Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

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

Vorgang: 2024-B-309 Depemokimab

Stand: März 2025

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

Depemokimab
[Add-on-Therapie zur Behandlung von Erwachsenen mit schwerer chronischer Rhinosinusitis mit Nasenpolypen (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.	Sinusoperation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	- Beschluss über die Nutzenbewertung nach § 35a SGB V für den Wirkstoff Dupilumab vom 14. Mai 2020 - Beschluss über die Nutzenbewertung nach § 35a SGB V für den Wirkstoff Mepolizumab vom 19. Mai 2022
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:	
Benralizumab R03DX10 Fasenra	<u>Geplantes Anwendungsgebiet laut Beratungsanforderung:</u> angezeigt als Add-on-Therapie zu intranasalen Kortikosteroiden zur Behandlung von erwachsenen Patienten mit schwerer chronischer Rhinosinusitis mit Nasenpolypen (chronic rhinosinusitis with nasal polyps, CRSwNP) mit Asthma, bei denen durch eine Therapie mit systemischen Kortikosteroiden und/oder durch einen chirurgischen Eingriff keine ausreichende Kontrolle der CRSwNP-Erkrankung erzielt wird.
monoklonale Antikörper	
Dupilumab D11AH05 Dupixent	Dupixent ist angezeigt als Add-on-Therapie mit intranasalen Corticosteroiden zur Behandlung von Erwachsenen mit schwerer CRSwNP, die mit systemischen Corticosteroiden und/oder chirurgischem Eingriff nicht ausreichend kontrolliert werden kann.
Omalizumab R03DX05 Xolair	Xolair wird als Zusatztherapie zu intranasalen Kortikosteroiden (INCS) zur Behandlung von Erwachsenen (ab 18 Jahren) mit schwerer CRSwNP angewendet, bei denen durch eine Therapie mit INCS keine ausreichende Krankheitskontrolle erzielt wird.
Mepolizumab R03DX09 Nucala	Nucala ist angezeigt als Zusatztherapie mit intranasalen Kortikosteroiden zur Behandlung von erwachsenen Patienten mit schwerer CRSwNP, die mit systemischen Kortikosteroiden und/oder chirurgischem Eingriff nicht ausreichend kontrolliert werden kann.
Glucokortikoide (topisch)	
Mometasonfuroat (generisch) R01AD09 z.B. Nasonex®	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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Nasenspray	
Budesonid R01AD05 (generisch) z.B. Budesonid acis® Nasenspray	Symptomatische Behandlung und Vorbeugung von saisonalem und ganzjährigem allergischen Schnupfen einschließlich Heuschnupfen sowie Nasenpolypen.
Glucokortikoide (systemisch), z.B.	
Prednison H02AB07 (generisch) z.B. Prednison ratiopharm	Erkrankungen der oberen Luftwege – schwere Verlaufsformen von Pollinosis und Rhinitis allergica, nach Versagen intranasal verabreichter Glucocorticoide (DS: c) […]
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 Schübe 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: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2024-B-309 (Depemokimab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	14. Januar 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

AERD	Aspirin-Exacerbated Respiratory Disease
ATAD	Aspirin treatment after desensitisation
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CRS	Chronic RS
CRSsNP	chronic rhinosinusitis without nasal polyps
CRSwNP	chronic rhinosinusitis with nasal polyps
DOX	doxycycline
ECRI	Emergency Care Research Institute
EOF	End of follow-up
FESS	Functional Endoscopic Sinus Surgery
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
HRQL	health-related quality of life
ICP	integrated care pathway
INCS	intranasal corticosteroids
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LMS	Lund-Mackay score
LoE	Level of Evidence
mAb	monoclonal antibody
NICE	National Institute for Health and Care Excellence
NMA	Network Meta Analysis
NPS	nasal polyp score
OCS	Oral corticosteroids
OR	Odds Ratio
PNIF	peak nasal inspiratory flow
RR	Relatives Risiko
RS	rhinosinusitis
SAE	Serious adverse events
SIGN	Scottish Intercollegiate Guidelines Network
SNOT-22	sinonasal outcome test-22
TRIP	Turn Research into Practice Database
UPSIT	University of Pennsylvania Smell Identification Test
VAS	visual analogue scale
WHO	World Health Organization

1 Indikation

Behandlung von erwachsenen Patienten mit schwerer chronischer Rhinosinusitis mit Nasenpolypen (chronic rhinosinusitis with nasal polyps, CRSwNP)

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *chronische Rhinosinusitis* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 28.08.2024 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 635 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 9 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Chong L et al., 2020 [2].

Biologics for chronic rhinosinusitis

Fragestellung

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

Methodik

Population:

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

Intervention:

- anti-IL-4R alpha mAb (dupilumab);
- anti-IL-13 (lebrikizumab, tralokinumab);
- anti-IL-5 mAb (reslizumab, benralizumab, mepolizumab);
- anti-IgE mAb (omalizumab).

Komparator:

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

Endpunkte:

- Health-related quality of life, Disease severity, Serious adverse events (SAEs), Avoidance of surgery

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

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

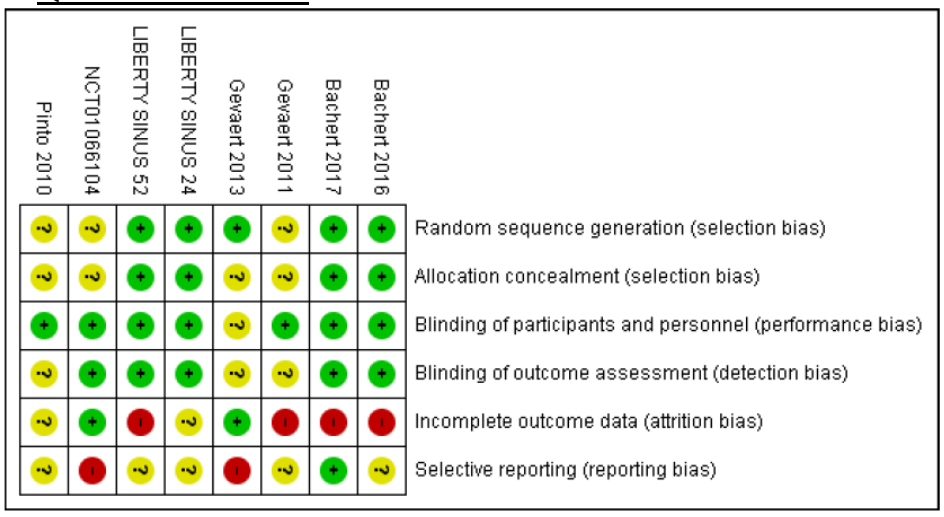
- 3 studies (784 participants) evaluated dupilumab.

Charakteristika der Population/Studien:

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

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

Qualität der Studien:



Studienergebnisse:

Summary of findings 1. Anti-IL-4Rα mAb (dupilumab) compared to placebo (on top of topical steroids) for chronic rhinosinusitis

Anti-IL-4Rα mAb (dupilumab) compared to placebo (on top of topical steroids) for chronic rhinosinusitis

Patients or population: patients with severe chronic rhinosinusitis with nasal polyps
Setting: tertiary care
Intervention: anti-IL-4Rα mAb (dupilumab)
Comparison: placebo (on top of topical steroids)

Outcomes	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
			Without anti-IL-4Rα mAb (dupilumab)	With anti-IL-4Rα mAb (dupilumab)	Difference		
Health-related quality of life - disease-specific (SNOT-22, range 0 to 110, lower = better) Follow-up (range): 16 to 24 weeks	784 (3 RCTs)	—	The median disease-specific health-related quality of life score without anti-IL-4Rα mAb (dupilumab) was 40.5 points	—	MD 19.61 points lower (22.54 lower to 16.69 lower)	⊕⊕⊕⊕ HIGH	At up to 24 weeks, aspects of health-related quality of life that are directly impacted by chronic rhinosinusitis were better in participants who received dupilumab. The size of the difference is clinically significant.
Disease severity - VAS (range 0 to 10, lower = better) Follow-up (range): 16 to 24 weeks	784 (3 RCTs)	—	The median disease severity score without anti-IL-4Rα mAb (dupilumab) was -1.3 points	—	MD 3 points lower (3.47 lower to 2.53 lower)	⊕⊕⊕⊖ MODERATE[1]	Overall chronic rhinosinusitis symptoms were probably better in participants who received dupilumab.
Serious adverse events Follow-up (range): 16 to 52 weeks	782 (3 RCTs)	RR 0.47 (0.29 to 0.76)	Study population 12.5%	5.9% (3.6 to 9.5)	6.6% fewer (8.9 fewer to 3 fewer)	⊕⊕⊖⊖ LOW[2]	Participants who had dupilumab may have had fewer serious adverse events than participants who received placebo in 3 RCTs (28/470 with dupilumab versus 39/312 with placebo), but we have limited confidence in this estimate because the sample size may be too small to estimate this accurately, or capture the range of adverse events that could possibly occur in a larger population or with longer follow-up.
Avoidance of surgery - number of patients who had surgery as rescue treatment Follow-up (range): 24 to 52 weeks	725 (2 RCTs)	RR 0.17 (0.05 to 0.52)	Study population 7.7%	1.3% (0.4 to 4)	6.4% fewer (7.3 fewer to 3.7 fewer)	⊕⊕⊕⊖ MODERATE[3]	Patients who had dupilumab probably have lower risk of requiring surgery due to severe chronic rhinosinusitis symptoms after 24 to 52 weeks of treatment. We have moderate confidence in this estimate as we are not sure which criteria were used to determine the need for 'rescue surgery'.
Extent of disease: endoscopic nasal polyp score (range 0 to 8, lower = better) Follow-up (range): 16 to 24 weeks	784 (3 RCTs)	—	The median nasal polyp score without dupilumab was 5.94 points.	—	MD 1.80 points lower (2.25 lower to 1.35 lower)	⊕⊕⊕⊖ MODERATE[1]	Dupilumab probably results in a reduction in nasal polyp score by 24 weeks of follow-up. This is likely to be a large effect, however we have moderate confidence in the estimate as it is unclear whether the scoring system used for nasal polyps is validated.
Extent of disease: CT scan score (Lund-Mackay, range 0 to 24, lower = better) Follow-up (range): 16 to 52 weeks	784 (3 RCTs)	—	The median CT scan score without anti-IL-4Rα mAb (dupilumab) was 17.9 points	—	MD 7 points lower (9.61 lower to 4.39 lower)	⊕⊕⊕⊕ HIGH	At up to 24 weeks, the extent of disease as assessed by CT scan was less severe in participants who received dupilumab - the difference is likely to be a large effect.
Health-related quality of life - generic (EQ-5D visual analogue scale, range 0 to 100, higher = better) Follow-up (range): 16 to 24 weeks	766 (3 RCTs)	—	The median change in generic HRQOL for the placebo group was an increase of 3.01 points	—	MD 8.29 points higher (5.73 higher to 10.85 higher)	⊕⊕⊕⊖ MODERATE[4]	The overall quality of life or health status, as assessed by the EQ-5D visual analogue scale was probably slightly higher in participants who received dupilumab. However, we are not sure if the size of this difference is noticeable or would be considered important enough by most patients.
Adverse events - nasopharyngitis, including sore throat (longest available data)	783 (3 RCTs)	RR 0.95 (0.72 to 1.25)	Study population 21.1%	20.0% (15.2 to 26.4)	1.1% fewer (5.9 fewer to 5.3 more)	⊕⊕⊖⊖ LOW[2]	We are uncertain whether there is an important difference in the risk of nasopharyngitis. Adverse events were reported by 94/470 participants who took dupilumab versus 66/313 who took placebo.

Follow-up (range): 16 to 52 weeks

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **CT:** computerised tomography; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio; **SNOT-22:** Sino-Nasal Outcome Test-22; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded by one level due to study limitations: methods or criteria used in the measurement of the outcome were not validated.
[2]Downgraded by two levels due to imprecision and indirectness: small sample size for the outcome estimated resulting in an imprecise estimation of effect size. Moreover, some serious adverse events are relatively rare; a larger and more heterogeneous population or longer periods of treatment and follow-up may be needed.
[3]Downgraded by one level due to serious limitations: the criteria used for requiring/not requiring 'rescue surgery' were unclear.
[4]Downgraded by one level for imprecision: the confidence interval crosses the minimally important difference (8 points), therefore the difference may or may not be of importance to participants.

Summary of findings 2. Anti-IL-5 mAb (mepolizumab) compared to placebo (on top of topical steroids) for chronic rhinosinusitis

Anti-IL-5 mAb (mepolizumab) compared to placebo (on top of topical steroids) for chronic rhinosinusitis

Patients or population: patients with severe chronic rhinosinusitis with nasal polyps
Setting: tertiary care
Intervention: anti-IL-5 mAb (mepolizumab)
Comparison: placebo (on top of topical steroids)

Outcomes	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
			Without anti-IL-5 mAb (mepolizumab)	With anti-IL-5 mAb (mepolizumab)	Difference		
Health-related quality of life - disease-specific (SNOT-22, range 1 to 100, lower = better) Follow-up: 25 weeks	105 (1 RCT)	—	The mean disease-specific health-related quality of life score without anti-IL-5 mAb (mepolizumab) was 40.36.	—	MD 13.26 lower (22.08 lower to 4.44 lower)	⊕⊕⊖⊖ LOW[1]	Aspects of health-related quality of life that are directly impacted by chronic rhinosinusitis may have been better in participants who received mepolizumab but we are uncertain about this estimate.
Disease severity - VAS (range 0 to 10, lower = better) Follow-up: 25 weeks	72 (1 RCT)	—	The mean disease severity score without anti-IL-5 mAb (mepolizumab) was 6.21.	—	MD 2.03 lower (3.65 lower to 0.41 lower)	⊕⊖⊖⊖ VERY LOW[1,2]	We are very uncertain about the impact of mepolizumab on overall chronic rhinosinusitis symptom severity.
Serious adverse events Follow-up (range): 25 to 40 weeks	135 (2 RCTs)	RR 1.57 (0.07 to 35.46)	Study event rates[3] 0.0%	1.37%		⊕⊖⊖⊖ VERY LOW[1,4]	We are very uncertain about the number of serious adverse events for chronic rhinosinusitis patients who use mepolizumab. The number of serious adverse events was 0/62 for placebo and 1/73 for mepolizumab.
Avoidance of surgery - patients still meeting the criteria for surgery At end of follow-up (range): 25 to 40 weeks	135 (2 RCTs)	RR 0.78 (0.64 to 0.94)	Study population 80.3%	62.7% (51.4 to 75.5)	17.7% fewer (28.9 fewer to 4.8 fewer)	⊕⊖⊖⊖ VERY LOW[1,2,4]	We are very uncertain whether mepolizumab can help participants reduce the need for surgery.
Extent of disease - endoscopic score Follow-up (range): 25 to 40 weeks	137 (2 RCTs)	—	The mean endoscopic score without anti-IL-5 mAb (mepolizumab) ranged from 0 to -0.7.	—	MD 1.23 lower (1.79 lower to 0.68 lower)	⊕⊖⊖⊖ VERY LOW[1,2]	We are very uncertain whether mepolizumab can reduce the extent of disease as measured by an endoscopic score.
Extent of disease - CT scan score (Lund-Mackay, range 0 to 24, lower = better) Follow-up: 8 weeks	27 (1 RCT)	—	One study reported that CT scan scores were "not significantly different between groups"	—	—	⊕⊖⊖⊖ VERY LOW[1,5]	We are very uncertain whether mepolizumab can reduce the extent of disease as measured by a CT scan score.
Health-related quality of life - generic, measured using the EQ-5D visual analogue scale (range 0 to 100; 0 = worst imaginable	105 (1 RCT)	—	The mean generic health-related quality of life score without anti-IL-5 mAb (mepolizumab) was 75.45	—	MD 5.68 higher (1.18 lower to 12.54 higher)	⊕⊕⊖⊖ LOW[1]	We are uncertain about the impact of mepolizumab on overall quality of life or health status, as assessed by the EQ-5D visual analogue scale.

