach vs another.	Clinicians should be flexible in their decision making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.

Empfehlungen 1

Table 3. Summary of Evidence-Based Statements.

Statement	Action	Strength
1A. Differential diagnosis	Clinicians should distinguish presumed ABRS from ARS caused by viral upper respiratory infections and noninfectious conditions. A clinician should diagnose ABRS when (a) symptoms or signs of ARS (purulent nasal drainage accompanied by nasal obstruction, facial pain-pressure-fullness, or both) *persist without evidence of improvement for at least 10 days* beyond the onset of upper respiratory symptoms, or (b) symptoms or signs of ARS worsen within 10 days after an initial improvement (double worsening).	Strong recommendation
1B. Radiographic imaging and ARS	Clinicians should not obtain radiographic imaging for patients who meet diagnostic criteria for ARS, unless a complication or alternative diagnosis is suspected.	Recommendation (against imaging)
2. Symptomatic relief of VRS	Clinicians may recommend analgesics, topical intranasal steroids, and/or nasal saline irrigation for symptomatic relief of VRS.	Option
3. Symptomatic relief of ABRS	Clinicians may recommend analgesics, topical intranasal steroids, and/or nasal saline irrigation for symptomatic relief of ABRS.	Option
4. Initial management of ABRS	Clinicians should either offer watchful waiting (without antibiotics) or prescribe initial antibiotic therapy for adults with uncomplicated ABRS. Watchful waiting should be offered only when there is assurance of follow-up, such that antibiotic therapy is started if the patient's condition fails to improve by 7 days after ABRS diagnosis or if it worsens at any time.	Recommendation
5. Choice of antibiotic for ABRS	If a decision is made to treat ABRS with an antibiotic agent, the clinician should prescribe amoxicillin with or without clavulanate as first-line therapy for 5 to 10 days for most adults.	Recommendation
6. Treatment failure for ABRS	If the patient worsens or fails to improve with the initial management option by 7 days after diagnosis or worsens during the initial management, the clinician should reassess the patient to confirm ABRS, exclude other causes of illness, and detect complications. If ABRS is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.	Recommendation
7A. Diagnosis of CRS or recurrent ARS	Clinicians should distinguish CRS and recurrent ARS from isolated episodes of ABRS and other causes of sinonasal symptoms.	Recommendation
7B. Objective confirmation of a diagnosis of CRS	The clinician should confirm a clinical diagnosis of CRS with objective documentation of sinonasal inflammation, which may be accomplished using anterior rhinoscopy, nasal endoscopy, or computed tomography.	Strong recommendation
8. Modifying factors	Clinicians should assess the patient with CRS or recurrent ARS for multiple chronic conditions that would modify management, such as asthma, cystic fibrosis, immunocompromised state, and ciliary dyskinesia.	Recommendation
9. Testing for allergy and immune function	The clinician may obtain testing for allergy and immune function in evaluating a patient with CRS or recurrent ARS.	Option
10. CRS with polyps	The clinician should confirm the presence or absence of nasal polyps in a patient with CRS.	Recommendation
11. Topical intranasal therapy for CRS	Clinicians should recommend saline nasal irrigation, topical intranasal corticosteroids, or both for symptom relief of CRS.	Recommendation
12. Antifungal therapy for CRS	Clinicians should not prescribe topical or systemic antifungal therapy for patients with CRS.	Recommendation (against therapy)

Abbreviations: ABRS, acute bacterial rhinosinusitis; ARS, acute rhinosinusitis; CRS, chronic rhinosinusitis; VRS, viral rhinosinusitis.

STATEMENT 2. SYMPTOMATIC RELIEF OF VIRAL RHINOSINUSITIS (VRS): Clinicians may recommend analgesics, topical intranasal steroids, and/or nasal saline irrigation for symptomatic relief of VRS. *Option based on randomized controlled trials with limitations and cohort studies with an unclear balance of benefit and harm that varies by patient*.

Action Statement Profile

- Quality improvement opportunity: To encourage consideration of supportive therapies that may improve quality of life for individuals with VRS and furthermore support the avoidance of unnecessary antibiotics in viral disease
- Aggregate evidence quality: Grade B and C, randomized controlled trials with limitations and cohort studies

- Level of confidence in evidence: Medium
- Benefit: Reduction of symptoms; avoidance of unnecessary antibiotics
- Risks, harms, costs: Adverse effects of decongestants, antihistamines, topical steroid sprays; cost of medications
- Benefits-harm assessment: Balance of benefit and harm
- Value judgments: A desire to call attention to VRS as a subset of the "common cold," yet distinct from ABRS, that may benefit from explicit diagnosis and discussion of management options for symptomatic relief
- Intentional vagueness: The specific "symptomatic relief" is at the discretion of the clinician and patient but should not include antibiotics
- Role of patient preferences: Large role in selection and use of therapies for symptomatic relief based on shared decision making
- Exceptions: None
- Policy level: Option
- Differences of opinion: Minor regarding the need to explicitly discuss VRS in a distinct key action statement

Supporting Text

The purpose of this statement is to encourage consideration of supportive therapies that may improve quality of life for individuals with viral rhinosinusitis (VRS) and to avoid unnecessary prescribing of antibiotics for viral disease. VRS is a self-limited disease characterized by cough, sneezing, rhinorrhea, sore throat, and nasal congestion.[67] The incidence of acute VRS is high, estimated to occur from 2 to 5 times per year in the average adult. In contrast, secondary bacterial infection is believed to complicate only 0.5% to 2.0% of these events.[19] While the presentation of viral vs bacterial infection can be very similar, clinical emphasis on duration, illness pattern, and severity of symptoms can help to differentiate between viral vs bacterial infection. Symptoms in acute VRS typically peak within 3 days then gradually decline and resolve within 10 to 14 days. Nasal purulence alone does not indicate a bacterial infection; discolored nasal discharge is a sign of inflammation and is not specific for infection. Coloration of nasal discharge is related to the presence of neutrophils not bacteria.[49,81-83] Normal transport of mucus requires robust ciliary action. VRS promotes a vigorous inflammatory response, causing epithelial disruption, edema, and excessive mucus production, which further impairs normal ciliary function.[84] Management of VRS is primarily directed toward relief of symptoms. Antibiotics are not recommended for treating VRS since antibiotics are ineffective for viral illness and do not provide direct symptom relief.[85] Therefore, palliative medications—such as analgesics, anti-inflammatory agents, nasal saline, decongestants, antihistamines, mucolytics, cough suppressants, and topical or oral corticosteroids—may be used alone or in varying combinations for symptom relief.[16] Analgesics or antipyretic drugs (acetaminophen, ibuprofen, or other nonsteroidal anti-inflammatory agents) may be given for pain or fever. Nasal saline may be palliative and cleansing with low risk of adverse reactions.[15] A Cochrane review[86] reported minor improvements in nasal symptom scores with the use of nasal saline in both physiologic and hypertonic concentrations.