health state, 100 = best imaginable health state) Follow-up: at week 25							
Adverse events - nasopharyngitis, including sore throat Follow-up (range): 25 to 40 weeks	135 (2 RCTs)	RR 0.73 (0.36 to 1.47)	Study population 22.6%	16.5% (8.1 to 33.2)	6.1% fewer (14.5 fewer to 10.6 more)	⊕⊕⊖⊖ LOW[1]	We are uncertain about the risk of nasopharyngitis in chronic rhinosinusitis patients who used mepolizumab.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio; **SNOT-22:** Sino-Nasal Outcome Test-22; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded by two levels due to imprecision: very small sample size resulting in a very imprecise estimation of effect sizes.
[2]Downgraded by one level due to study limitations: methods or criteria used in the measurement of the outcome were not validated.
[3]No events were reported in the placebo arm of these trials. We have therefore presented the study event rates rather than anticipated absolute events.
[4]Downgraded by one level due to indirectness: one study only assessed patients for two doses (Gevaert 2011). The other study evaluated six doses (24 weeks), but had a more than 30% dropout rate (Bachert 2017). Therefore, the length of follow-up is inadequate and it is unclear whether this evidence related to safety is generalisable.
[5]Downgraded by one level due to study limitations: high risk of attrition bias, insufficient information to judge other aspects of study design and no numerical data presented for this outcome.

Summary of findings 3. Anti-IgE mAb (omalizumab) compared to placebo (on top of topical steroids) for chronic rhinosinusitis

Anti-IgE mAb (omalizumab) compared to placebo (on top of topical steroids) for chronic rhinosinusitis

Patients or population: patients with chronic rhinosinusitis with nasal polyps
Setting: tertiary care
Intervention: anti-IgE mAb (omalizumab)
Comparison: placebo (on top of topical steroids)

Outcomes	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
			Without anti-IgE mAb (omalizumab)	With anti-IgE mAb (omalizumab)	Difference		
Health-related quality of life - disease-specific (SNOT-22, range 0 to 110, lower = better) Follow-up: 24 weeks	265 (2 RCTs)	—	The mean change in disease-specific HRQOL for the placebo group was -7.57 points	—	MD 15.62 points lower (19.79 lower to 11.45 lower)	⊕⊕⊕⊖ MODERATE[1]	At 24 weeks, omalizumab probably results in an improvement in disease-specific health-related quality of life (as measured with the SNOT-22 questionnaire). The size of the difference was clinically significant. However, we have limited confidence in this estimate because the sample size may be too small to estimate this accurately.
Disease severity, as measured by validated, patient-reported symptom score	—	—	—	—	—	—	None of the studies reported this outcome.
Serious adverse events Follow-up (range): 20 weeks to 6 months	329 (5 RCTs)	RR 0.32 (0.05 to 2.00)	2.5%	0.8% (0.1 to 5.1)	1.7% fewer (2.4 fewer to 2.5 more)	⊕⊖⊖⊖ VERY LOW[2,3]	There is too little information. We are very uncertain whether omalizumab changes the incidence of serious adverse events because the sample size may be too small to estimate this accurately, or capture the range of adverse events that might occur in a larger population or with longer follow-up. Serious adverse events were reported by 1/171 participants who took omalizumab versus 4/158 who took placebo.
Avoidance of surgery Nasal polyp score ≤4 (≤ 2 on each side) and an improvement in SNOT-22 score of ≥ 8.9 points Follow-up: 24 weeks	265 (2 RCTs)	RR 5.60 (1.99 to 15.76)	3.1%	17.1% (6.1 to 48.1)	14.0% more (3 more to 45.1 more)	⊕⊕⊕⊖ LOW[1,4]	At up to 24 weeks, the evidence suggests that the number of participants in whom surgery was not thought to be necessary was greater in those who received omalizumab. However, we have limited confidence in this estimate because the sample size may be too small to estimate this accurately, and there are no widely agreed criteria to determine which patients need surgery for nasal polyps. Avoidance of surgery was reported in 23/134 participants who took omalizumab versus 4/131 participants who took placebo.

Extent of disease: endoscopic nasal polyp score (range 0 to 8, lower = better) Follow-up: up to 24 weeks	312 (4 RCTs)	—	The median change in endoscopic nasal polyp score for the placebo group was -0.05 points	—	MD 1.26 points lower (2.2 lower to 0.31 lower)	⊕⊕⊖⊖ LOW[4,5]	At up to 24 weeks, the evidence suggests that omalizumab may result in a reduction in the nasal polyp score. However, there are inconsistencies in the size of effect between studies, and it is unclear whether the method used is validated.
Extent of disease: CT scan (lower score = better) Follow-up: 20 weeks	47 (2 RCTs)	—	The mean CT scan score without anti-IgE mAb (omalizumab) ranged from -8.9 to 18.3	—	SMD 0.2 lower (1.55 lower to 1.14 higher)	⊕⊖⊖⊖ VERY LOW[2,6]	There is too little information - we are very uncertain whether there is a difference in the extent of disease with omalizumab. There are inconsistencies in the size and direction of effect. In the NCT01066104 study, the results favoured the placebo group, while in Gevaert 2013 they favoured the omalizumab group.
Health-related quality of life - generic (SF-36) Follow-up (range): 20 weeks to 6 months	38 (2 RCTs)	One study found no significant differences (P > 0.05, all comparisons) except for one domain, 'vitality' (omalizumab 9.4, placebo 12.5, P < 0.05). A second study found that physical health was significantly improved in the omalizumab group (P = 0.02) but not in the placebo group (P = 0.75). Mental health did not significantly improve in either treatment group.				⊕⊖⊖⊖ VERY LOW[7,8]	We are very uncertain about the impact of omalizumab on health-related quality of life.
Adverse events - nasopharyngitis, including sore throat Follow-up (range): 20 weeks to 6 months	329 (5 RCTs)	RR 0.71 (0.29 to 1.73)	6.9%	4.9% (2 to 12)	2.0% fewer (4.9 fewer to 5.1 more)	⊕⊕⊖⊖ LOW[2]	The evidence suggests that omalizumab may result in little to no difference in the incidence of nasopharyngitis, including sore throat. However, we have limited confidence in this estimate because the sample size may be too small to estimate this accurately. Nasopharyngitis or sore throat was reported by 8/170 participants who took omalizumab versus 11/159 who took placebo.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **CT:** computerised tomography; **RCT:** randomised controlled trial; **SMD:** standardised mean difference; **SNOT-22:** Sino-Nasal Outcome Test-22

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded by one level due to imprecision: small sample size resulting in an imprecise estimate of effect size.
[2]Downgraded by two levels due to imprecision: small sample size for the outcome estimated resulting in an imprecise estimation of effect size; confidence interval includes potential for considerable benefit or considerable harm.
[3]Downgraded by one level due to indirectness: some serious adverse effects are relatively rare - a larger and more heterogeneous population or longer period of treatment and follow-up may be needed.
[4]Downgraded by one level due to study limitations: method of assessment not validated.
[5]Downgraded by one level due to inconsistency: high and unexplained heterogeneity as the size of effect differed between the studies (I^2 = 90%).
[6]Downgraded by one level due to inconsistency: high and unexplained heterogeneity as the size and direction of effect differed between the studies (I^2 = 80%).
[7]Downgraded by two levels due to imprecision: very small sample size for the outcome measured.
[8]Downgraded by one level due to indirectness: a larger range of treatment doses and duration, and a more heterogeneous population, may be required to identify the effect of the intervention on quality of life.

Anmerkung/Fazit der Autoren

We identified randomised controlled trials (RCTs) evaluating the effectiveness of three different drugs, representing three different types of monoclonal antibodies. These were dupilumab (an anti- IL-4R@ mAb), mepolizumab (an anti-IL-5 mAb) and omalizumab (an anti-IgE mAb). For this update of the review we identified two additional trials that provide evidence on mepolizumab.

All of the drugs were evaluated in adults with chronic rhinosinusitis and nasal polyps who were also using regular topical nasal steroids. In these patients, we found high-certainty evidence from three studies (with nearly 800 participants) that dupilumab results in a large improvement in disease-specific health-related quality of life (HRQL) compared to placebo, and a large reduction in the extent of the disease as measured on a computerised tomography (CT) scan. Moderate-certainty evidence shows that it probably also results in a large improvement in symptoms, increases generic HRQL (as measured by overall health

status) and results in a large reduction in the size of polyps (as measured by nasal polyp scores). It probably results in a large reduction in the need for further surgery but it is difficult to interpret the clinical implications of this finding due to methodological limitations. There may be little or no difference in the risk of nasopharyngitis.

Mepolizumab has been evaluated in similar patients but the certainty of evidence is either low or very low. It may improve both disease-specific and generic HRQL. It may also improve nasal polyp scores, but the evidence is very uncertain. We are very uncertain whether it reduces the need for surgery, as there are important limitations of the methodology that limit the clinical interpretation of the data. There may be little or no difference in the risk of nasopharyngitis. It is very uncertain if there is a difference in the risk of serious adverse events.

We identified moderate-certainty evidence from two studies that omalizumab probably results in a large improvement in disease specific HRQL compared to placebo. It may also result in a large reduction in the need for surgery, but the evidence for this was of low certainty. Omalizumab may also result in a reduction in the extent of disease, as assessed with an endoscopic nasal polyps score, although there were differences in the extent of this change between the four studies that reported this measure. Similarly, when the extent of disease was assessed with CT scores, there were differences in the size and direction of effect in the two studies, and the evidence was of very low certainty. Omalizumab may result in little to no difference in nasopharyngitis when compared to placebo, although the risk of serious adverse events is very uncertain.

Patients with chronic rhinosinusitis, with and without nasal polyps, often need long-term treatment. Many have surgery and revision surgery is common, with a 10-year revision rate in excess of 15% in a large population study (Smith 2019), and with over 50% of patients in a UK epidemiological study reporting previous surgery for chronic rhinosinusitis with nasal polyps (CRSwNP) (Philpott 2015). Patients with chronic rhinosinusitis with nasal polyps and comorbid asthma are at a higher risk of undergoing revision surgery, and many of these patients experience poor symptom control, the need for repeated systemic steroids and multiple surgeries. The majority of trials included in this review have selected patients with severe chronic rhinosinusitis with nasal polyps, as defined by polyp size and the need for systemic steroids and/or surgery, both of which carry a risk of significant adverse effects. These severely affected patients, who had effectively failed other treatment options, experienced significant improvements in health-related quality of life and reduced disease severity on radiological imaging. Importantly, there does not appear to be any increased risk of serious adverse events, at least in the short term. This has the potential, therefore, to be a 'game-changer' in the management of patients with severe disease, allowing them to avoid other treatments associated with higher risk.

We are currently unable to predict which patients will respond to biologics. The included studies report response rates between 50% and 70%, and therefore not all patients will respond to these drugs. Nor is it clear how to choose the optimum biologic, and when to consider these drugs, particularly with regards to using them before or after surgery. This review considers studies that compare a biologic to placebo or no treatment, therefore we re unable to draw conclusions regarding the relative efficacy of the different biologic agents. We also do not know if these drugs are effective in patients with less severe disease so we must highlight the potentially limited generalisability of the reported findings to the wider population of patients with chronic rhinosinusitis. Finally, although not considered in this review, currently these drugs are high-cost compared to conventional treatment with topical and systemic corticosteroids and surgery, and patients require ongoing treatment with them.

In adults with severe chronic rhinosinusitis and nasal polyps, using regular topical nasal steroids, dupilumab improves disease-specific HRQL compared to placebo, and reduces the

extent of the disease as measured on a CT scan. It probably also improves symptoms and generic HRQL and there is no evidence of an increased risk of serious adverse events. It may reduce the need for further surgery. There may be little or no difference in the risk of nasopharyngitis.

Kommentare zum Review

Reviews mit ähnlicher Fragestellung und vergleichbaren Ergebnissen:

- Agache I et al., 2021 [1].

3.2 Systematische Reviews

Kariyawasam HH et al., 2023 [4].

Biologic treatment for severe chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis

Fragestellung

Biologics that target key inflammatory pathways have the potential to treat this disease; this study aimed to evaluate their effectiveness.

Methodik

Population:

- Symptomatic CRSwNP despite standard treatment. Studies were excluded if participants had a known aetiology for their sinus disease e.g. cystic fibrosis/immunodeficiency.

Intervention:

- Monoclonal antibodies used for the treatment of CRSwNP.

Komparator:

- Placebo, no treatment or current standard of care

Endpunkte:

- Extent of disease (nasal polyp score (NPS), radiological scoring with Lund-Mackay score (LMS)); peak nasal inspiratory flow (PNIF); Formal olfactory testing (University of Pennsylvania Smell Identification Test, UPSIT); Health-related quality of life (QoL) measured with validated disease-specific QoL scores e.g. sinonasal outcome test-22 (SNOT-22); Subjective disease severity measured with validated patient reported symptom scores e.g., visual analogue scale (VAS) for overall disease severity and/or specific symptoms of nasal congestion, discharge.

Recherche/Suchzeitraum:

- MEDLINE (1946 – 9 November 2021), EMBASE (1980 – 9 November 2021), Global Health (1973 - 9 November 2021), the Cochrane Library, including the Central Register of Controlled Trials (on 9 November 2021), and clinicaltrials.gov (on 9 November 2021).

Qualitätsbewertung der Studien:

- Cochrane risk-of-bias tool for randomized trials (RoB2)

Ergebnisse

Anzahl eingeschlossener Studien:

- The search returned 8217 results. Screening identified 14 records for full-text review; nine of these met the inclusion criteria, reporting 11 different trials (Figure 1). All 11 were randomised double blind placebo-controlled trials including 2035 patients.

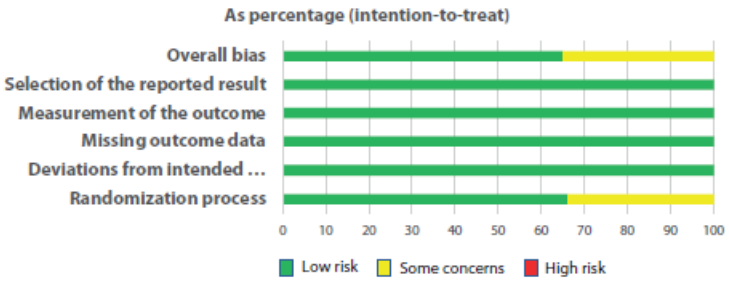
Charakteristika der Population/Studien:

Randomised controlled trial	Subjects active / placebo	Mean age (years) active / placebo	Asthma % active / placebo	N-ERD % active / placebo	Intervention	Follow-up / outcomes measured (weeks)	Outcome measures
Bachert et al. 2022 [13]	413 (207 / 206)	50·1 / 50·2	68·6% / 67·0%	30·0% / 29·1%	Benralizumab 30 mg SC every 4 weeks x 3 then every 8 weeks to 40 weeks	40 / 40	NPS LMS SNOT-22 NBS Time to surgery and/ or SCS use
Tversky et al. 2021 [9]	24 (12/12)	49·8 / 50·8	83·0% / 100%	25·0% / 67·0%	Benralizumab 30 mg SC every 4 weeks x 3 doses then once after 8 weeks	24 / 24	NPS LMS UPSIT SNOT-22 NBS
Bachert et al. 2019 [10]: SINUS-24	276 (143 / 133)	52·0 / 50·0	57·0% / 59·0%	32·0% / 29·0%	Dupilumab 300 mg SC every 2 weeks to 24 weeks	48 / 24	NPS LMS PNIF UPSIT SNOT-22 Disease severity VAS NCS Nasal discharge score Time to surgery or SCS use
Bachert et al. 2019 [10]: SINUS-52	448 (150 / 145 / 153)*	51·0 / 53·0 / 53·0*	57·0% / 63·0% / 59·0%*	23·0% / 28·0% / 29·0%*	Dupilumab 300 mg SC every 2 weeks to 52 weeks OR Dupilumab 300mg SC every 2 weeks to 24 weeks then every 4 weeks to 52 weeks*	52 / 24	NPS LMS PNIF UPSIT SNOT-22 Disease severity VAS NCS Nasal discharge score Time to surgery or SCS use
Bachert et al. 2016 [14]	60 (30 / 30)	47·4 / 49·3	53·3% / 63·3%	20·0% / 30·0%	Dupilumab 600 mg SC loading dose then 300 mg weekly to 16 weeks	32 / 16	NPS LMS PNIF UPSIT SNOT-22 Disease severity VAS NCS Nasal discharge score
Han et al. 2021 [11]	407 (206 / 201)	48·6 / 48·9	68·8% / 74·0%	22·0% / 31·0%	Mepolizumab 100 mg SC every 4 weeks to 52 weeks	52 / 52	NPS PNIF UPSIT SNOT-22 Nasal obstruction VAS Time to surgery
Bachert et al. 2017 [4]	105 (54 / 51)	51·0 / 50·0	81·0% / 75·0%	Data not available	Mepolizumab 750 mg IV every 4 weeks x 6 doses	25 / 25	NPS PNIF SNOT-22 Disease severity VAS Nasal obstruction VAS Nasal discharge VAS
Gevaert et al. 2020 [12]: POLYP 1	138 (72 / 66)	50·0 / 52·2	58·3% / 48·5%	22·2% / 16·7%	Omalizumab 75 mg – 600 mg SC every 2 – 4 weeks to 24 weeks†	24 / 24	NPS UPSIT SNOT-22 NCS

Gevaert et al. 2020 [12]: POLYP 2	127 (62 / 65)	49·0 / 51·0	61·3% / 60·0%	38·7% / 32·3%	Omalizumab 75 mg – 600 mg SC every 2 – 4 weeks to 24 weeks†	24 / 24	NPS UPSIT SNOT-22 NCS
Gevaert et al. 2013 [15]	23 (15 / 8)	50·0 / 45·0	100% / 100%	53·0% / 50·0%	Omalizumab SC every 2 – 4 weeks to 16 weeks with maximum total dose 375mg†	16 / 16	NPS LMS NCS Nasal discharge score

N-ERD = non-steroidal exacerbated respiratory disease; SC = subcutaneous; NPS = nasal polyp score; LMS = Lund-Mackay score; SNOT-22 = sinonasal outcome test-22; NBS = nasal blockage score; SCS = systemic corticosteroids; UPSIT = University of Pennsylvania smell identification test; PNIF = peak nasal inspiratory flow; VAS = visual analogue scale; NCS = nasal congestion score. *SINUS-52 had 2 active groups (with different dosing regimes) - the first 2 results are both active groups and the third is the placebo group. † omalizumab dose and frequency calculated based on pre-treatment serum immunoglobulin E (IU/ml) and body weight (kg).

Qualität der Studien:



Studienergebnisse:

- Nasal Poly Score (NPS)
  - Ten studies (4, 9-15) reported change in NPS from baseline, estimating a larger reduction of -1.25 (95% CI -1.68 to -0.81, p<0.001) in the treatment group compared to control (Figure 3a), meaning that the treatment group had a greater reduction in polyp size.
  - The studies evaluating dupilumab (10, 14) showed a much larger subgroup effect than the other drugs, producing a pooled effect of -1.89 (95% CI -2.15 to -1.64); this effect is significantly larger than equivalent pooled effects of benralizumab and mepolizumab (p<0.001) but nonsignificant compared with omalizumab (p=0.385).
- SNOT-22
  - Nine studies (4, 9-14) reported change in disease-specific QoL using SNOT-22 scores (Figure 3e). The overall pooled effect was -14.53 (95% CI -18.28 to -10.79, p<0.001) with moderate heterogeneity between studies (τ2=21.48, I2=69.23%, p=0.001), indicating a significant improvement in QoL.
  - Some heterogeneity can be explained by splitting studies by the intervention drug (p<0.001); this is mainly due to smaller non-significant effect sizes being observed in the two benralizumab studies (effect=-4.57, 95% CI -9.69 to 0.55, p=0.080) (9, 13). Mepolizumab, dupilumab and omalizumab studies reported similar positive intervention effects (4, 10-12, 14).
- Disease severity
  - Three dupilumab (10, 14) and one mepolizumab (4) studies reported change in overall subjective disease severity using a VAS. This resulted in a statistically significant overall pooled mean difference of -2.71 (95% CI -3.33 to -2.09, p<0.001) (Figure 3f), with a lower VAS indicating improvement in disease severity.

- The effect was smaller in the mepolizumab study (effect=-1.80, 95% CI -2.90 to -0.7) (4) compared to those investigating dupilumab (effect=-2.99, 95% CI -3.43 to -2.57) (10, 14)

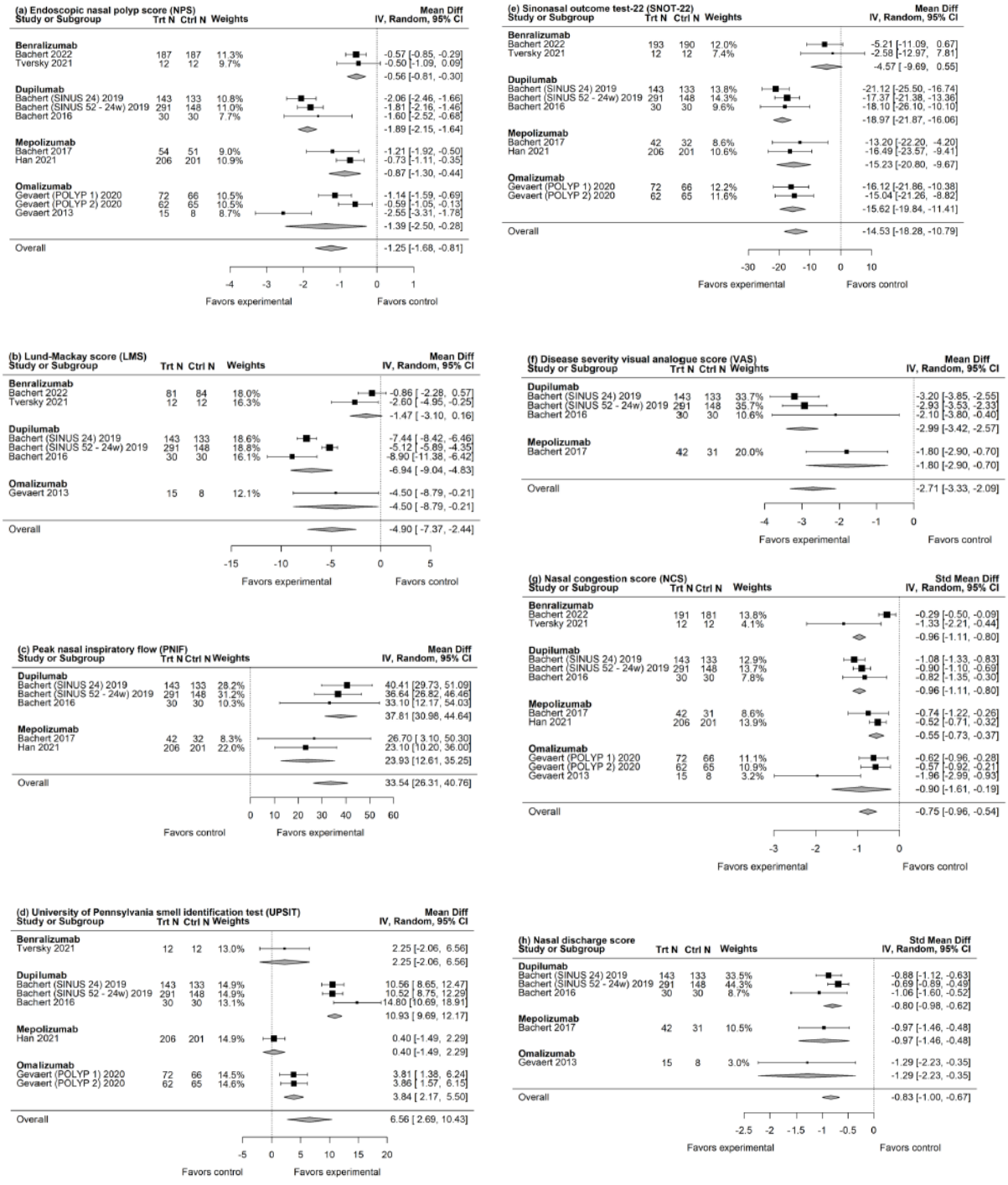


Figure 3. Forest plots showing meta-analyses of mean difference in the following outcomes: a) endoscopic nasal polyp score (NPS); b) Lund-Mackay score (LMS); c) peak nasal inspiratory flow (PNIF); d) University of Pennsylvania smell identification test (UPSIT); e) sinonasal outcome test-22 (SNOT-22); f) disease severity visual analogue score (VAS); g) nasal congestion score (NCS); and h) nasal discharge score with biologic use.

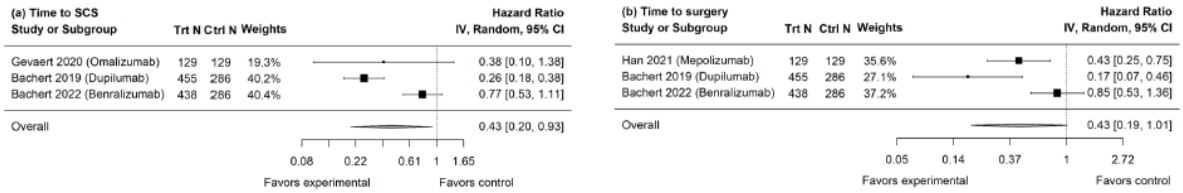


Figure 4. Forest plots showing meta-analyses of: a) a) time to systemic corticosteroids (SCS); and b) time to surgery with biologic use.

Anmerkung/Fazit der Autoren

This meta-analysis analysed key clinical outcome measures in a total of 2021 patients with CRSwNP enrolled in 10 RCTs of at least 12 weeks duration of treatment with the biologics benralizumab (9, 13), dupilumab (10, 14), mepolizumab (4, 11) and omalizumab (12, 15). The overall results confirm improvements in disease outcomes that are relevant to patient care, but the analysis also shows that individual biologics differ in clinical efficacy. None of the studies reported any serious adverse events. Our work allows insight into how biologics may impact patients with CRSwNP in a real-world setting. It shows that biologics modulated disease with improvements in clinical outcomes, although these were measured at different time points in different studies, ranging from 16 weeks to 52 weeks. In addition, some studies included patients who had previously undergone surgery and required revision surgery despite ongoing medical treatment (4, 9, 11) whilst others included subjects who had failed medical treatment but had not necessarily undergone surgery (10, 12-15) so might be considered to have less severe disease. Some biologics performed better than others. However, high heterogeneity in efficacy was present, and no studies directly compared one biologic to another.

In summary, we confirm the clinical efficacy of biologics in treating CRSwNP. Subgroup analysis suggests that dupilumab has a more significant effect than the other biologics. However, as variable inclusion criteria were used for both the active and control groups in each trial, it is difficult to draw firm conclusions as to the efficacy of individual biologics at this stage. The drugs appear to be clinically relevant in CRSwNP refractory to standard treatment.

Kommentare zum Review

Reviews mit ähnlicher Fragestellung und vergleichbaren Ergebnissen:

- Wang Q et al., 2022 [8].
- Wu Q et al., 2021 [9].

Kim DH et al., 2024 [5].

A comparison of doxycycline and conventional treatments of refractory chronic hinosinusitis with nasal polyps: a systematic review and meta-analysis

Fragestellung

To compare the effects of doxycycline (DOX) and conventional management in patients with refractory chronic rhinosinusitis and nasal polyps (CRSwNP).

Methodik

Population:

- refractory CRSwNP

Intervention:

- doxycycline

Komparator:

- conventional treatments, Placebo

Endpunkte:

- k.A.