Oral decongestants may provide symptomatic relief and should be considered barring any medical contraindications, such as hypertension or anxiety. The use of topical decongestant is likely to be palliative, but continuous duration of use should not exceed 3 to 5 days, as recommended by the manufacturers, to avoid rebound congestion and rhinitis medicamentosa.[87] Clinical experience suggests oral antihistamines may provide symptomatic relief of excessive secretions and sneezing, although there are no clinical studies supporting the use of antihistamines in acute VRS. Guaifenesin (an expectorant) and dextromethorphan (a cough suppressant) are often used for symptomatic relief of VRS symptoms, but evidence of clinical efficacy is lacking and decisions regarding their use are largely related to patient and provider preference.

Topical intranasal steroids may have a role in managing VRS, even though they do not have a Food and Drug Administration (FDA) indication for this purpose. A systematic review[88] found that topical nasal steroids relieved facial pain and nasal congestion in patients with rhinitis and acute sinusitis, even though many patients likely had viral illness. The magnitude of effect, however, was small: 66% of patients improved with placebo at 14 to 21 days, rising to 73% with steroid therapy. Adverse events, however, were rare, so the choice of whether or not the modest clinical benefit of therapy justifies the cost is a decision that should be based largely on patient preference.

STATEMENT 3. SYMPTOMATIC RELIEF OF ACUTE BACTERIAL RHINOSINUSITIS (ABRS): Clinicians may recommend analgesics, topical intranasal steroids, and/or nasal saline irrigation for symptomatic relief of ABRS. Option based on randomized controlled trials with heterogeneous populations, diagnostic criteria, and outcome measures with a balance of benefit and harm.

Action Statement Profile

- Quality improvement opportunity: Promote interventions that may relieve ABRS symptoms (analgesics, saline irrigation, topical intranasal steroids) and discourage interventions with questionable or unproven efficacy (antihistamines, systemic steroids, guaifenesin)
- Aggregate evidence quality: Grade A, systematic review of RCTs for topical nasal steroids; Grade B, randomized controlled trials with heterogeneous populations, diagnostic criteria, and outcomes measures for saline irrigation and systemic steroids; grade D, first principles, for analgesics, decongestants, antihistamines (in non-atopic patients) and guaifenesin.
- Level of confidence in evidence: Medium
- Benefit: Relief of facial pain with analgesics, modest increase in symptom relief from topical nasal steroids (number needed to treat 14), and possible symptom relief from saline irrigations; avoidance of adverse events from ineffective therapies
- Risks, harms, costs: Side effects of medications, which include local and systemic adverse reactions; cost of medications
- Benefits-harm assessment: Balance of benefit and harm
- Value judgments: Provide symptomatic relief while minimizing adverse events and costs
- Intentional vagueness: We use the broad term symptomatic relief to acknowledge there are several interventions available for this purpose and to encourage a conversation between clinicians and patients about which specific intervention(s) may be best for their specific ABRS symptoms
- Role of patient preferences: Large role for shared decision making regarding use of analgesics, topical nasal steroids, and saline irrigation
- Exceptions: None
- Policy level: Option
- Differences of opinion: None

Supporting Text

The purpose of this statement is to raise awareness of interventions that may be used to provide symptomatic relief of ABRS (analgesics, saline irrigation, topical nasal steroids), to discourage use of interventions with questionable or unproven efficacy (antihistamines, systemic steroids), and to provide information on commonly used interventions (decongestants, guaifenesin) with unknown effects on ABRS symptoms. Adjunctive treatments for rhinosinusitis that may aid in symptomatic relief include analgesics, decongestants (α-adrenergic), corticosteroids, saline irrigation, and mucolytics. None of these products has been specifically approved by the FDA for use in acute rhinosinusitis (as of March 2014), and only some have data from controlled clinical studies supporting this use. Moreover, existing trials often include cointerventions and a heterogeneous population of patients with viral, recurrent bacterial, chronic, and allergic rhinosinusitis. Nonetheless, clinicians may wish to consider adjuvant therapy for ABRS on an individualized basis, and we therefore provide a brief overview of evidence in the remainder of this section.

Analgesic Therapy

Pain relief is a major goal in managing ABRS and often a reason that patients with this condition seek health care.52,53 Facial pain is a cardinal symptom for diagnosing ABRS (**Table 4**) and may involve the anterior face, periorbital region, or manifest with diffuse or localized headache. Over-the-counter analgesics, such as nonsteroidal anti-inflammatory drugs or acetaminophen, are usually sufficient to relieve facial pain associated with ABRS. Narcotics are rarely necessary and should be discouraged because of potential adverse events.

Topical and Oral Steroids

Topical nasal steroids have been used alone or in combination with oral antibiotics for symptomatic relief of ABRS. Prescription drugs studied in these trials include mometasone, 89-91 fluticasone,92 flunisolide,93 and budesonide.94 An over-the-counter intranasal steroid, triamcinolone acetonide, is also available but has not been studied explicitly for ABRS.

A Cochrane review,95 which included 4 RCTs of topical intranasal steroid vs placebo or no intervention as monotherapy for ABRS, found that steroids increased the rate of symptom improvement from 66% to 73% after 15 to 21 days (risk ratio, 1.10; 95% CI, 1.02-1.18). The studies had low risk of bias, and only minor adverse events were reported, which included epistaxis, headache, and nasal itching. The authors concluded that clinicians should weigh the modest (number needed to treat of 14) but clinically important benefits of intranasal steroid therapy against the associated cost and minor adverse events. Although intranasal steroid therapy has been used as an adjunct to oral antibiotic therapy for managing ABRS, the results may not

apply to patients with sporadic ABRS as defined in this guideline. Dolor and colleagues92 increased the rate of treatment success for ABRS at 3 weeks from 74% to 93% when adding fluticasone nasal spray to oral cefuroxime, but all the patients studied had a history of CRS or recurrent ARS. Conversely, Williamson and colleagues94 studied patients with nonrecurrent ARS and found no benefits for amoxicillin alone, or with topical budesonide, over placebo. This study, however, may have included many patients with VRS, because most patients had symptoms for less than 10 days (median of 7 days) and would not meet our diagnostic criteria for ABRS (**Table 4**).