Recherche/Suchzeitraum:

- PubMed, SCOPUS, Embase, the Web of Science, Google Scholar, and the Cochrane database. All retrieved articles were published before September 2023

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 RCTs

Charakteristika der Population/Studien:

Study (year)	Study design	Sample Size	Age (mean, range, or standard deviation)	Sex (Male/ Female)	Nation	Treatment method	Outcomes
Van Zele (2010)	RCT	47	54.67 (3.07)	38/9	Netherlands	Administration of doxycycline for 20 days ((200 mg on the first day, followed by 100 mg once daily)	Total polyp score, total nasal symptom score, nasal congestion
Pinto Bezerra Soter (2017)	Balanced randomization, open label, trial, non-placebo-controlled study	58	47.50 (16)	27/31	Brazil	Administration of nasal steroids, saline irrigation, and doxycycline (200 mg on the first day, followed by 100 mg once daily) for 12 weeks vs only nasal steroids and saline irrigation	SNOT-20, Lund-Kennedy outcome, nasal congestion
Jain (2018)	RCT	26	49 ± 13	13/13	New Zealand	Administration of doxycycline 100 mg twice daily for 7 days + nasal steroids and saline irrigation vs only nasal steroids and saline irrigation	SNOT-20, Lund-Kennedy outcome
Parasher (2019)	RCT	41	51.5 ± 13.8	26/23	USA	Administration of 20-day course of oral corticosteroids and doxycycline or placebo	SNOT-22, Nasal polyp scores
Mostafa Hashemi (2022)	RCT	104	42.32 ± 12.54	40/29	Iran	Administration of 100 mg of doxycycline with intranasal fluticasone spray, vs intranasal fluticasone spray alone, 12 weeks	SNOT-22, Lund-Kennedy score
Nabavi (2023)	RCT	90	39.9 ± 10.8	41/39	Iran	Administration of doxycycline (200 mg on the first day followed by 100 mg daily with fluticasone, montelukast, and nasal irrigation) or placebo for 6 weeks (with fluticasone, montelukast, and nasal irrigation)	SNOT-22, Nasal congestion, Nasal polyps score, nasal congestion

Qualität der Studien:

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Free of selective reporting	Risk of Bias of randomized studies
Van Zele (2010)	Yes	Yes	Yes	No	Yes	Yes	High
Pinto Bezerra Soter (2017)	Unclear	Yes	Yes	No	Yes	Yes	Unclear
Jain (2018)	Yes	Yes	Yes	No	Yes	Yes	Low
Parasher (2019)	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Mostafa Hashemi (2022)	Unclear	Unclear	No	Unclear	Yes	Yes	High
Nabavi (2023)	Yes	Yes	Yes	No	Yes	Yes	Low

Studienergebnisse:

- The postoperative endoscopic scores
  - DOX significantly reduced clinician-determined Lund- Kennedy (LK) scores [− 0.3670 (range − 0.6173; − 0.1166); I2 = 92.8%] and nasal polyposis scores [− 0.9484 (− 1.2287; − 0.6680); I2 = 92.5%] (Fig. 2). However, significant heterogeneity (I2 > 50%) was apparent because the timepoints of analyses varied. On subgroup analyses by the timepoints (Table 2), the extent of nasal polyposis was significantly lower in DOX groups during treatment [− 1.0600 (− 1.3344; − 0.7856); I2 = NA], at the end of treatment [− 0.8193 (− 1.4950; − 0.1436); I2 = 96.8%], 4 weeks later [− 1.2183 (− 1.3984; − 1.0383); I2 = 0.0%], and 8 weeks later [− 0.7636 (− 1.0139; − 0.5133); I2 = 54.6%]. Endoscopically validated scores indicated improvements during treatment [− 0.2215 (− 0.3240; − 0.1190); I2 = 37.8%] and at the end of treatment [0.5112 (1.0306; 0.0081); I2 = 94.9%].
- Postoperative patient-reported symptom scores
  - DOX improved the patient-reported SNOT score [− 0.3141 range (− 0.4622; − 0.1660); I2 = 91.2%] and nasal obstruction score [− 0.1813 (− 0.3382; − 0.0243); I2 = 86.2%] (Fig. 3). However, these outcomes exhibited significant heterogeneity (I2 > 50%) because the time points of analysis differed. The SNOT score tended to decrease in treatment groups as time passed [during treatment: − 0.1698 (− 0.3722; 0.0326); I2 = 85.0%, at the end of treatment: − 0.3982 (− 0.7446; − 0.0519); I2 = 94.8%), 4 weeks later: − 0.3548 (− 0.8581; 0.1486); I2 = 95.3%, and 8 weeks later: − 0.4670 (− 0.6636; − 0.2704); I2 = NA]. Nasal obstruction symptoms also improved [during treatment: 0.1400 (− 0.0952; 0.3752); I2 = NA, at the end of treatment: − 0.3192 (− 0.5760; − 0.0624); I2 = 89.8%, and 4 weeks later: − 0.1125 (− 0.1943; − 0.0307); I2 = 0.0%] (Table 2).

Anmerkung/Fazit der Autoren

DOX improved the LK and nasal polyposis scores, and the overall sinonasal quality-of-life, of CRSwNP patients.

3.3 Leitlinien

Fokkens W et al., 2020 [3].

European Position Paper on Rhinosinusitis and Nasal Polyps 2020

Zielsetzung/Fragestellung

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

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt, aber Umgang damit im Abstimmungsprozess nicht beschrieben.
- 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 unklar: The EPOS group plans to come with yearly smaller updates on the most relevant changes. Updates wurden nicht indentifiziert.

Recherche/Suchzeitraum:

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

LoE/GoR

- GRADE was used whenever possible

Sonstige methodische Hinweise

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

Empfehlungen

Management of chronic rhinosinusitis in adults

An important difference compared to EPOS2012 is that we have decided to move away from differentiating between the management of CRSsNP and CRSwNP per se. The understanding of the last decade of endotyping of CRS and the consequences of endotypes for the management of disease has led to the decision to describe management of CRS based on endotyping and phenotyping. We propose a new clinical classification based on the disease being localized (often unilateral) or diffuse (always bilateral). (…)

1.6.2. Management of CRS: an integrated care pathway

For the management of CRS, a full systematic review of the literature has been performed. Many forms of localised CRS in general, either type 2 or non-type 2, are not responsive to medical treatment and need surgery. For that reason, we advise patients with unilateral

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

1.6.3. New treatment options with biologicals (monoclonal antibodies)

The acceptance of dupilumab (anti IL-4Rα) for the treatment of CRSwNP by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2019 has significantly changed the treatment options in type 2 type CRS and it is expected that other monoclonal antibodies will follow. (…)

Figure 1.6.2. EPOS2020 management scheme on diffuse CRS.

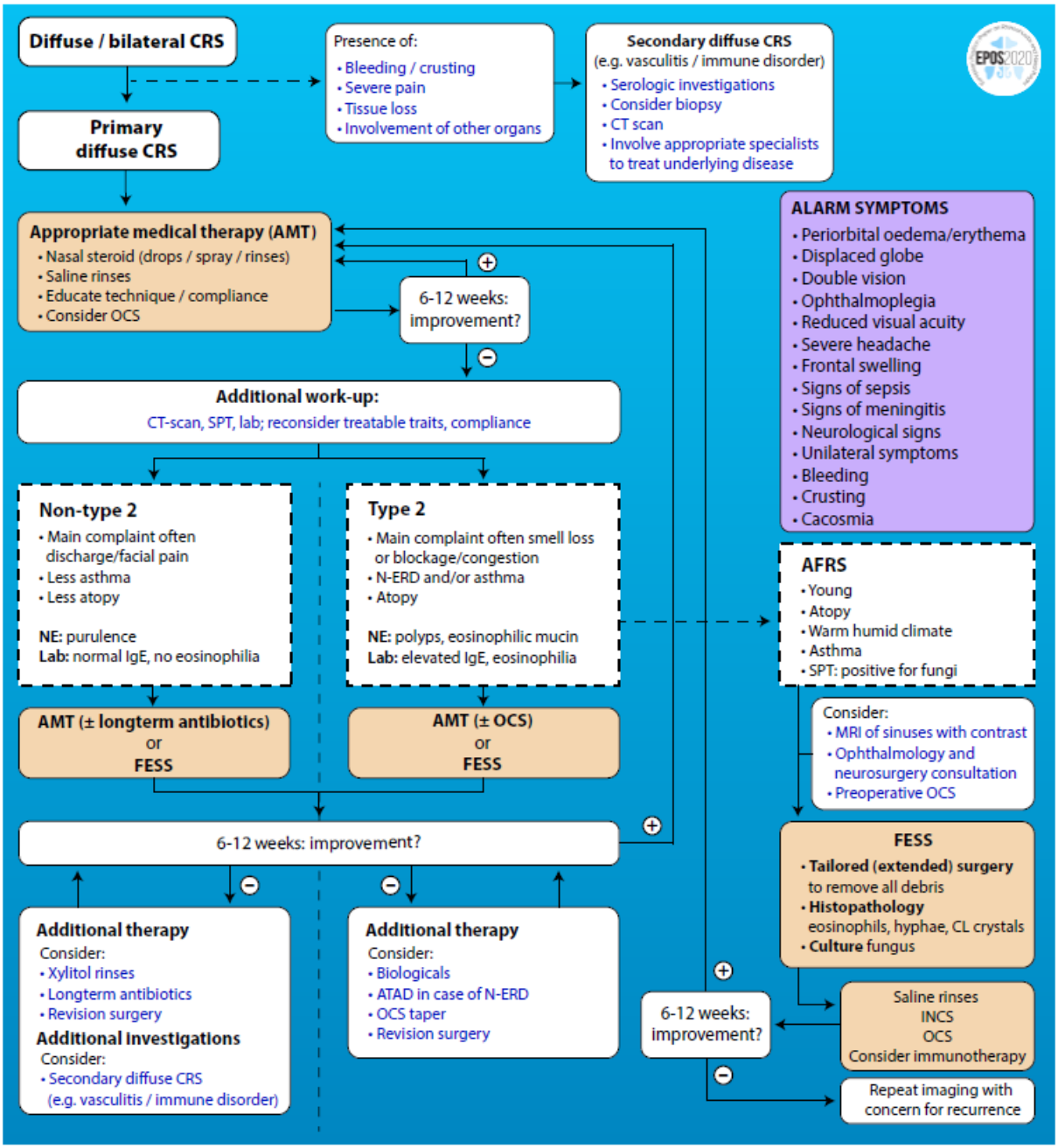
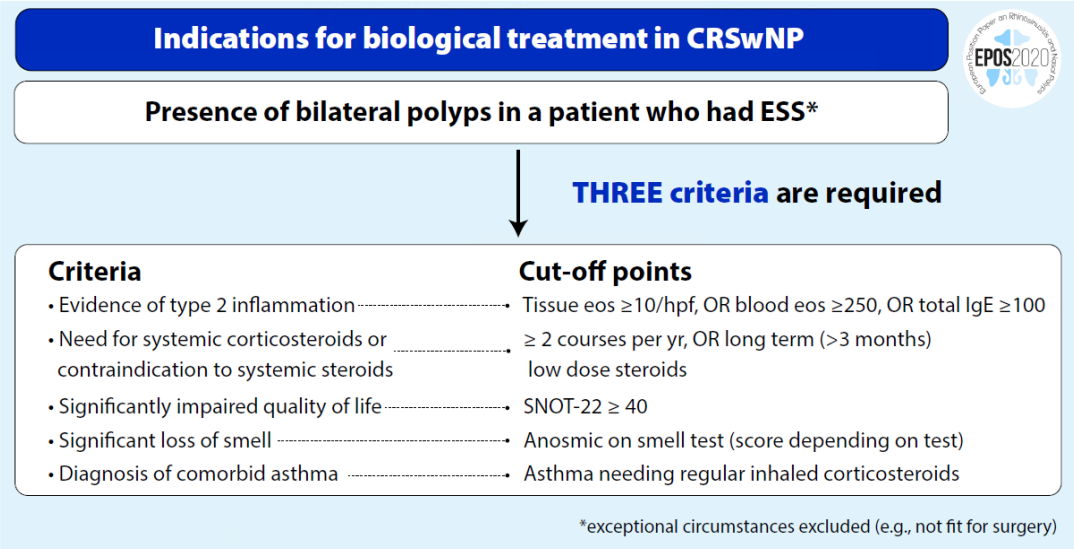


Figure 1.6.3. Indications for biological treatment in CRS.



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

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

Therapy	Level of evidence	GRADE recommendation
Short term antibiotics for CRS	1b (-)	There are only two small placebo-controlled studies, one in CRS and one in acute exacerbation of CRS. Both show no effect on symptomatology apart from significantly reduced postnasal drip symptom scores at week 2 in the CRS study. Seven studies evaluated two different antibiotics regimes, of which only one was placebo-controlled. One out of seven studies in patients with CRS showed a significant effect on SNOT at 2 and 4 weeks and also one study a significant improvment in symptoms of infection at day 3 to 5 in one antibiotic versus another in a mixed group of patients with CRS and with acute exacerbation. The other 5 studies showed no difference in symptomatology. Only two of these seven studies, both of which were negative, evaluated the effect after one month. The EPOS2020 steering group, is uncertain, due to the very low quality of the evidence, whether or not the use of a short course of antibiotics has an impact on patient outcomes in adults with CRS compared with placebo. Also, due to the very low quality of the evidence, it is uncertain whether or not the use of a short course of antibiotics has an impact on patient outcomes in adults with acute exacerbations of CRS compared with placebo. Gastrointestinal-related adverse events (diarrhoea and anorexia) are frequently reported.
Short term antibiotics for acute exacerbation of CRS	1b (-)	The EPOS2020 steering group, is uncertain, due to the very low quality of the evidence, whether or not the use of a short course of antibiotics has an impact on patient outcomes in adults with acute exacerbations of CRS compared with placebo. Gastrointestinal-related adverse events (diarrhoea and anorexia) are frequently reported.
Longterm antibiotics for CRS	1a (-)	The EPOS2020 steering group, due to the low quality of the evidence, is uncertain whether or not the use of long-term antibiotics has an impact on patient outcomes in adults with CRS, particularly in the light of potentially increased risks of cardiovascular events for some macrolides. Further studies with larger population sizes are needed and are underway .

Topical antibiotics	1b (-)	Topical antibacterial therapy does not seem to be more effective than placebo in improving symptoms in patients with CRS. However, it may give a clinically non-relevant improvement in symptoms, SNOT-22 and LK endoscopic score compared to oral antibiotics. The EPOS2020 steering group, due to the very low quality of the evidence, is uncertain whether or not the use of topical antibiotic therapy has an impact on patient outcomes in adults with CRS compared with placebo.
Nasal corticosteroids	1a	There is high-quality evidence that long term use of nasal corticosteroids is effective and safe for treating patients with CRS. They have impact on nasal symptoms and quality of life improvement, although the effect on SNOT-22 is smaller than the minimal clinically important difference. The effect size on symptomatology is larger in CRSwNP (SMD -0.93, 95% CI -1.43 to -0.44) than in CRSsNP (SMD -0.30, 95% CI -0.46). The meta-analysis did not show differences between different kinds of nasal corticosteroids. Although in meta-analysis higher dosages and some different delivery methods seem to have a larger effect size on symptomatology, direct comparisons are mostly missing. For CRSwNP, nasal corticosteroids reduce nasal polyp size. When administered after endoscopic sinus surgery, nasal corticosteroids prevent polyp recurrence. Nasal corticosteroids are well tolerated. Most adverse events reported are mild to moderate in severity. Nasal corticosteroids do not affect intraocular pressure or lens opacity. The EPOS2020 steering group advises to use nasal corticosteroids in patients with CRS. Based on the low to very low quality of the evidence for higher dosages or different delivery methods and the paucity of direct comparisons the steering committee cannot advise in favour of higher dosages or certain delivery methods.
Corticosteroid-eluting implants	1a	The placement of corticosteroid-eluting sinus implants in the ethmoid of patients with recurrent polyposis after sinus surgery has a significant but small (0.3 on a 0-3 scale) impact on nasal obstruction but significantly reduces the need for surgery and reduces nasal polyp score. Based on the moderate to high quality of the evidence the steering group considered the use of corticosteroid-eluting sinus implants in the ethmoid an option.
Systemic corticosteroids	1a ,	A short course of systemic corticosteroid, with or without local corticosteroid treatment results in a significant reduction in total symptom score and nasal polyp score. Although the effect on the nasal polyp score remains significant up to three months after the start of treatment by that time there is no longer an effect on the symptom score. The EPOS2020 steering group felt that 1-2 courses of systemic corticosteroids per year can be a useful addition to nasal corticosteroid treatment in patients with partially or uncontrolled disease. A short course of systemic corticosteroid postoperatively does not seem to have an effect on quality of life. Systemic corticosteroids can have significant side effects.
Antihistamines	Ib	There is one study reporting on the effect of antihistamines in partly allergic patients with CRSwNP. Although there was no difference in total symptom score, the days with a symptom score ≤1 was higher in the treated group. The quality of the evidence comparing antihistamines with placebo was very low. There is insufficient evidence to decide on the effect of the regular use of antihistamines in the treatment of patients with CRS.
Anti-leukotrienes	1b (-)	Based on the very low quality of the available evidence, the EPOS2020 steering group is unsure about the potential use of montelukast in CRS and does not recommend its use unless in situations where patients do not tolerate nasal corticosteroids. Also, the quality of the evidence comparing montelukast with nasal corticosteroid is low. Based on the evidence, the steering group does not advise adding montelukast to nasal corticosteroid but studies evaluating the effect of montelukast in patients that failed nasal corticosteroids are missing.
Decongestant	Ib	There is one small study in CRSwNP patients showing a significantly better effect of oxymetazoline combined with MFNS than MFNS alone without inducing rebound swelling. There was no effect of xylometazoline compared to saline in the early postoperative period. This review found a low level of certainty that adding a nasal decongestant to intranasal corticosteroids improves symptomatology in CRS. Although the risk of rebound swelling was not shown in this study, the EPOS2020 steering group suggests in general not to use nasal decongestants in CRS. In situations where the nose is very blocked, the temporary addition of a nasal decongestant to nasal corticosteroid treatment can be considered.
Nasal irrigation with saline	Ia	There are a large number of trials evaluating the efficacy of nasal irrigation. However, the quality of the studies is not always very good which makes it difficult to give a strong recommendation. However, the data show: Nasal irrigation with isotonic saline or Ringer's lactate has efficacy in CRS patients. There is insufficient data to show that a large volume is more effective than a nasal spray. The addition of xylitol, sodium hyaluronate, and xyloglucan to nasal saline irrigation may have a positive effect. The addition of baby shampoo, honey, or dexpanthenol as well as higher temperature and higher salt concentration do not confer additional benefit. The steering group advises the use of nasal saline irrigation with isotonic saline or Ringer's lactate with or without the addition of xylitol, sodium hyaluronate, and/or xyloglucan and advises against the use of baby shampoo and hypertonic saline solutions due to side effects.
Anti-IgE	Ib	Anti-IgE (amalizumab) therapy has been proposed as a promising biologic therapy for CRS. Two RCTs that evaluated anti-IgE monoclonal antibody (omalizumab) did not show impact on disease specific QOL but one study did show an effect on the physical domain of SF-36 and AQLQ. One study demonstrated lower symptom scores (change from baseline in anti IgE group) for nasal congestion, anterior rhinorrhoea, loss of sense of smell, wheeze and dyspnoea, a significant reduction of NPS on endoscopic examination, and Lund-MacKay scores on radiologic imaging. Due to the small study population in the existing studies, further studies with larger population sizes are needed and are underway. The available data are insufficient to advise on the use of anti-IgE in CRSwNP at this moment.
Anti-Il-5	Ib	There is only one large sufficiently powered study with mepolizumab that showed a significant reduction in patients' need for surgery and an improvement in symptoms. Unlike in CRS, there is a significant experience with anti-Il5 in other type 2 driven diseases like asthma that do show a favourable safety profile so far. The EPOS2020 steering group advises use of mepolizumab in patients with CRSwNP fulfilling the criteria for treatment with monoclonal antibodies (when approved).
Anti IL-4/IL-13 (IL-4 receptor α)	Ia	At the moment the only anti-Il-4 treatment studied in CRS is dupilumab. Dupilumab is the only monoclonal antibody that is approved for the treatment of CRSwNP so far. When evaluating all trials with dupilumab, the drug seems to induce conjunctivitis in trials in patients with atopic dermatitis but not in trials with asthma and CRSwNP. No other adverse events have been reported in the literature until now. The EPOS steering group advises to use dupilumab in patients with CRSwNP fulfilling the criteria for treatment with monoclonal antibodies.

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

Rank MA et al., 2023 [7].

The Joint Task Force on Practice Parameters GRADE guidelines for the medical management of chronic rhinosinusitis with nasal polyposis

Zielsetzung/Fragestellung

These evidence-based guidelines support patients, clinicians, and other stakeholders in decisions about the use of intranasal corticosteroids (INCS), biologics, and aspirin therapy after desensitization (ATAD) for the management of chronic rhinosinusitis with nasal polyposis (CRSwNP). It is important to note that the current evidence on surgery for CRSwNP was not assessed for this guideline nor were management options other than INCS, biologics, and ATAD.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt, aber Umgang damit im Abstimmungsprozess nicht beschrieben.
- 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 unklar.

Recherche/Suchzeitraum:

- Bis September 2021

LoE/GoR

- GRADE was used

- The strength of a recommendation is expressed as either strong ("the guideline panel recommends"), or conditional ("the guideline panel suggests") and has the following interpretations.
- Strong recommendation.
  - For clinicians: Most individuals should receive the intervention or test. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
- Conditional recommendation.
  - For clinicians: Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences. For each conditional recommendation we provide key conditions to guide working with patients in choosing their best treatment course.

Empfehlungen

Question 1: Should INCS (topical corticosteroid), rather than no INCS, be used in CRSwNP?

Recommendation.

In people with CRSwNP, the guideline panel suggests INCS rather than no INCS (conditional recommendation based on low certainty of evidence).

Remarks.

The conditional recommendation for INCS was driven by the small-to-moderate treatment effect size across the 2 critical outcomes, low certainty evidence (particularly in quality of life and harms), and uncertain but anticipated variability in patient values and preferences. Only INCS spray has an effect size whose estimate and 95% CI does not cross the MID achieved for nasal obstruction symptoms:20.51 (95% CI:20.61,20.41) with MID of 0.3.

There are many conditions that may be important during shared decision making for using INCS for CRSwNP. The delivery method of INCS is potentially important. INCS stent, spray, and exhalation delivery system are among the most beneficial of the INCS delivery methods across multiple patient-important outcomes (symptoms, smell, need for rescue surgery). The costs and availability of the different methods of INCS delivery are relevant. Prespecified subgroups, such as studies where surgery occurred at the beginning of the study, did not alter the overall treatment effect. There is moderate certainty of evidence in the safety of INCS spray, but undesirable effects may vary among different INCS treatment types.

Summary of the evidence, benefits, and harms.

Summary of findings and the EtD tables for this question are posted in Table E3 in this article's Online Repository (available at www.jacionline.org; see also Fig 1). For this question the de novo systematic review was updated up to September 1, 2021.8 For disease-specific quality of life using the SNOT-22 scale where a difference of >8.9 points is considered important to patients, the mean difference (MD) compared to placebo of intervention with INCS rinse (MD: 26.83; 95% confidence interval [CI]: 211.94, 21.71) and exhalation delivery system (MD: 27.96; 95% CI: 214.64, 21.08) were among the most beneficial.8 It is important to note that these changes in SNOT-22 score (eg, 26.83 and 27.96) represent the differences from baseline to end of study that exceed the changes in the comparison arm of the trial (ie, between-group difference). For nasal obstruction symptoms score, where >0.3 points on a 0 to 3 symptom scale is considered patient-important, interventions with stent (MD: 20.31; 95% CI: 20.54, 20.08), spray (MD: 20.51; 95% CI: 20.61, 20.41), and exhalation delivery system (MD: 20.35; 95% CI:20.51,20.18) were among the most beneficial.8 Discussion among the guideline panel centered around small versus moderate for judgment of desirable effects, given that both point estimates were very near to the MID. Consensus was that smallto-moderate desirable effects are noted with INCS.

There were no differences found in rates of adverse events, serious adverse events, adverse events requiring a clinical intervention, or adverse events associated with discontinuation of the study for any comparison. There is low or very low certainty in the safety of INCS using delivery methods other than spray. Rates of serious adverse events were 1.6% in the placebo group and ranged from 1.3% to 0.8% in the intervention group depending on the delivery method.7 Specific adverse events (eg, epistaxis) and cortisol axis suppression were not consistently reported, and adverse effects requiring long-term exposure such as osteoporosis were not assessed. The type of topical corticosteroid, dose, and the possibility that patients are

taking additional forms of topical corticosteroid, such as inhalers and skin creams in addition to the INCS, led the group to conclude that undesirable effects may vary in patients.

Assumed values and preferences.

Panel members agreed that there is probably uncertainty in the value and importance patients put on the outcomes of disease-specific quality of life and nasal symptoms scores. The panel members noted a report from Hopkins et al20 detailing results from an online survey with 235 people with CRS (155 practitioners who have patients with CRS and 80 patients with CRS). Symptom based outcomes were suggested by both practitioners and patients to be the most important. The JTF-PP guideline patient partners indicated that ther outcomes such as sense of smell and quality of sleep may be the most important outcomes for some people. For detailed consideration of values and preferences, acceptability of interventions, feasibility of implementation, and required resources please see the EtD table (Table E3).

Balance between desirable and undesirable health effects.

Panel members thought that the overall balance of effects favored INCS. However, they acknowledged that using INCS depends on values and preferences of patients and/or their caregivers for individual outcomes. For those who value the improvement in disease-specific quality of life and nasal symptoms more than the small and varying risk of adverse effects, the balance may favor INCS use. Other management options for CRSwNP that patients and their caregivers could consider include saline rinse, surgery, biologics, and antibiotics.

Question 2: Should biologics, rather than no biologics, be used in CRSwNP?

Recommendation.

In people with CRSwNP, the guideline panel suggests biologics rather than no biologics (conditional recommendation based on moderate certainty of evidence).

Remarks.

The factor driving the conditional recommendation is the availability of other options that should be considered or used together with biologics such as INCS, surgery, and in patients with AERD, ATAD. There are several conditions that may be important during shared decision making about biologics for CRSwNP. Patients who have not sufficiently benefitted from treatments other than biologics, such as any combination of INCS, surgery, or ATAD, may be more likely to value the higher certainty and magnitude of benefits that dupilumab, omalizumab, or mepolizumab are likely to provide. Not all patients, however, need to try medical therapies that are likely to deliver little to no patient-important benefits, or whose efficacy or safety are uncertain. For example, the panel inferred those patients with high baseline disease severity, would likely value the higher certainty and magnitude of benefits over the lower certainty for modest benefits delivered by other medical therapies (eg. INCS [see recommendation 1], ATAD, antibiotics) and harms (eg. ATAD). Conversely, patients with low disease burden, regardless of nasal polyp size, and who have not tried other therapies, might prefer to avoid the burden of systemic therapy with a biologic and its associated payment and insurance negotiation, and accept the lower certainty for modest benefits and less-invasive nature of INCS.

The linked systematic review and NMA showed that the biologics vary in their magnitude of benefits and harms and certainty of evidence across outcomes.9 Dupilumab and omalizumab are the most beneficial for the most patient important outcomes when comparing with other biologics, followed by mepolizumab.9 Patients with comorbid diseases and dual indications for a specific biologic may help direct clinicians to choose a specific biologic (eg, dupilumab improves both atopic dermatitis and CRSwNP; dupilumab's increase in peripheral eosinophilia and possible unmasking of EGPA26-29 may not be optimal for patients with EGPA and mepolizumab or benralizumab might be preferred instead). Biologics may be preferred over ATAD in AERD, especially for patients who have increased risk of harm with ATAD (history of gastrointestinal [GI] bleeding, prednisone use, hypertension, diabetes, smoking, male sex, and lower weight or body mass index).

Summary of the evidence, benefits, and harms.

Summary of findings and the EtD table (Table E4 in this article's Online Repository at www.jacionline.org) for this question are posted in the Online Repository (see also Fig 2). For this question the de novo systematic review was updated up to August 4, 2021.9 For the MD in disease-specific quality of life using the SNOT-22 scale where a difference of >8.9 points is considered patient important, dupilumab (MD: 219.91; 95% CI: 222.50, 217.32) and omalizumab (MD: 216.09; 95% CI: 219.88, 212.30) were the most beneficial.9 For nasal symptoms scores, where 1 point is the MID on a 0- to 10-point symptom, dupilumab (MD: 23.25; 95% CI: 24.31, 22.18), omalizumab (MD: 22.09; 95% CI: 23.15, 21.03), and mepolizumab (MD: 21.82; 95% CI: 23.13, 20.50) were the most beneficial.9 None of the biologics had a significantly different adverse event rate than placebo; however, the certainty of evidence was low or very low.9 Data from use of biologics for other conditions suggest some infrequent risks, such as anaphylaxis with omalizumab (0.09% for people with asthma)24 and conjunctivitis with dupilumab (2% for patients with CRSwNP).25

Assumed values and preferences.

Similarly to questions 1 and 3, panel members agreed that there is probably uncertainty in the value and importance patients put on the critical outcomes of disease-specific quality of life and nasal symptoms scores. For detailed consideration of values and preferences, acceptability of interventions, feasibility of implementation, and required resources please see Table E4, the EtD table .

Balance between desirable and undesirable health effects.

Panel members thought that the overall balance of effects favored biologics over no biologics. However, they acknowledged that using biologics depends on the values and preferences of patients and/or their caregivers for individual outcomes. For those who value the improvement in disease specific quality of life and nasal symptoms more than the small and varying risk of adverse effects, the balance may favor biologic use. Other management options for CRSwNP that patients and their caregivers could consider include saline rinse, surgery, INCS, antibiotics, and, for people with AERD, ATAD.

Orlandi R et al., 2021 [6].

International consensus statement on allergy and rhinology: rhinosinusitis 2021

Zielsetzung/Fragestellung

ICAR-RS-2021 provides a critical review of the diagnosis, pathophysiology, management, and complications of Acute RS (ARS), Recurrent ARS, Chronic RS (CRS) with and without nasal polyps (CRSwNP and CRSsNP), Acute Exacerbation of CRS (AECRS), and Pediatric RS.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt.
- Systematische Suche, Auswahl und Bewertung der Evidenz.
- Formale Konsensusprozesse und externes Begutachtungsverfahren: keine Information;
- 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 2019), EMBASE (1974 to July 2019), and Cochrane Review databases was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standardized guidelines

LoE

Level	Diagnosis	Therapy/Prevention/Etiology
1	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Systematic review of randomized trials or *n*-of-1 trials
2	Individual cross sectional studies with consistently applied reference standard and blinding	Randomized trial or observational study with dramatic effect
3	Cohort study or control arm of randomized trial*	Non-randomized controlled cohort/follow-up study**
4	Case-series or case control studies, or poor quality prognostic cohort study**	Case-series, case-control studies, or historically controlled studies**
5	Not applicable	Mechanism-based reasoning

*Level may be graded down on the basis of study design, inconsistency between studies, indirectness of evidence, imprecision, or because the absolute effect size is very small; level may be graded up if there is a large or very large effect size or if a significant dose-response relationship is demonstrated.
**As always, a systematic review is generally better than an individual study.