A Cochrane review96 of systemic steroids for ABRS found no benefit over placebo when oral steroids were used as monotherapy. Limited data from 5 trials were found to suggest that oral steroids used in combination with antibiotics may have a modest short-term beneficial effect for symptom relief (number needed to treat of 7), but confidence in results was limited by a significant risk of attrition bias caused by missing outcomes. Adverse events were mild (nausea, vomiting, gastric complaints), but the authors conclude that additional research is needed for adequate confidence in the true effect of systemic steroids.

Saline Irrigation, Decongestants, Antihistamines, and Guaifenesin

Nasal saline irrigation, alone or in conjunction with other adjunctive measures, may improve quality of life, decrease symptoms, and decrease medication use for ABRS, particularly in patients with frequent sinusitis. Buffered hypertonic (3%-5%) saline irrigation showed a modest benefit for ARS in 2 clinical trials.97,98 Compared with isotonic saline, hypertonicsaline may have a superior anti-inflammatory effect and better ability to thin mucous and transiently improve mucociliary clearance.99-101 One randomized controlled trial of patients with the common cold and ARS, however, found no difference in outcomes for hypertonic saline, normal saline, or observation.102 There are no systematic reviews assessing the use of nasal saline irrigation in ABRS in adults.

Topical and systemic decongestants (sympathomimetics)

have been used to treat nasal congestion associated with the common cold for many years.103-107 There are no RCTs that specifically study the efficacy of decongestants for ABRS, but 2 small studies have shown that xylometazoline nasal spray reduces congestion of sinus and nasal mucosa on imaging studies65,108 and is superior to a single orally administered dose of pseudoephedrine.108 Another small, nonrandomized study showed improved outcomes when xylometazoline spray was added to antibiotics for ABRS.97 Topical decongestants should not be used more than 3 to 5 consecutive days without a prolonged intervening drug-free period due to their propensity to cause rebound congestion and rhinitis medicamentosa.87 Antihistamines have no role in the symptomatic relief of ABRS in nonatopic patients.47,59,109 No studies support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa. Conversely, 1 randomized controlled trial in allergic patients with ABRS showed reduced sneezing and nasal congestion for loratadine vs placebo when used as an adjunct to antibiotics and oral corticosteroids.110 Antihistamine therapy, therefore, can be considered for patients with ABRS whose symptoms support a significant allergic component. In this regard, second-generation H1-antagonists cause less sedation and anticholinergic side effects than do older first-generation H1-antagonists.111 Guaifenesin is a water- and alcohol-soluble agent that is used as an expectorant to loosen phlegm and bronchial secretions. The product is available over the counter and is sometimes recommended to “loosen” nasal discharge, but there is no evidence regarding the effect, if any, on symptomatic relief of ABRS.

STATEMENT 4. INITIAL MANAGEMENT OF ACUTE BACTERIAL RHINOSINUSITIS (ABRS): Clinicians should either offer watchful waiting (without antibiotics) or prescribe initial antibiotic therapy for adults with uncomplicated ABRS. Watchful waiting should be offered only when there is assurance of follow-up, such that antibiotic therapy is started if the patient’s condition fails to improve by 7 days after ABRS diagnosis or if it worsens at any time. *Recommendation based on systematic reviews of double-blind randomized controlled trials with some heterogeneity in diagnostic criteria and illness severity and a relative balance of benefit and risk.*

Action Statement Profile

- Quality improvement opportunity: Make explicit to clinicians and patients that not prescribing antibiotics for clinically diagnosed ABRS is an appropriate initial management strategy, because many patients will improve spontaneously and antibiotics could be started later if follow-up was assured.
- Level of confidence in evidence: Medium
- Aggregate evidence quality: Grade A, multiple systematic reviews of randomized controlled trials with some heterogeneity in diagnostic criteria and illness severity
- Benefit: Promote more informed, shared decision making regarding whether or not to prescribe initial antibiotics for ABRS given the favorable natural history in placebo groups, the small to modest benefits of antibiotic therapy, and the higher rates of adverse events when antibiotics are prescribed; more selective initial use of antibiotics will reduce adverse events and the risk of bacterial resistance

- Risks, harms, costs: Antibiotics could be withheld from patients who would have derived benefit from their use; antibiotics could be prescribed to patients who would have improved equally on their own.
- Benefits-harm assessment: Preponderance of benefit over harm (regarding the decision for initial management)
- Value judgments: Perception by the GUG that watchful waiting, without antibiotics, is an underused strategy for initial management of uncomplicated ABRS, despite existing guidelines and systematic reviews that support this approach.
- Intentional vagueness: No restrictions have been stated for illness severity (eg, mild, moderate, or severe), which was done in the prior guideline, because insufficient evidence to determine that severity would affect outcomes of antibiotic therapy, including the potential for complications.
- Role of patient preferences: Large role for shared decision making
- Exceptions: Complicated sinusitis, immune deficiency, or coexisting bacterial illness; the clinician should also consider the patient's age, general health, cardiopulmonary status, and comorbid conditions when assessing suitability for watchful waiting.
- Policy level: Recommendation
- Differences of opinion: No difference of opinion regarding the choice to initially observe or prescribe antibiotics (one abstention); minor difference of opinion (1 against, 9 in favor) regarding the decision to remove severity (eg, mild illness) as a criterion for watchful waiting

Supporting Text

The purpose of this statement is to emphasize that both watchful waiting and antibiotic therapy are appropriate, evidencebased strategies for the initial management of uncomplicated ABRS. The precursor to this guideline1 endorsed watchful waiting without an antibiotic as an option for initial management, even when ABRS signs and symptoms had persisted for 10 days or longer. More recent evidence, however, allows elevating watchful waiting to the status of a recommendation (not just an option). Moreover, whereas the prior guideline restricted watchful waiting to patients with only "mild" ABRS, current evidence supports offering this to patients regardless of illness severity. Watchful waiting for ABRS refers to deferring antibiotic treatment of selected patients for up to 7 days after diagnosis of ABRS and limiting management to symptomatic relief. Patients are candidates for watchful waiting when follow-up is ensured and a system is in place that permits reevaluation if the illness persists or worsens. Antibiotics are started if the patient's condition fails to improve by 7 days following ABRS diagnosis or worsens at any time.