GoR

Evidence Quality	Preponderance of Benefit over Harm	Balance of Benefit and Harm	Preponderance of Harm over Benefit
A. Well-designed RCT's	*Strong Recommendation*	*Option*	*Strong Recommendation Against*
B. RCT's with minor limitations; Overwhelmingly consistent evidence from observational studies	*Recommendation*		
C. Observational studies (case control and cohort design)			*Recommendation Against*
D. Expert opinion, Case reports, Reasoning from first principles	*Option*	*No Recommendation*	

Sonstige methodische Hinweise

- An GRADE angelehnte Methodik
- Keine Patienten einbezogen, keine Information zu Konsensusentwicklung
- RCTs und non-RCTs eingeschlossen

Empfehlungen zu CRSwNP:

X.D.1 Management of CRSwNP: Saline (Spray and Irrigation)

Saline for CRSwNP

Aggregate Grade of Evidence:
Saline sprays: No study.
Saline nebulization: B (Level 1: 1 study; level 3: 1 study; Table X-17).
Saline irrigations: No study.
Benefit: Mechanical removal of mucus and improved mucociliary function.
Harm: Minor adverse effects of throat irritation, nasal burning, and epistaxis (see Table II-1).
Cost: Minimal (US$0.24/day).
Benefits-Harm Assessment: Balance of benefit and harm.
Value Judgments: Patients with CRSwNP usually present with thick nasal and postnasal discharge, which requires topical management. Nebulized saline (5 mL) treatment with effective delivery may be given for mechanical removal of thick mucus.
Policy Level: Option.
Intervention: Nebulized saline (5 mL) treatment is an option for treating CRSwNP, particularly patients with thick mucus.

X.D.2 Management of CRSwNP: Topical Corticosteroids

Intranasal Corticosteroids (Standard Delivery) for CRSwNP

Aggregate Grade of Evidence: A (Level 1: 2 studies, Level 2: 5 studies; Table X-18).
Benefit: Improved symptoms, endoscopic appearances, polyp size, and QoL, objective tests of olfaction, airway analysis (NPIF) and polyp recurrence but the magnitude of the clinical effect is small.
Harm: Epistaxis, nasal irritation, headache (see Table II-1).
Cost: Moderate depending on preparation.
Benefits-Harm Assessment: Benefit outweighs harm.
Value Judgments: Twice daily dosing should be considered if the magnitude of observed clinical benefit is limited.
Policy Level:
INCS: Strong Recommendation.
Twice Daily Dosing: Option.
High concentration/dose: No recommendation due to mixed and insufficient evidence.
Intervention: Topical nasal corticosteroids (sprays or drops) are recommended for CRSwNP before or after sinus surgery. Consideration for twice daily dosing or additional short-term corticosteroid drop if initial treatment effect is small.

X.D.2.a. Topical Corticosteroids: Standard Delivery (Drops and Sprays)

The use of INCS for CRSwNP has been well studied, with ICAR-RS-2016 demonstrating level A aggregate evidence. From 2014 to 2020, a new search on INCS use in CRSwNP resulted in 1213 publications, Medline (154) and Embase (1059). From these citations, an additional 5 RCTS1539–1543 and 2 systematic reviews with metaanalyses1544,1545 have been identified. As the prior review of the literature demonstrated 36 RCTs in the setting of CRS which compared topical corticosteroid against placebo,1064,1068,1355,1546–1578 lower levels of evidence were not considered. A summary of these updated outcomes is provided in Table X-16 with all demonstrating a significant benefit from the use of INCS as sprays or drops over placebo alone.

The updated Cochrane review included 14 studies on CRSwNP alone.1545 The reported improvement in nasal polyp score was higher in patients on INCS (RR, 1.77; 95% CI, 1.06-2.95; 676 participants; 5 studies; I2 = 66%). When the absolute proportions of patients improving their polyp score were combined from 8 studies, the overall pooled odds ratio (OR) was 2.07 (95% CI, 1.48-2.91; 1984 participants; 8 studies) favoring the INCS group. For individual symptoms, the corticosteroid group was favored in nasal blockage: MD −0.40 (95% CI, −0.52 to −0.29; 1702 participants; 6 studies; I2 = 47%), rhinorrhea:MD −0.25 (95% CI, −0.33 to −0.17; 1702 participants; 6 studies; I2 = 6%), and loss of sense of smell: MD −0.19 (95% CI, −0.28 to −0.11; 1345 participants; 4 studies; I2 = 0%) but not for facial pain/pressure: MD −0.27 (95% CI, −0.56 to 0.02; 243 participants; 2 studies; I2 = 78%).

Twice daily dosing. Previous reviews and meta-analyses have been published to explain variations in observed clinical effect such as technique, surgical state and agent. Notably, a systematic review on the use of twice daily dosing of INCS in the setting of CRSwNP was performed.1544 The authors' conclusion was that across 6 RCTs (which include some with exhalation delivery) and 1712 patients, there was a preponderance of evidence favoring twice daily dosing, with 4 RCTs supporting twice daily dosing over once a day. The authors of this study simply assessed the studies in their dose groupings and a formal meta-analysis was not performed. In a separate RCT by Khan et al., 310 adult patients used mometasone 200 µg once or twice daily (and placebo). Over a 4-month period, the authors report a greater improvement in rhinorrhea, post-nasal mucus, nasal peak inspiratory flow (NPIF) and polyp score in the twice daily over once daily group. However,

the data reporting in this study is poor.1542 A small cohort study, assessing post ESS CRSwNP patients that had mild recurrent polyps on once daily mometasone 200 µg were evaluated on twice daily regime, finding reduced polyp score over once daily therapy.1581

Higher concentration dosing. Although prior studies have compared low dose to high dose of topical corticosteroid,1064,1555,1558,1561,1563,1564,1568,1571 recent RCTs from Zhou et al.1543 and Seiberling et al.1541 used higher concentrations of mometasone and dexamethasone, respectively. These studies did not find an observed clinical benefit. Remarkably, only limited clinical improvement is seen by a twice daily mometasone study1543 and the improved measures of inflammatory changes in NP tissue are also limited.1582

The addition of budesonide drops (1 mg/d + budesonide spray 256 µg/d)was assessed for a 1week period, compared to oral methylprednisolone (24 mg/d + budesonide spray 256 µg/d), and a control group (budesonide spray 256 µg/d). Improved endoscopic scores were reported and a change of total nasal symptoms score of 5.71 ± 6.34 in the control group, 9.33 ± 8.78 in nasal drop group and 8.99 ± 7.09 in oral corticosteroid group. These data are not in press but are from conference proceedings.1540

Adverse effects. From the Cochrane review, the evidence for the risk of epistaxis was high. Epistaxis is the most common adverse event together with nasal irritation producing itching, sneezing and dryness. The risk of epistaxis was higher in the INCS group compared to placebo (RR, 2.74; 95% CI, 1.88 to 4.00; 2508 participants; 13 studies; I2 = 0%). No increase in infection or specifically candidiasis has been detected. These minor or moderate adverse events are generally tolerated by patients. None of the studies treated or followed up patients for long enough to report adverse events related to systemic side-effects. Additionally, systemic bioavailability of INCS varies from <1% up to 40-50%, which will influence the risk of systemic adverse effects.1583

Long-term administration of INCS to the respiratory mucosa, evaluated by systematic review, does not show any evidence of damage to the nasal mucosa. This review demonstrated that from 34 studies that assessed the nasal mucosa via biopsy, including 11 randomized controlled trials, 5 cohorts, and 20 case series (with a duration of treatment ranging from5 days to 5.5 years), no atrophic changes were observed. There were 2 studies that demonstrated the protective effects of INCS against remodeling changes such as squamous metaplasia.1584 This protection against mucosal remodeling1584 is relevant as such changes have been implicated in poorer clinical outcomes.1585

X.D.2.b. Topical Corticosteroids: Nonstandard Delivery

Intransal Corticosteroids (Nonstandard Delivery) for CRSwNP

Aggregate Grade of Evidence (Versus standard delivery):
Corticosteroid Irrigation: A (Level 1: 5 studies, level 3: 1 study).
Exhalation delivery: A (Level 1: 4 studies).
Atomization/nebulization: A (Level 1: 4 studies).
Direct injection: N/A (Level 1: 1 study; Table X-19).
Benefit:
Corticosteroid Irrigation: Benefit over INCS.
Exhalation delivery: Benefit only over placebo.
Atomization/nebulization: Benefit over INCS.
Direct injection: Potential avoidance of oral corticosteroid.
Harm: Some evidence of systemic absorption with first generation corticosteroid especially with multiple modalities of therapy (see Table II-1).
Cost: Moderate. Exhalation system costs are significantly higher than standard therapy.
Benefits-Harm Assessment: Negligible side effects compared with oral corticosteroids but caution in patients on multiple topical therapies.
Value Judgments: Corticosteroid irrigations and atomization are likely to be of value in those patients not controlled with standard delivery. Exhalation has not been proven to be better than standard delivery. Direct injection needs more safety data.
Policy Level:
Corticosteroid Irrigation: Strong Recommendation.
Exhalation delivery: Option.

Atomization/nebulization: Recommendation.
Direct injection: No recommendation due to insufficient evidence.
Intervention: Following sinus surgery, those patients with CRSwNP that have moderate-severe disease or are not controlled with simple INCS should be offered corticosteroid irrigation and/or atomized delivery.

X.D.3 Management of CRSwNP: Steroid-Eluting Implants (Nonsurgical)

Steroid Eluting Implants for CRSwNP

Aggregate Grade of Evidence: A (Level 1: 1 study; level 2: 3 studies; Table X-20).
Benefit: Reduction in ethmoid sinus obstruction and polyp grade leading to decreased need for revision ESS and reduced nasal obstruction patient scores.
Harm: No prior findings of increased risk of elevated intraocular pressure or cataracts.
Cost: Cost of implant and risk of nasal discomfort and/or epistaxis.
Benefits-Harm Assessment: Benefit outweighs harm.
Value Judgments: Corticosteroid eluting implants have been shown to have beneficial impact on ethmoid polyposis and obstruction, and 1 study has shown them to be cost-effective in preventing revision ESS. Experience is early and although evidence is high level, only short-term outcomes are currently available.
Policy Level: Option.
Intervention: Corticosteroid-eluting implants can be considered as an option in a previously operated ethmoid cavity with recurrent nasal polyposis.

X.D.4 Management of CRSwNP: Oral Corticosteroids

Oral Corticosteroids for CRSwNP

Aggregate Quality of Evidence: A (Level 2: 7 studies; Table X-21).
Benefit: Significant short-term improvements in subjective and objective measures in CRSwNP patients. Duration of improvement may last 8-12 weeks in conjunction with topical intranasal corticosteroid use.
Harm: More GI symptoms in steroid group, rare severe reactions occur. Transient adrenal suppression, insomnia, and increased bone turnover. All known corticosteroid risks exist, particularly with prolonged treatment. See Table II-1.
Cost: Low.
Benefits-Harm Assessment: Preponderance of benefit to harm with short-term burst with limited, short-term follow-up.
Value Judgments: Significant short-term improvements in subjective and objective measures based on high quality data, low risk and low cost.
Policy Level: Strong recommendation for short-term use.
Intervention: Strong recommendation for the use of oral corticosteroids in the **short-term** management of CRSwNP. Longer term use of steroids for CRSwNP is not supported by the literature and carries and increased risk of harm to the patient.

Since the publication of ICAR-RS-2016, there have been 2 Cochrane Reviews analyzing the data on oral corticosteroid use in the management of CRSwNP. Both reviews were from the same group in the United Kingdom and very thoroughly summarize the existing data.

The first review evaluated the data on short courses of oral corticosteroids alone for CRS.1613 The authors identified 7 studies, all of which were randomized controlled trials. Two studies were unblinded while the remaining 5 blinded both the patients and the health care providers to the treatment group. All patients were adults with the diagnosis of CRSwNP with varying degrees of severity of the disease amongst the studies. Three studies had no minimal grade of nasal polyps for inclusion, 2 required moderate-to-severe bilateral polyps, and 3 studies only included severe nasal polyposis.

All studies reported positive results for short course of oral corticosteroids compared to placebo (5 studies) or no treatment (2 studies). Corticosteroid courses ranged from 14-21 days and included prednisone, prednisolone and methylprednisolone. Total doses ranged from 210 mg to over 1000 mg of prednisone equivalent.

The review reported low quality evidence of an improvement in disease-specific health-related QoL as well as in disease severity after treatment with oral corticosteroids compared to the controls at various time points. After the treatment period had ended, there was no difference in the change frombaseline symptom severity between the treatment groups.

There was evidence that immediately after treatment, oral corticosteroids provided improvement in nasal polyp scores. The magnitude of this improvement months after treatment may not be sustained. A high risk of bias existed for both statements.

When analyzing data on the side effects of corticosteroids, there was low quality evidence of increase in insomnia and gastrointestinal disturbances in the steroid group. There was low quality evidence regarding mood disturbances between the 2 groups and any difference between groups was unclear.

The second review evaluated the data on oral corticosteroids as an adjunct in patients with CRSwNP.1614 The authors identified 2 studies, only 1 of which included adults. This study was an unblinded, quasi-randomized controlled trial in 30 adults with CRSwNP based on endoscopic examination. Patients were treated with a 21 day course of topical INCS alone, oral methylprednisolone alone, or both. The included outcome was the endoscopic nasal polyp score measured on a 4 point scale. The patients receiving the oral

corticosteroids plus topical intranasal steroids had an improvement in the nasal polyp score compared to the topical intranasal corticosteroid alone, though there was a high risk of bias in these data.

Providers must also consider the potential risks associated with oral corticosteroid use. A cost analysis compared the risks of corticosteroids with those of sinus surgery in CRSwNP patients. The authors evaluated reported complication rates, QoL changes and Medicare costs between the 2 treatments. They concluded that the breakeven threshold, favoring surgery over medical therapy, occurred when more than 1 corticosteroid course was given every 2 years in CRSwNP patients, once per year in CRSwNP patients with asthma, and twice per year in AERD patients. Of note, CRSsNP patients were not included in the analysis.1615

In summary, evidence exists to support short-term use of oral corticosteroids, either alone or as an adjunct, in symptomatic treatment and polyp size regression in patients with CRSwNP. Variable drugs, dosing and duration were used in the reviewed literature. The beneficial effects last for a short duration only and potential adverse effects of a single burst or multiple short-term bursts must be considered when treating patients.