Outcomes of Placebo vs Antibiotic Therapy

Four systematic reviews of RCTs, all published since the prior version of this guideline,1 have addressed the performance of antibiotics compared with placebo for the management of ABRS.112-115 All of the analyses included RCTs that diagnosed patients on clinical signs and symptoms only. Some of the included RCTs also used radiology, serology, or microbiology studies to confirm the diagnosis. Collectively, the systematic review findings can be summarized as follows:

- Cure or improvement rates at 7 to 15 days favoured antibiotics but the clinical benefit was small: 91% for antibiotic therapy vs 86% for patients who received placebo. The number needed to treat for benefit ranged from 11 to 15 patients and odds ratios for overall treatment effect ranged from 1.25 to 1.87.
- Duration of pain or illness associated with ABRS did not show any consistent relationship to initial management.113
- Adverse events were more common in the antibiotictreated patients (odds ratio, 1.87 to 2.10; number needed to harm, 8.1), but the rate of dropout due to adverse events was small (1%-1.5%) and similar between both groups.
- Complications were similar regardless of initial management.

While the RCTs that comprised these meta-analyses typically excluded from randomization patients with "severe" disease, they did not specifically or consistently define what was meant by this term. As a result, there is no evidence supporting or refuting the stance that patients with more severe ABRS should always be treated with initial antibiotics. One study found ARS patients with pharyngeal purulence to be more likely to benefit from antibiotics.114 Unfortunately, the literature is otherwise lacking on which patients may benefit more or less from antibiotic therapy. Further, there is no conclusive evidence that increased age or allergic rhinitis predicts a prolonged or chronic course of ABRS116,117 or any evidence that older patients benefit more from antibiotic therapy.114 This guideline differs from its previous version1 in no longer restricting watchful waiting to patients with mild to moderate ABRS because evidence is lacking to support additional benefits of antibiotic therapy for more severe presentations. This approach also differs from other guidelines and consensus statements that recommend antibiotics for patients with severe ABRS, manifesting as high fever and severe or worsening facial pain.15,19,69 Shared Decision Making with Patients Clinicians deciding whether or not to treat ABRS with antibiotics

should also solicit and consider patient preference and determine the relevance of existing evidence to their specific practice setting and patient population. Some patients may place great value on avoiding antibiotic therapy, whenever possible, but others may request initial antibiotics because they value the small but significant increase in clinical improvement they provide. Regardless of which initial strategy is used, clinicians should provide patients with clear information on management options, including symptomatic relief (Table 6). Clinicians may also find it helpful to evaluate the patient's preexisting knowledge and attitudes about antibiotic therapy and ABRS, because they could affect treatment preference.

Some patients will fail a period of watchful waiting and will benefit from antibiotics. To avoid the expense and inconvenience of another office visit in these patients, the clinician way wish to use a WASP (wait-and-see antibiotic prescription) or a SNAP (safety net antibiotic prescription). Such a prescription, with instructions on when to fill, can provide a sense of security for the patient who agrees to initial watchful waiting and is concerned about accessing the clinician to obtain an antibiotic prescription, if necessary. Patients are informed that they should fill the prescription and begin antibiotic therapy if they fail to improve within 7 days or if they worsen at any time. They should also call the physician's office and let them know they have begun antibiotic therapy.

STATEMENT 5. CHOICE OF ANTIBIOTIC FOR ACUTE BACTERIAL RHINOSINUSITIS (ABRS): If a decision is made to treat ABRS with an antibiotic agent, the clinician should prescribe amoxicillin with or without clavulanate as first-line therapy for 5 to 10 days for most adults. *Recommendation based on randomized controlled trials with heterogeneity and noninferiority design with a preponderance of benefit over harm.*

Action Statement Profile

- Quality improvement opportunity: Discourage initial prescribing of antibiotics other than amoxicillin, with or without clavulanate, that may have lower efficacy or have comparable efficacy but more adverse events.
- Aggregate evidence quality: Grade A, systematic reviews of randomized controlled trials with heterogeneity and noninferiority design
- Level of confidence in evidence: Moderate regarding choice of antibiotic but lower regarding the optimal duration of antibiotic therapy because of limited supporting evidence and statistical power
- Benefit: Clinical outcomes that are comparable to broader spectrum antibiotics for initial therapy; potential reduced bacterial resistance by using a narrow-spectrum antibiotic as first-line therapy; cost-effectiveness of amoxicillin vs other antibiotic choices
- Risks, harms, costs: Potential increased gastrointestinal adverse effects with amoxicillin-clavulanate compared with other antibiotics; adverse effects from penicillin allergy Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: Promote safe and cost-effective initial therapy
- Intentional vagueness: Whether to prescribe amoxicillin or amoxicillin-clavulanate is at the discretion of the clinician, as is the duration of therapy because systematic review has not shown consistent benefits for 10 days of therapy compared with shorter courses. A longer course of therapy may be appropriate for more severe illness or when symptoms persist despite a shorter course.
- Role of patient preferences: Moderate role for shared decision making; large role in determining duration of antibiotic therapy since adverse events are reduced with shorter duration of therapy.
- Exceptions: Patients with penicillin allergy for whom amoxicillin is contraindicated
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this statement is to promote prescribing of antibiotics with known efficacy and safety for ABRS and to reduce prescribing of antibiotics with potentially inferior efficacy because of more limited coverage of the usual pathogens that cause ABRS in adults. A secondary goal is to promote cost-effective antibiotic therapy of ABRS. The rationale for antibiotic therapy of

ABRS is to eradicate bacterial infection from the sinuses, hasten resolution of symptoms, and enhance disease-specific quality of life. Antibiotic therapy should be efficacious, cost-effective, and result in minimal side effects. Dozens of RCTs have assessed the comparative clinical efficacy of antibiotics for ABRS in adults,112 with many trials either funded by pharmaceuticalcompanies or conducted by authors associated with the pharmaceutical industry.48

Choice of Initial Antibiotic for ABRS

No significant differences have been found in clinical outcomes for ABRS among different antibiotic agents. A systematic review112 and 2 RCTs118,119 of sinusitis patients with radiologic or bacteriologic confirmation found no significant difference in rates of clinical resolution for patients treated with amoxicillin or amoxicillin-clavulanate compared with cephalosporins or macrolides. Another review48 found no differences in 11 comparative meta-analyses but did find a small decrease in failure rates for amoxicillin-clavulanate vs cephalosporins (number needed to treat of 30). The justification for amoxicillin as first-line therapy for most patients with ABRS relates to its safety, efficacy, low cost, and narrow microbiologic spectrum.5,11,112,120-122 Consideration to prescribing amoxicillin-clavulanate for adults with ABRS is given to those at a high risk of being infected by an organism resistant to amoxicillin. Factors that would prompt clinicians to consider prescribing amoxicillin-clavulanate instead of amoxicillin are listed in Table 7.123,124

The use of high-dose amoxicillin with clavulanate (2 g orally twice daily or 90 mg/kg/d orally twice daily) is recommended15 for adults with ABRS who are at a high risk of being infected with an amoxicillin-resistant organism. High-dose amoxicillin is preferred over standard-dose amoxicillin primarily to cover penicillin nonsusceptible (PNS) Streptococcus pneumoniae. This risk exists in those from geographic regions with high endemic rates (>10%) of invasive PNS S pneumoniae, those with severe infection (eg, evidence of systemic toxicity with temperature of 39°C [102°F] or higher, and threat of suppurative complications), age >65 years, recent hospitalization, antibiotic use within the past month, or those who are immunocompromised.125

Penicillin-Allergic Patients

For penicillin-allergic patients, either doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended as an alternative agent for empiric antimicrobial therapy. Fluoroquinolones, however, are not recommended for first-line therapy of ABRS in patients without penicillin allergy because outcomes are comparable to amoxicillinclavulanate, and adverse events are higher in some trials.126 Combination therapy with clindamycin plus a third-generation oral cephalosporin (cefixime or cefpodoxime) is recommended in adults with a history of non–type I hypersensitivity to penicillin. Macrolide antibiotics and trimethoprim-sulfamethoxazole are not recommended for initial therapy of ABRS. The high prevalence of macrolide-resistant S pneumoniae in the United States (>40%)124 and the high rates of resistance to trimethoprimsulfamethoxazole among both S pneumoniae (50%) and Haemophilus influenzae (27%) may result in treatment failures, 127 but this concern has not been substantiated by comparisons in RCTs.

Duration of Therapy and Adverse Events

Most trials of ABRS administer antibiotic for 10 days. A systematic review of 12 randomized controlled trials with radiologically confirmed ABRS found no difference in clinical success for antibiotics given for 3 to 7 days vs a 6- to 10-day course of therapy.128 Similar findings have been noted in other trials, with similar resolution rates up to 3 weeks after treatment regardless of therapy duration.48,129-131 When 5 days of antibiotic therapy is compared with 10 days, similar success rates are again observed.128 Adverse events are common with antibiotic therapy, but the diverse reporting among studies precludes meaningful comparisons of rates across different antibiotic classes.48 An average event rate of 15% to 40% is observed, with the most frequent complaints being nausea, vomiting, diarrhea, abdominal pain, headache, skin rash, photosensitivity, and vaginal moniliasis. Adverse events rarely are of sufficient severity to cause a change in therapy, but the impact of antibiotics on bacterial resistance must also be considered. Adverse events are more common with antibiotic therapy ompared with watchful waiting and are more common with 10 days of therapy compared to shorter courses. Antibiotic therapy increases adverse event rate by, on average, 10% to 12% over placebo,112,113 with an odds ratio of 1.8 to 2.1.113,115 Conversely, the incidence of adverse events is lower when antibiotics are given for 5 days instead of 10 days (odds ratio, 0.79),128 so short courses should be considered for patients with less severe illness.

Bacteriology of ABRS

The most common bacterial species isolated from the maxillary sinuses of patients with initial episodes of ABRS are S pneumoniae, H influenzae, and Moraxella catarrhalis,5,132 the latter being more common in children. A review of sinus aspiration studies performed in adults with ABRS suggests that S pneumoniae is isolated in approximately 20% to 43% of aspirates, H influenzae in 22% to 35%, M catarrhalis in 2% to 10%, and Staphylococcus aureus in 10%.66,133-136 Resistance patterns must be considered when prescribing antibiotics for ABRS to avoid using an antibiotic that may be rendered ineffective by bacterial resistance. For example, β-lactamase producing H influenzae has a prevalence of 27% to 43% in the United States137 and would not be expected to respond to amoxicillin unless clavulanate was added. Similarly, the prevalence of penicillin-resistant S pneumonia varies geographically, being highest in the Southeast (about 25%) and lowest in the Northwest (about 9%). Last, S aureus, which is found in up to 10% of cases of ABRS, nearly always produces β-lactamase,136,138 making it resistant to amoxicillin but not amoxicillin-clavulanate.

The bacteriology of ABRS has changed since immunization of children with pneumococcal conjugate vaccine (PCV) was introduced in 2000. When patients with ABRS underwent middle meatal culture, the recovery of S pneumoniae decreased (35% postvaccination vs 46% prevaccination), but recovery of H influenza increased (36% prevaccination vs 43% postvaccination).123 In addition to a shift in organism prevalence, PCV has decreased the prevalence of invasive pneumoniae isolates that are penicillin resistant to about 8% to 11%.127,138,139 The introduction of the 13-valent PCV in 2010 may further decrease the prevalence of invasive pneumococcal infections,140 making it easier to manage pneumococcus as an ABRS pathogen.

STATEMENT 11. TOPICAL INTRANASAL THERAPY FOR CHRONIC RHINOSINUSITIS (CRS): Clinicians should recommend saline nasal irrigation, topical intranasal corticosteroids, or both for symptom relief of CRS. *Recommendation based on a preponderance of benefit over harm.*

Action Statement Profile

- Quality improvement opportunity: Address underutilization; promote awareness of efficacy; reduce confusion over delivery method, frequency, and duration; educate patients on optimal administration
- Aggregate evidence quality: Grade A, systematic reviews of RCTs
- Level of confidence in evidence: High
- Benefit: Symptomatic relief, promoting awareness of effective over-the-counter interventions, discouraging improper and ineffective usage, and avoiding adverse events from systemic therapies
- Risks, harms, costs: Intranasal discomfort, burning, stinging; epistaxis; direct costs of saline or steroid
- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: None
- Intentional vagueness: The choice of saline, steroid, or both is a shared decision; it is not clear how long the treatment should last as the natural history is unknown
- Role of patient preferences: Large role for deciding which products to use and their duration
- Exceptions: None
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this statement is to highlight the importance of intranasal saline and intranasal corticosteroid therapy in providing symptomatic relief and improved quality of life for patients with CRS. Despite the benefits of these interventions seen in RCTs and systematic reviews, the GUG felt they were underused by clinicians managing patients with CRS.