X.D.5 Management of CRSwNP with Antibiotics

X.D.5.a. Antibiotics for CRSwNP: Oral Non-Macrolide Antibiotics for <3Weeks

Oral Non-Macrolide Antibiotics for <3 Weeks for CRSwNP

Aggregate Grade of Evidence: B (Level 2: 1 study, Level 3: 2 studies; Table X-22).
Benefit: Potential reduction in polyp size with doxycycline without change in symptoms.
Harm: Adverse events in the medication groups included gastrointestinal upset, skin rash, insomnia, and headache; delay of more effective interventions (see Table II-1).
Cost: Variable depending on the antibiotic.
Benefits-Harm Assessment: Preponderance of harm over benefits.
Value Judgments: A lack of evidence and known adverse effects outweigh the possible benefit for routine use.
Policy Level: Recommendation against.
Intervention: Short courses (<3 weeks) of non-macrolide antibiotics should generally not be prescribed for CRSwNP except in acute exacerbations.

Since ICAR-RS-2016 there has been little change in the literature to support the use of short-term antibiotics for CRSwNP.Most articles are concerned with antibiotic treatment of AECRS.

In an EBRR on antimicrobials in CRS published in 2013, Soler et al. found only 6 studies examining the short-term (<3 weeks) use of antibiotics in CRS.1119 Only 1 of these, Van Zele et al., differentiated CRSwNP from CRSsNP patients.1619 A recent Cochrane review on antibiotic use in CRS, both systemic and topical, also highlighted this article.1105 Van Zele et al. designed a double-blind prospective RCT of 47 total patients in which 1 study group took doxycycline 200 mg once followed by 100 mg daily for 20 days. This was compared to 2 groups, one who received a tapering dose of methylprednisolone and another prescribed a placebo. The authors found that this short course of antibiotics resulted in a small but significant decrease in nasal polyp score as measured on endoscopy. The effect lasted the full 12 weeks of the study but was modest in effect; symptoms were also not significantly affected long-term. The authors point out that the intrinsic anti-inflammatory effects of doxycyclinemay have been responsible for the reduction in polyp size in addition to or instead of the anti-microbial effect.

Since the Soler et al. review there have been only a few trials examining antibiosis in CRSwNP. Sreenath et al. prospectively treated CRSwNP patients with a variable duration of antibiotics.1622 The primary outcome was whether patients were recommended surgery after treatment. The authors randomized nasal polyposis patients to take doxycycline 100 mg twice daily for either 3 or 6 weeks. At follow-up they found no statistical difference in provider recommendation for surgical intervention; at 3 weeks they recommended that 7 out of 7 patients have surgery (100%) whereas in the 6-week cohort they recommended that 5 out of 7 patients have surgery (71%). Between these groups there was no significant difference in symptoms as measured by RSDI nor post-treatment Lund-Mackay CT scores. In fact, the authors noted that symptom scores worsened

with longer antibiotic prescriptions. They concluded that in treating CRS with maximal medical therapy the duration of antibiotics may be unimportant and that antibiotics are potentially not indicated. These results are limited by the small sample size, but this is surprisingly the largest cohort study of this kind in the literature.

At the World Allergy Conference in 2015, Schryver et al. described a series of RCTs for medical therapy for CRSwNP.1623 They randomized patients to either 1) a 20- day course of doxycycline, 2) a 20-day steroid taper, 3) 2 injections of mepolizumab, 4) 2-4 injections of omalizumab, or 5) placebo. The patients were then evaluated at 4 and 8weeks for changes in endoscopic polyp score, symptoms, or inflammatory markers as measured in serum and nasal secretions. They reported significant improvement in polyp score in all groups, including doxycycline. However, these results were only published in abstract form, so no determination was made on the quality of this study. Most recently, Parasher et al. attempted to study doxycycline against placebo in an RCT for CRSwNP with moderate to severe symptoms as measured on a VAS.1624 Patients were randomized to a 20-day course of doxycycline or placebo; both groups were also prescribed an oral methylprednisolone taper. The primary endpoint was change in SNOT-22 score as measured at 12 weeks. Unfortunately, the authors found this patient population quite difficult to study; 26 of the 49 recruited patients dropped out of the study (53%) and the study was terminated before reaching the expected number needed to properly power their hypothesis. The majority of the dropouts were due to acute exacerbations of asthma or CRS symptoms (58%) and 81% of the dropouts occurred after the treatment period but before the end of the trial period. There was no difference in dropouts between the treatment arms. The authors found no significant difference in SNOT-22 scores, VAS scores, nor endoscopic nasal polyp score when they performed amixed-effect model analysis. They concluded that the early end to their trial likely meant that the addition of doxycycline had limited utility in the medical management of moderate to severe CRSwNP.

Despite the widespread use of antibiotics in CRSwNP there is actually little evidence, some of it conflicting, of their efficacy. Given the potential adverse effects of antibiotics, as discussed in previous sections, the use of short courses of oral non-macrolide antibiotics in a nonacute exacerbation of CRSwNP should be discouraged.

X.D.5.b. Antibiotics for CRSwNP: Oral Non-Macrolide Antibiotics for ≥3Weeks

Oral Non-Macrolide Antibiotics for >3 Weeks for CRSwNP

Aggregate Grade of Evidence: D (Level 3: 1 study, Level 4: 2 studies; Table X-23).
Benefit: Potential symptom relief.
Harm: Adverse effects of antibiotics include skin rash, gastrointestinal upset, and anaphylaxis; delay in more effective therapy (see Table II-1).
Cost: Variable depending on the antibiotic.
Benefits-Harm Assessment: Balance of benefit and harm.
Value Judgments: A lack of evidence and known adverse effects may outweigh the possible benefit.
Policy Level: No recommendation.
Intervention: Practitioners should weight the risks and benefits of extended courses (>3 weeks) of non-macrolide antibiotics for CRSwNP and know that the literature is sparse.

X.D.5.c. Antibiotics for CRSwNP: Macrolide Antibiotics

Macrolide Antibiotics for CRSwNP

Aggregate Grade of Evidence: B for CRS overall with limited evidence regarding CRSwNP specifically (Level 1: 5 studies; level 2: 3 studies; level 3: 5 studies; Table X-24).
Benefit: Macrolides may improve symptom scores and endoscopic scores in CRSwNP patients. But results are mixed among 3 RCTs.
Harm: Significant potential for medication interactions. Rare mild adverse events, such as gastrointestinal side effects, ototoxicity, hepatotoxicity, cardiotoxicity. See Table II-1.
Cost: Low.
Benefits-Harm Assessment: Unclear benefit-to-harm ratio in CRSwNP patients. Benefits of treatment over placebo, and benefits of adding macrolides to other treatment were seen in some studies but not others.
Value Judgments: Optimal drug, dosage, and duration of therapy are not known.
Policy Level: Option.
Intervention: In CRSwNP, macrolides may be beneficial, especially in neutrophil-dominant polyps or in those who are unresponsive to corticosteroids.

X.D.7 Management of CRSwNP: Biologic Therapy

Dupilumab

Dupilumab for CRSwNP

Aggregate Grade of Evidence: A (Level 2: 3 studies).
Benefit: Dupilumab decreased polyp size, improved nasal congestion, sinus imaging scores, sense of smell and asthma control.
Harm: Conjunctivitis and hypereosinophilia are rare.
Cost: High cost per injection; total duration of therapy not yet defined.
Benefits-Harm Assessment: Likely benefit over harm in patients with CRSwNP not responsive to medical and surgical standard of care.
Value Judgments: Cost-effectiveness, optimal dose and duration of therapy not yet clear.
Policy Level: Recommendation for dupilumab in patients with severe CRSwNP.
Intervention: Dupilumab may be considered for patients with severe CRSwNP who have not improved despite other medical and surgical treatment options.

This is one of two biologics with US FDA approval for use in CRSwNP. We identified 3 trials with dupilumab as the intervention for CRSwNP. In 2016, an RCT found a reduction in nasal polyp score in participants receiving dupilumab compared to placebo.56 In 2019, Bachert et al. published the phase 3 trial results of dupilumab;

the report included results from 2 RCT arms (LIBERTY NP SINUS-24 and −52).60 Nasal polyp score (NPS) was graded from 0-4 on each side, with 8 being the maximum and worst score; a minimum score of 5 was necessary for enrolment into the study.

Subjects in both trials were given 100 µg mometasone nasal sprays twice daily in addition to dupilumab or control. In the first trial, participants received dupilumab 300 mg subcutaneously every 2 weeks (n = 143) x 24 weeks or placebo (n = 133). In the second trial, participants received dupilumab 300 mg every 2 weeks for the first 24 weeks (n = 295) or placebo (n = 153) and then subjects were either given dupilumab 300mgQ2weeks (n=150) or dupilumab 300 mg Q 4 weeks (n = 145) for 52 weeks.

In the larger 2019 study, the authors reported a least mean square difference of −2.06 and −1.8 at 24 and 52 weeks in NPS with use of dupilumab vs placebo. The difference in Lund-Mackay CT scores in study vs placebo group was –7.44 and –5.13 at 24 and 52 weeks, respectively. The magnitude of improvements in patient subgroups with comorbid asthma, NSAID-exacerbated respiratory disease, or previous surgery was similar to that in the overall treatment population. Participants who continued to receive treatment every 2 weeks during weeks 24 to 52 had overall similar results compared to those who received treatment every 4 weeks during weeks 24 to 52. The most commonly reported adverse events in the study groupwere nasopharyngitis, injection-site reactions, and headache, all more common than in the placebo group. Conjunctivitis was reported in 7 patients receiving dupilumab and in 1 patient receiving placebo, none severe enough to discontinue therapy. Four patients had eosinophilia with clinical symptoms reported as treatment-emergent adverse events: 1 patient had eosinophilic granulomatosis with polyangiitis (EGPA) during treatment with dupilumab; 1 had eosinophilia associated with arthralgia, asthma exacerbation, and insomnia during dupilumab treatment; 1 had EGPA more than 300 days after a single dupilumab dose; and 1 had EGPA while receiving placebo.

The results from the study should be considered in the context of standard treatments for CRSwNP such as oral corticosteroids, office-based nasal polypectomy and formal revision surgery. Dupilumab had a modest effect on nasal polyp size (average reduction about 25% of total 8-point nasal polyp scale), nasal congestion and smell improvement when considering the overall study group. Dramatic effects in nasal polyp size and smell recovery was reported in some but not all patients, reinforcing the need to better identify factors that most likely predicate response to the therapy. This need to predict response is even more important in light of the high costs of this treatment. The effect of dupilumab on the need for surgery was modest. Based on the data60 the absolute risk reduction for the study period was 10/143 (dupilumab) vs 25/133 (placebo), an absolute risk reduction estimated to be 10%. In summary, dupilumab is recommended for patients with CRSwNP, especially those who have failed more conventional treatment. Further studies are needed to help decide how to use dupilumab in the context of other medical and surgical treatment options, as well as optimal dose and duration of dupilumab treatment.

Mepolizumab

Mepolizumab for CRSwNP

Aggregate Grade of Evidence: C (Level 3: 2 studies).
Benefit: Mepolizumab decreased polyp size and need for surgery.
Harm: Adverse medication side effects; most common being injection site reaction.
Cost: High cost per injection; total duration of therapy not yet defined.
Benefits-Harm Assessment: Benefit for CRSwNP not clear.
Value Judgments: Consider for CRSwNP in context of asthma or EGPA; dosage used for trial in CRSwNP is higher than available for standard therapy of asthma and EGPA.
Policy Level: Option for patients CRSwNP and asthma.
Intervention: Consider as option for severe CRSwNP with concomitant poorly controlled eosinophilic asthma.

Two trials have been conducted for mepolizumab in patients with CRSwNP.57,1644 The earlier study was performed by Gevaert in 2011, who reported efficacy in reducing polyp size in severe nasal polyposis.1644 Bachert in 2017 conducted an RCT that showed reduced need for revision sinus surgery following treatment with mepolizumab. Both mepolizumab studies involved an intervention dose of 750 mg IV, the formulation and strength available at the time of study, which is not currently available (100 mg for asthma and 300 mg, both subcutaneous, available for asthma and EGPA, respectively). In summary, mepolizumab is an option for patients with CRSwNP who have comorbid eosinophilic asthma.

Reslizumab

Reslizumab for CRSwNP

Aggregate Grade of Evidence: C (Level 3: 1 study).
Benefit: Reslizumab decreased polyp size.
Harm: Adverse medication side effects including anaphylaxis (rare).
Cost: High cost per injection; total duration of therapy not yet defined.
Benefits-Harm Assessment: Benefit for CRSwNP not clear.
Value Judgments: Consider in context of CRSwNP with uncontrolled asthma (indication for which reslizumab is US FDA approved).
Policy Level: Option for patients with CRSwNP and asthma.
Intervention: Can be considered as option for severe CRSwNP with concomitant poorly controlled eosinophilic asthma.

A single RCT was identified using reslizumab for CRSwNP. There was inconsistency between the outcomes for the 3 mg/kg and 1 mg/kg dosing, and the study included a small number of participants.59

Omalizumab

Omalizumab for CRSwNP

Aggregate Grade of Evidence: B (Level 2: 1 study; level 3: 2 studies; level 4: 2 studies).
Benefit: Omalizumab improved polyp size in 1 study and patient-reported outcomes in 3 studies.
Harm: Risk for anaphylaxis (rare).
Cost: High cost per injection; total duration of therapy not yet defined.
Benefits-Harm Assessment: Likely benefit over harm in patients with CRSwNP not responsive to medical and surgical standard therapy.
Value Judgments: Cost-effectiveness, optimal dose, and duration of therapy not yet clear.
Consider for CRSwNP in context of allergic asthma uncontrolled with standard therapy.
Policy Level: Option to weak recommendation for patients with severe CRSwNP who have not improved despite other medical and surgical treatments. Weaker recommendation is based on limited body of evidence and high costs.
Intervention: Consider for severe CRSwNP with concomitant poorly controlled allergic asthma.