Saline Irrigation for CRS

The beneficial effects of saline in improving symptoms and quality of life include improvement in mucous clearance, enhanced ciliary activity, disruption and removal of antigens, biofilms and inflammatory mediators, and direct protection of the sinonasal mucosa. Nasal saline irrigation has been recommended by clinicians both as adjunctive therapy for chronic sinonasal symptoms and in the postoperative period to moisten and cleanse sinonasal clots and crust, as well as to promote mucosal healing. A beneficial effect of nasal irrigation for symptomatic relief of CRS has been shown in a Cochrane review264 and in other systematic reviews.258,265 Nasal saline irrigation is effective as sole treatment for CRS or as an adjunct to topical nasal steroids, but compared directly with topical nasal steroids, the benefits of saline irrigation are less pronounced.264 The safety and minimal side effects of saline irrigation, however, make it an attractive sole therapy for CRS. Common side effects of nasal irrigation include fluid dripping from the nose. Clinicians should not confuse saline spray with saline irrigation, because irrigation is more effective in expelling secretions and improving quality of life.265,266 Irrigation can be performed with isotonic or hypertonic nasal solution, but evidence is insufficient to support superiority of either approach.265 In addition, the optimal frequency or method of irrigation is uncertain.264 This uncertainty, combined with the time commitment required for regular saline irrigation, may explain underuse despite well-established efficacy in relieving CRS symptoms.

Availability of delivery devices and ready-made saline solutions over the counter may make it easier for the patients to perform nasal irrigation. Commercially available preparations, however, are expensive compared with homemade solutions. Costs of nasal irrigation vary but are generally low, especially when patients are instructed to make their own solution.267 Recipes for preparation of homemade solutions and delivery methods vary widely (pot, pulsatile irrigation, atomizer, bulb/syringe, squeeze bottle, and low-pressure irrigation [Neti pot]).

Topical Intranasal Steroids

Inflammation is considered the pathological basis for CRS, and therefore corticosteroids are widely recommended.268 Corticosteroids are effective as anti-inflammatory agents due to their actions on reducing proinflammatory and increasing anti-inflammatory gene transcription, reducing airway inflammatory cell infiltration, and suppressing proinflammatory mediators, cell chemotactic factors, and adhesion molecules.269 The efficacy of topical steroid therapy for reducing symptoms of CRS is supported by systematic reviews of randomized controlled trials from Cochrane authors270 and others256-258,271 that show benefits with excellent safety and minimal adverse events. In some reviews, however, subgroup analyses show benefits of topical steroids for CRS with polyps but absent or unknown efficacy for CRS without associated polyps.256,258 Classes of topical steroids include first-generation intranasal steroids such as beclomethasone dipropionate, triamcinolone acetonide, flunisolide, and budesonide and newer preparations, such as fluticasone propionate, mometasone furoate, ciclesonide and fluticasone furoate. Topical nasal steroids are most effective when properly administered. Since patients may not be familiar with the optimal method for using the medication, we recommend that clinicians describe or demonstrate how to properly administer a nasal steroid. Patient-friendly instructions are summarized in Table 10 and may assist in this educational process. Adverse events of topical nasal steroids are generally minor (epistaxis, headache, and nasal itching), but when steroids are used for long-term control of CRS, additional concerns arise regarding systemic absorption and ocular effects. Long-term use, however, has not been shown

to affect systemic cortisol levels273 or to increase the risk of lens opacity, elevated intraocular pressure, or any other ocular symptoms.274 Patients on long-term topical nasal steroids should consult their physicians to determine if regular ophthalmic monitoring is appropriate. The GUG agreed, based on expert consensus, that topical nasal steroids should be used for a least 8 to 12 weeks because of the time needed for symptomatic relief and to assess benefit to the patient. Moreover, there was strong agreement that patients may not know how to best deliver steroid to the nasal cavity and should therefore be given simple instructions on how to use the medication. The GUG felt that no statement can be made regarding a specific length of treatment and that decisions should be individualized based on the degree of symptom relief, patient preference, and clinician experience.

Referenzen aus Leitlinien
Siehe Guideline

Orlandi R et al., 2016 [8].

International Consensus Statement on Allergy and Rhinology: Rhinosinusitis Executive Summary

Siehe auch: Orlandi R et al., 2016 [7].

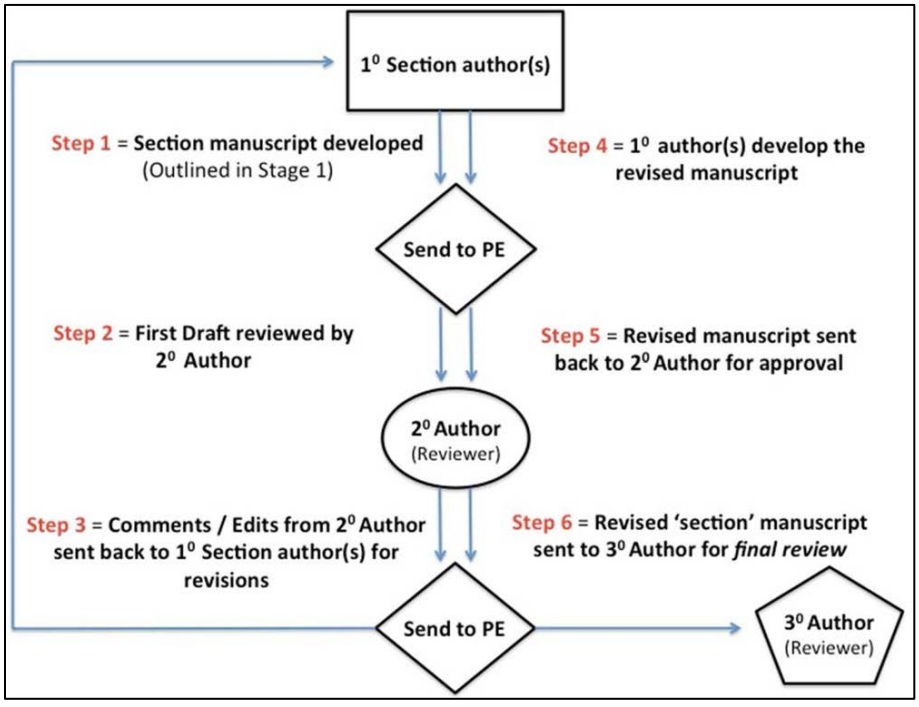
Leitlinienorganisation/Fragestellung

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.

Empfehlungen

Evidence-Based Rhinosinusitis Management Recommendations – ARS

TABLE III-2. Summary of recommendations for ARS management

Intervention	LOE	Benefit	Harm	Cost	Benefit-harm assessment	Policy level
Antibiotics (whether to prescribe)	A	Potential for shorter duration of symptoms; reduced pathogen carriage	GI complaints greater than observed in placebo for both drugs, more pronounced for amoxicillin-clavulanate. Potential for resistance and for anaphylaxis	Low to moderate	Benefit of treatment over placebo is small	Antibiotic use in suspected ABRS: Option
Antibiotics (choosing amoxicillin or amoxicillin-clavulanate)	B	Potential for shorter duration of symptoms; reduced pathogen carriage	GI complaints greater than observed in placebo for both drugs, more pronounced for amoxicillin-clavulanate. Potential for resistance and for anaphylaxis	Low to moderate	Benefit of treatment over placebo is small	If an antibiotic is chosen, amoxicillin-clavulanate vs amoxicillin: Option
Corticosteroids (nasal [INCS] and systemic)	A	INCS improved patient symptoms as monotherapy or adjuvant to antibiotics in severe cases, and hastened recovery; Systemic minimal benefit	Minimal harm with rare mild adverse event	Low	Benefit of treatment over placebo small, but tangible; minimal harm with INCS, greater risk for prolonged systemic corticosteroids	Use of INCS: Strong recommendation. Use of systemic corticosteroid: No recommendation
Decongestants	N/A					Insufficient evidence for a recommendation
Antihistamines	N/A					Insufficient evidence for a recommendation
Nasal saline irrigation	A	Possible nasal symptom improvement. Improved saccharin transit times	Occasional patient discomfort	Minimal	Benefit likely to outweigh harm	Option

ABRS = acute bacterial rhinosinusitis; GI = gastrointestinal; INCS = intranasal corticosteroids; LOE = level of evidence; N/A = not applicable.

Antibiotics: *Although antibiotics have traditionally been prescribed for acute bacterial RS, this practice has recently been questioned. There is substantial evidence that ARS has a high spontaneous resolution rate and the adverse events and costs from adding antibiotics may outweigh any potential benefits. Four recent systematic reviews of randomized controlled trials (RCTs) found that antibiotics conferred a benefit but it was small, improving cure rates at 7 to 15 days from 86% with placebo to 91% with antibiotics.*

- Aggregate Grade of Evidence: A for choosing whether to prescribe antibiotics (Level 1a: 4 studies) B for amoxicillin vs amoxicillin-clavulanate (Level 1b: 2 studies; Level 2b: 2 studies; Level 4: 3 studies).
- Benefit: Potential for shorter duration of symptoms; reduced pathogen carriage.
- Harm: Gastrointestinal (GI) complaints greater than observed in placebo for both drugs, more pronounced for amoxicillin-clavulanate. Potential for resistance and for anaphylaxis.
- Cost: Low to moderate.
- Benefits-Harm Assessment: Benefit of treatment over placebo is small.
- Value Judgments: Improvement in patient symptoms is limited with risk of adverse events. Patient preference may be strong and education regarding benefit-harm balance may be necessary.

- Policy Level: Antibiotic use in suspected ABRS: Option. If an antibiotic is chosen, amoxicillinclavulanate vs amoxicillin: Option.
- Intervention: Withholding antibiotics with close follow-up is an option in suspected ABRS. If an antibiotic is chosen, both amoxicillin and amoxicillin-clavulanate are options for treatment of uncomplicated ARS. Consider amoxicillinclavulanate for potentially complicated infection or when resistant organisms are suspected.

Intranasal Corticosteroids and Systemic Corticosteroids: *With infrequent adverse events and limited systemic uptake, intranasal corticosteroid (INCS) use in ARS is a recommendation with grade A aggregate quality of evidence. Additional studies comparing ideal INCS formulation, dose, and timing will provide important insight into tailoring INCS treatment in ARS. Studies that have looked at systemic corticosteroid therapy in ARS have used heterogeneous methods and had varying results. Given the lack of clear benefit and substantial risk of harm, systemic corticosteroids in cases of uncomplicated ARS are not recommended, with a grade B aggregate quality of evidence*

- Aggregate Grade of Evidence: A (Level 1a: 7 studies; Level 1b: 11 studies).
- Benefit: INCS improved patient symptoms as monotherapy or adjuvant to antibiotics in severe cases, and hastened recovery; Systemic minimal benefit.
- Harm:Minimal harm with rare mild adverse event.
- Cost: Low for both interventions.
- Benefits-Harm Assessment: Benefit of treatment over placebo small, but tangible; minimal harm with INCS, greater risk for prolonged systemic corticosteroids.
- Value Judgments: INCS improved patient symptoms with low risk for adverse event.
- Policy Level: Use of INCS: Strong recommendation. Use of systemic corticosteroid: No recommendation.
- Intervention: INCS should be trialed as monotherapy in moderate or as adjuvant to antibiotic therapy in severe cases of ARS. Systemic corticosteroidsmay be useful in palliation when predominant symptoms are facial pain or headaches, otherwise no tangible benefit.

Decongestants: *Several systematic reviews on this topic have been published. None have found sufficient evidence to allow a recommendation to be made.*

Antihistamines: *No evidence to support their use in this setting was demonstrated. A review of the literature was unable to identify any studies upon which to make recommendations.*

Nasal Saline Irrigation: *A number of systematic reviews and clinical guidelines on the subject of saline irrigation in ARS have been published and have found an overall benefit in symptom reduction. While the studies individually do not provide a compelling case for the use of saline in ARS, taken together they can be interpreted as demonstrating a likely benefit in terms of nasal function and patient symptoms with minimal likely harms.*

- Aggregate Grade of Evidence: A (Level 1a: 3 studies; Level 1b: 4 studies; Level 2b: 1 study).
- Benefit: Possible nasal symptom improvement. Improved nasal saccharin transit times.
- Harm: Occasional patient discomfort.
- Cost: Minimal.

- Benefits-Harm Assessment: Benefit likely to outweigh harm.
- Value Judgments: None.
- Policy Level: Option.
- Intervention: Use of saline may benefit patients in terms of improved symptoms and is unlikely to lead to significant harm.