Omalizumab is the other biologic with FDA approval for use in CRSwNP patients. We identified 6 studies for omalizumab and nasal polyposis. Gevaert et al. reported results of 2 identical replicate (POLYP 1 and POLYP 2) DBRCTs studying omalizumab added to mometasone nasal spray vs placebo with mometasone nasal spray for 24 weeks. Inclusion criteria were patients aged 18-75 years with persistent bilateral nasal polyps, nasal congestion, impaired HRQoL, and weight and serum IgE level permitting omalizumab dosing per weight of 30-50 kg and serum IgE level of 30- 1500 IU/mL).Co-primary end points included change from baseline to week 24 in Nasal Polyp Score (NPS) and Nasal Congestion Score. Secondary end points included change from baseline to week 24 in Sino-Nasal Outcome Test-22 (SNOT-22) score, UPSIT, sense of smell, postnasal drip, runny nose, and adverse events. In POLYP 1 and POLYP 2, the mean changes from baseline at week 24 for omalizumab vs placebo were as follows: NPS, –1.08 vs 0.06 ($p < 0.0001$) and –0.90 vs –0.31 (P 5 .0140); Nasal Congestion Score, –0.89 vs –0.35 (P 5.0004) and –0.70 vs –0.20 (P 5.0017); and SNOT-22 score, –24.7 vs –8.6 ($p < 0.0001$) and –21.6 vs –6.6 ($p < 0.0001$). Adverse events were similar between groups.1645 Pinto et al.1174 in 2010 studied CRS in 14 patients (12 CRSwNP) and found no difference on the primary endpoint of sinus CT. The study was limited by a small sample size. Gevaert et al.58 studied 20 subjects with CRSwNP in an RCT and reported benefits in nasal polyp size and symptoms. Bidder et al. reported a small case control study suggesting patients taking omalizumab have improved patient-reported outcome scores.1642 Mostafa et al. performed a single-blinded and small study in patients with CRSwNP (AFRS subtype) and reported that patients taking omalizumab have improved patient-reported outcome scores.1643 Hayashi et al. used omalizumab in 21 patients with CRSwNP and AERD. They identified reduction in urinary LTE4 and the PGD2 metabolite, suggests a mechanism of action of omalizumab that may work irrespective of “allergy” status.1646

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 08 of 12, August 2024) am 28.08.2024

#	Suchfrage
1	[mh Sinusitis]
2	[mh Rhinitis]
3	[mh "Nasal Polyps"]
4	(rhinosinusitis OR rhino-sinusitis OR nasosinusitis OR pansinusitis OR ethmoiditis OR sphenoiditis OR kartagener*):ti,ab,kw
5	((inflamm* OR maxilla* OR frontal*) AND sinus*):ti,ab,kw
6	((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
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	#7 with Cochrane Library publication date from Aug 2019 to present

Systematic Reviews in PubMed am 28.08.2024

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	Sinusitis[mh]
2	Rhinitis[mh]
3	rhinosinusitis[tiab] OR rhino-sinusitis[tiab] OR nasosinusitis[tiab] OR pansinusitis[tiab] OR ethmoiditis[tiab] OR sphenoiditis[tiab] OR kartagener*[tiab]
4	(inflamm*[tiab] OR maxilla*[tiab] OR frontal*[tiab]) AND sinus*[tiab]
5	#1 OR #2 OR #3 OR #4
6	Nasal Polyps[mh]
7	(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]) AND (papilloma*[tiab] OR polyp[tiab] OR polyps[tiab] OR polyposis[tiab])
8	#6 OR #7
9	Chronic Disease[mh] OR Recurrence[mh]
10	chronic[tiab] OR persis*[tiab] OR recurren*[tiab]
11	#9 OR #10
12	(#5 OR #8) AND #11
13	CRSwNP[tiab] OR CRSwp[tiab]
14	#12 OR #13

#	Suchfrage
15	(#14) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
16	(#15) AND ("2019/08/01"[PDAT] : "3000"[PDAT])
17	(#16) NOT "The Cochrane database of systematic reviews"[Journal]
18	(#17) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 28.08.2024

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	Sinusitis[mh]
2	Rhinitis[mh]
3	rhinosinusitis[tiab] OR rhino-sinusitis[tiab] OR nasosinusitis[tiab] OR pansinusitis[tiab] OR ethmoiditis[tiab] OR sphenoiditis[tiab] OR kartagener*[tiab]
4	(inflamm*[tiab] OR maxilla*[tiab] OR frontal*[tiab]) AND sinus*[tiab]
5	#1 OR #2 OR #3 OR #4
6	Nasal Polyps[mh]
7	(nose*[tiab] OR nasal*[tiab] OR nasi[tiab] OR intranasal*[tiab] OR paranasal*[tiab] OR rhinosin*[tiab] OR rhinitis[tiab] OR sinus*[tiab] OR

#	Suchfrage
	sinonasal*[tiab]) AND (papilloma*[tiab] OR polyp[tiab] OR polyps[tiab] OR polyposis[tiab])
8	#6 OR #7
9	CRSwNP[tiab] OR CRSwp[tiab]
10	#5 OR #8 OR #9
11	(#10) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
12	(#11) AND ("2019/08/01"[PDAT] : "3000"[PDAT])
13	(#12) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 28.08.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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

Verfahrens-Nr.: 2024-B-309

Verfasser	
Name der Institution	DGHNO, DEGAM
Namen aller beteiligten Sachverständigen	
Datum der Erstellung	28. Januar 2025

Indikation
…ist angezeigt als Zusatztherapie bei erwachsenen Patienten mit nicht ausreichend kontrollierter chronischer Rhinosinusitis mit Nasenpolypen (Chronic rhinosinusitis with nasal polyps, CRSwNP).
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Die Empfehlungen der deutschen AWMF-Leitlinie von 2017 [1] sowie dem Update 2023 in Bezug auf die Therapie mit monoklonalen Antikörpern (Biologika) [2] können derzeit als Standard gelten. Sie lauten zur medikamentösen Behandlung bei CRS: • eine nasale Anwendung von Salzlösungen z. B. als hochvolumige (≥150 ml), iso- bis leicht hypertone Spülung sollte für die symptomatische Therapie der CRS zum Einsatz kommen (starker Konsens, 7/7) [1] • Dekongestiva sollten bei der CRS aufgrund der Gefahr der Entstehung einer Rhinitis medicamentosa nicht angewendet werden (starker Konsens, 7/7) [1] • Topische Kortikosteroide sollten zur Therapie der CRSsNP und insbesondere der CRScNP (=CRSwNP) zur Anwendung kommen (starker Konsens, 6/6) [1] • Die Therapie mit systemischen Kortikosteroiden kann in Einzelfällen erwogen werden (starker Konsens, 7/7) [1] • Bei CRScNP kann im Falle einer Rezidiv-Polyposis eine längerdauernde Therapie mit Doxycyclin erwogen werden (starker Konsens, 7/7) [1] • Bei Versagen einer konservativen Therapie sollte eine operative Therapie erwogen werden (starker Konsens, 6/6) [1] • Im Einzelfall kann auch eine primäre operative Therapie sinnvoll sein (starker Konsens, 5/5) • Ausgewählte Biologika können bei Versagen etablierter Therapieformen im Einzelfall bei CRScNP eingesetzt werden (starker Konsens, 6/6). [1] • In dieser Indikation zugelassene Biologika sollen bei erwachsenen Patienten mit schwerer CRScNP bei fehlender Krankheitskontrolle als Zusatztherapie zu intranasalen Kortikosteroiden erwogen werden, wobei präparatespezifische Zulassungskriterien zu beachten sind (Konsens, Zustimmung 88%). [2] • Der Schweregrad der Erkrankung sollte durch die Erhebung objektiver und subjektiver Kriterien vor Therapieeinleitung mit Biologika dokumentiert werden (starker Konsens, Zustimmung 100%).[2] • Die Wirksamkeit einer Therapie mit Biologika bei CRScNP sollte nach einem angemessenen Zeitraum überprüft werden (Konsens, Zustimmung 88%).[2]

- Bei Vorliegen von relativen Kontraindikationen sollte nur nach differenzierter Abwägung durch erfahrene Ärzt*innen und als Einzelfallentscheidung ein Therapieversuch mit Biologika eingeleitet werden (Konsens, Zustimmung 88%).[2]
- Zur standardisierten Dokumentation von verschiedenen Aspekten zur Indikationsstellung und zur Verlaufskontrolle des Einsatzes von Biologika bei CRScNP sollte ein Dokumentationsbogen verwendet werden (Konsens, Zustimmung 88%). [2]

Zusammenfassend:
Der Behandlungsstandard bei CRSwNP ist national wie international [1,3] die nasale Anwendung von (natürlichen) Kochsalzlösungen sowie die Applikation topischer Steroide (Standardtherapie). In Einzelfällen können auch zusätzlich systemisch verabreichte Steroide (jeweils für einen kurzen Zeitraum) erwogen werden. Bei ausbleibender Symptomkontrolle ist als nächster Eskalationsschritt in der Regel eine endoskopisch durchgeführte Nasennebenhöhlenoperation (Functional Endoscopic Sinus Surgery, FESS) unter Beibehaltung der Standardtherapie indiziert [1,3]. Bei weiterhin fehlender Symptomkontrolle oder Rezidiv kommen Re-Operationen, Biologika oder weniger Evidenz-basierte Therapieoptionen (längerfristige antibiotische Therapie mit Doxicyclin; Aspirin-Treatment After Desensitization (ATAD) bei PatientInnen mit Analgetikainoleranzsyndrom mit CRSwNP) – immer in Kombination mit der Standardtherapie – in Frage [1-4].
Die Versorgungspraxis in Deutschland greift diese Empfehlungen auf und setzt sie um. Die Therapie mit Biologika hat sich bei therapierefraktären Fällen inzwischen in der Routineversorgung durchgesetzt. So gaben in einer kürzlich publizierten Umfrage 80% der antwortenden HNO-Kliniken an, dass durch Sie Biologika in der Therapie der CRSwNP zum Einsatz gelangen [5].

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)

Ja, es gibt Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation (hier nur für Biologika aufgeführt), welche wie folgt Berücksichtigung finden:

- Klinische Effektivität (hinsichtlich Symptomverbesserung der CRSwNP):
  - Es liegen keine randomisierten Studien zum Vergleich der Effektivität von Nebenhöhlen(revisions)operationen im Vergleich zur Biologikatherapie vor. Vergleichende Analysen (z.B. [6,7]) zeigen, dass beide Therapieverfahren eine ähnlich starke Symptomverbesserung innerhalb eines mittleren Beobachtungszeitraums von 52 Wochen zeigen.
  - Ebenfalls liegen keine randomisierten Vergleichsstudien zwischen den 3 derzeit für diese Indikation zugelassenen Präparate (Dupilumab, Mepolizumab, Omalizumab) vor. Eine vergleichende Analyse gematchter Fälle aus den Zulassungsstudien für Mepolizumab und Dupilumab (Indirect Treatment Comparison, ITC) lässt auf eine höhere klinische Effektivität von Dupilumab schließen [8].
- Begleiterkrankungen & begleitende Umstände:
  - Die 3 Biologika (s.o.) haben – neben der Indikation zur Behandlung der therapierefraktären CRSwNP – noch weitere Indikationsgebiete (siehe Packungsbeilagen der Präparate), die voneinander differieren. Im Falle zusätzlich vorliegender Typ-II-Erkrankungen sind diese bei der Biologika-Therapieauswahl zu berücksichtigen.
  - In Schwanger- und Stillzeit ist – unter sorgfältiger Nutzen-Risiko-Abwägung und nur nach sorgfältiger Prüfung von Alternativen – nach www.embryotox.de Omalizumab als Präparat zu bevorzugen, da nur hierfür Erfahrungswerte vorliegen.
- Nebenwirkungen:
  Da das Nebenwirkungsprofil (siehe jeweilige Packungsbeilage) für die 3 Biologika (s.o.) deutlich voneinander abweicht, ist dieses in die Therapieentscheidung mit einzubeziehen.

Im Vergleich scheint die Anwendung von Mepolizumab seltener als die Anwendung mit Dupilumab mit den Auftreten von Nebenwirkungen einherzugehen [9]. Ob dies jedoch häufiger zu Therapieabbrüchen bei einer der beiden Substanzen führt, ist allerdings bislang nicht geklärt.

- Kosteneffizienz:
  Vergleichende Daten zur Kosteneffizienz der 3 Biologika untereinander sowie im Vergleich zur Nasennebenhöhlen(revisions)operation liegen aus Deutschland nicht vor. Daten aus dem Ausland lassen vermuten, dass die operative Versorgung kosteneffizienter als die Behandlung mit Biologika sein könnte [z.B. 10], und dass von den 3 Biologika (s.o.) untereinander möglicherweise Omalizumab die höchste Kosteneffizienz aufweist [11], wobei eine Übertragung der Aussagen auf die Situation in Deutschland fragwürdig ist.

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

Verfahrens-Nr.: 2024-B-309

Verfasser	
Name der Institution	Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Bundesärztekammer, Dezernat 6 – Wissenschaft, Forschung und Ethik, Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de)
Namen aller beteiligten Sachverständigen	
Datum der Erstellung	28. Januar 2025

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
…ist angezeigt als Zusatztherapie bei erwachsenen Patienten mit nicht ausreichend kontrollierter chronischer Rhinosinusitis mit Nasenpolypen (Chronic rhinosinusitis with nasal polyps, CRSwNP).
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Bei Patientinnen und Patienten mit chronischer Rhinosinusitis mit Nasenpolypen (CRSwNP) erfolgt grundsätzlich eine medikamentöse Behandlung. Diese umfasst Kochsalzspülungen der Nase, die intranasale Anwendung eines topischen Steroids (z. B. Budesonid oder Mometason); bei ausbleibendem Ansprechen auf diese Therapie kann eine zeitlich begrenzte systemische Glukokortikoid-Behandlung (z. B. für die Dauer von zwei Wochen) Anwendung finden. Liegen Komorbiditäten wie allergische Rhinitis und/oder eine ASS-Intoleranz vor, so können eine allergenspezifische Immuntherapie und eine adaptive Desaktivierung mit Acetylsalicylsäure erfolgen. Bei Versagen der konservativen Behandlung wird ggf. – insbesondere abhängig von den subjektiven Beschwerden der Patientinnen und Patienten – die Indikation zu einer operativen Therapie (mikroendoskopisches endonasales Vorgehen) gestellt. Dieses Therapiekonzept entspricht der derzeitigen Versorgungspraxis in Deutschland.
Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o. g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Wesentliche Kriterien für unterschiedliche Behandlungsentscheidungen sind Krankheitsverläufe mit unzureichender Rückbildung polypöser Schleimhautveränderungen und entsprechender klinischer Symptomatik (Nasenatmungsbehinderung, Riechstörung, Nasensekretion), die häufig mit einer Beeinträchtigung der Lebensqualität einhergehen. Daneben sind Komorbiditäten wie schweres Asthma bronchiale zu berücksichtigen. Bei Versagen der konservativen Behandlung –

insbesondere der intranasalen Steroidtherapie – und entsprechendem Leidensdruck der Betroffenen sind eine operative Therapie oder auch die Behandlung mit einem monoklonalen Antikörper wie Dupilumab, Omalizumab oder Mepolizumab weitere Behandlungsoptionen.

Insbesondere um operative Folgeeingriffe zu vermeiden, ist bei Patientinnen und Patienten mit einem Mehrfachrezidiv der chronisch-polypösen Rhinosinusitis trotz vorangegangener ausreichend langer konservativer Behandlung und NNH-Operationen ein Therapieversuch mit monoklonalen Antikörpern indiziert. Wichtig sind während dieser Therapie klinische und HNO-ärztliche Kontrolluntersuchungen – z. B. sechs Monate nach Beginn der Antikörperbehandlung, um das Ansprechen auf diese Therapie zu überprüfen.

Referenzliste:

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