Evidence-Based Rhinosinusitis Management Recommendations – Recurrent Acute Rhinosinusitis

Intranasal Corticosteroids (INCS): *Three double-blinded RCTs (DBRCTs) have been published, with the primary objective of assessing the effect of INCS on symptom outcomes of patients with RARS. All studies reported improvement in symptoms in the treatment groups.*

- Aggregate Grade of Evidence: B (Level 2b: 3 studies)
- Benefit: Generally well tolerated. May decrease time to symptom relief. May decrease overall symptom severity, as well as specific symptoms of headache, congestion, and facial pain
- Harm: Mild irritation
- Cost: Moderate depending on preparation
- Benefits-Harm Assessment: Balance of benefit and harm
- Value Judgments: Patient populations studied did not adhere to the AAO-HNS clinical practice guidelines definition of RARS, and therefore conclusions may not be directly applicable to this population
- Policy Level: Option
- Intervention: Option for use of INCS spray for acute exacerbations of RARS

Antibiotics: *Uncomplicated ARS in patients with RARS should be prescribed antibiotics based on the same criteria used to manage primary or sporadic episodes of ARS. After performing an exhaustive review of the literature, there are no available data to provide additional recommendations for the use of antibiotics in RARS different from recommendations for treating ABRS.*

Endoscopic Sinus Surgery (ESS): *Three noncomparative studies have examined this issue and found improvement following ESS. The lower level of evidence in these studies weakens the recommendation to an option.*

- Aggregate Grade of Evidence: C (Level 3b: 3 studies; Level 4: 1 study).
- Benefit: Postoperative improvement in patient symptoms.May reduce postoperative antibiotic utilization, number of acute episodes, and missed workdays. Results appear comparable to CRS cohorts.
- Harm: Surgery is associated with potential complications.
- Cost: Significant costs are associated with ESS.
- Benefits-Harm Assessment: Balance of benefit and harm.
- Value Judgments: Properly selected patients with RARS may benefit both symptomatically and medically from ESS. This option should be assessed and utilized cautiously, however, because data remain limited.

- Policy Level: Option.
- Intervention: ESS is an option for properly selected patients with RARS.

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.

- Cost: Minimal (US$0.24/day). Patient time for application.
- 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. The summary for CRSsNP follows:*

- Aggregate Grade of Evidence: A (Level 1a: 2 studies; Level 1b: 2 studies).
- Benefit: Improved symptom scores, improved endoscopy scores.
- Harm: Epistaxis, headache.
- Cost: Low to moderate (US$0.61 to US$4.80 per day depending on medication).
- Benefits-Harm Assessment: Preponderance of benefit over harm.
- Value Judgments: Direct sinus delivery methods showed greater effects on symptom scores, therefore should be considered in more complex cases of CRS, or following failure of treatment with simple sprays.
- Policy Level: Recommendation.
- Intervention: Standard metered dose INCS should be used in treatment of CRSsNP.

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.
- Cost: Moderate depending on preparation
- 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). Evidence for CRSsNP is low level:*

- Aggregate Grade of Evidence: Irrigations - C (Level 4: 3 studies);MAD- N/A (Level 1b: 1 study);MAST tubes - B (Level 1b: 1 study; Level 4: 1 study); YAMIK - N/A (Level 1b: 1 study).
- Benefit: Irrigations - Improvement in HR-QoL, subjective symptom scores and endoscopic appearance in postoperative patients. MAD – Improvement in HR-QoL.

MAST - Improvement in HR-QoL, subjective symptom scores and endoscopy scores. YAMIK - No benefit seen.

- Harm: Irrigations - minor (epistaxis, nasal irritation). No evidence of adrenal suppression at studied doses. MAD - Trend toward reduced stimulated cortisol levels. MAST - Invasive insertion, epistaxis. YAMIK - Patient discomfort, epistaxis.
- Cost: Moderate to High (from US$2.50 per day for budesonide respules, MAST tube US$100 for each tube + variable costs associated with insertion).
- Benefits-Harm Assessment: Irrigations – Preponderance of benefit over harm, with relatively high cost. MAD - Balance of benefit and harm. MAST - Balance of benefit and harm. YAMIK – Limited evidence shows preponderance of harm over benefit.
- Value Judgments: Early evidence for irrigations is low level and there is a higher cost compared to sprays. Strongest evidence of improvement is seen in postoperative patients.
- Policy Level: Irrigations - Option in postoperative patients.MAD- Option. MAST - Option. YAMIK - Recommendation against.
- Intervention: Corticosteroid nasal irrigations are an option in CRSsNP. They may be most beneficial in postoperative patients. The use of MAD or MAST is an option. Use of the YAMIK device is not recommended based on current evidence.

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.
- Cost: Moderate.
- 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.
- Cost: Low.
- 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.
- Cost: Variable, depending on antibiotic chosen.
- 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: *A few RCTs concerning macrolides in CRSsNP have been published and 2 have rather compelling findings about the short-term efficacy while 1 shows no benefit. The subgroup of CRSsNP patients that best benefit frommacrolides is not currently known. Various drugs and dosages have been studied so that the optimal drug and dosages are also not currently known.*

- Aggregate Grade of Evidence: B (Level 1a: 2 studies; Level 1b: 2 studies; Level 1a-2a: 2 studies; Level 2b: 3 studies).
- Benefit: Reduction in endoscopy scores and some symptoms in patients with CRSsNP, particularly in patients without elevated IgE. Effects appear to be comparable to INCS. Benefit may not last long following cessation of therapy.
- 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 harms. Benefit of treatment over placebo is seen in most but not all studies. Harm, though rare is significant.
- Value Judgments: Macrolides appear to confer a benefit in the short term. The benefit may not last following cessation of therapy. Optimal drug, dosage, and length of therapy are not known.
- Policy Level: Option.
- Intervention: Macrolides are an option for patients with CRSsNP.

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.
- Cost: High.
- 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.
- Cost: Moderate to high (US$2.64 to US$7.64) per dose, depending on antibiotic and formulation.
- 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.
- Cost: Direct cost of medications.
- 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.
    - **For CRSsNP:** Appropriate medical therapy prior to surgical intervention should include INCS, saline irrigations, and antibiotics. Oral corticosteroids 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.
- Cost: Direct cost of medications.
- 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 4 of 12, March 2019) am 30.04.2019

#	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 Apr 2014 to Apr 2019

Systematic Reviews in Medline (PubMed) am 30.04.2019

#	Suchfrage
1	sinusitis[mh]
2	rhinitis[mh]
3	paranasal sinus diseases[mh:noexp]
4	#1 OR #2 OR #3
5	rhinosinusitis[tiab] OR nasosinusitis[tiab] OR pansinusitis[tiab] OR ethmoiditis[tiab] OR sphenoiditis[tiab] OR kartagener*[tiab]
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 studies[pt] OR validation studies[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 ("2014/04/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
	(#N) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 30.04.2019

#	Suchfrage
1	sinusitis[mh]
2	rhinitis[mh]
3	paranasal sinus diseases[mh:noexp]
4	#1 OR #2 OR #3
5	rhinosinusitis[tiab] OR nasosinusitis[tiab] OR pansinusitis[tiab] OR ethmoiditis[tiab] OR sphenoiditis[tiab] OR kartagener*[tiab] OR CRSwNP[tiab] OR CRSwp[tiab]
6	(inflamm*[tiab] OR maxilla* OR frontal*) 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	(#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 ("2014/04/01"[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[ptyp]

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