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: 2025-B-104 Tezepelumab

Stand: Juni 2025

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

Tezepelumab

[als Add-on Therapie zur Behandlung der schweren chronischen 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 Übersicht „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:	
Tezepelumab R03DX11 Tezspire	Anwendungsgebiet laut Beratungsanforderung: Tezspire ist 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), bei denen durch eine Therapie mit systemischen Kortikosteroiden und/oder durch einen chirurgischen Eingriff keine ausreichende Krankheitskontrolle erreicht 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. Stand FI: November 2024
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. Stand FI: Juni 2024
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 Stand FI: November 2023
Glucokortikoide (topisch) z.B.	
Mometasonfuroat (generisch) R01AD09	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	
z.B. Nasonex® Nasenspray	Stand FI: März 2024
Budesonid R01AD05 (generisch) z.B. Budesonid – 1A Pharma Nasenspray	Behandlung und Vorbeugung von Anzeichen und Symptomen der saisonalen und ganzjährigen allergischen Rhinitis bei Erwachsenen und Kindern ab 6 Jahren Behandlung von Anzeichen und Symptomen von Nasenpolypen bei Erwachsenen Stand FI: November 2024
Glucokortikoide (systemisch), z.B.	
Prednison H02AB07 (generisch) z.B. Prednison acis	Erkrankungen der oberen Luftwege – schwere Verlaufsformen von Pollinosis und Rhinitis allergica, nach Versagen intranasal verabreichter Glucocorticoide (DS: c) […] Stand FI: März 2022
Antibiotika, z.B.	
Doxycyclin J01AA02 (generisch) z.B. Doxycyclin 1A Pharma	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. Stand FI: Oktober 2023

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2025-B-104 (Beratung nach § 35a SGB V) Tezepelumab

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	2. Mai 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
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
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
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), bei denen durch eine Therapie mit systemischen Kortikosteroiden und/oder durch einen chirurgischen Eingriff keine ausreichende Krankheitskontrolle erreicht wird.

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 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 der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 11.04.2025 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 696 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. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. 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 5 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews im Anwendungsgebiet identifiziert.

3.2 Systematische Reviews

Kariyawasam HH et al., 2023 [2].

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.

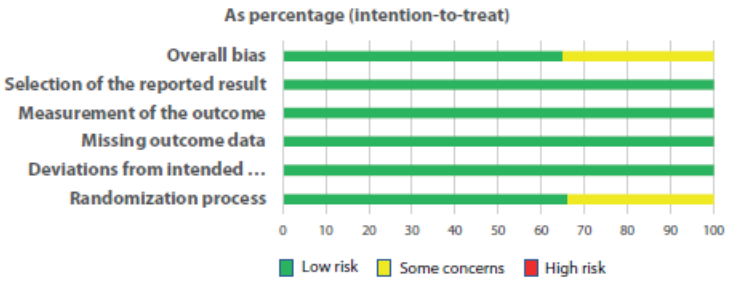
Charakteristika der Population/Studien:

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)

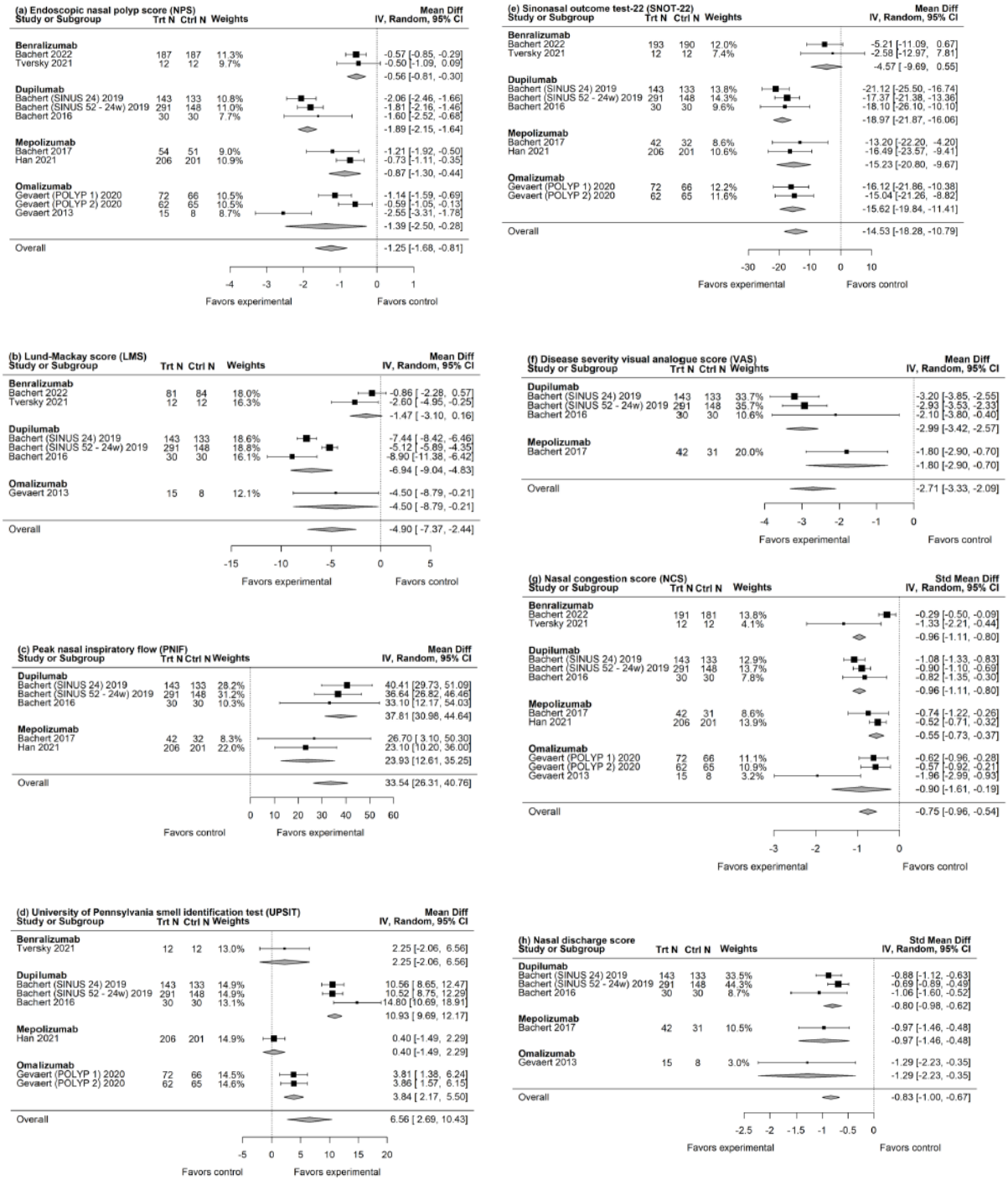


Figure 3. Forest plots showing meta-analyses of mean difference in the following outcomes: a) endoscopic nasal polyp score (NPS); b) Lund-Mackay score (LMS); c) peak nasal inspiratory flow (PNIF); d) University of Pennsylvania smell identification test (UPSIT); e) sinonasal outcome test-22 (SNOT-22);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

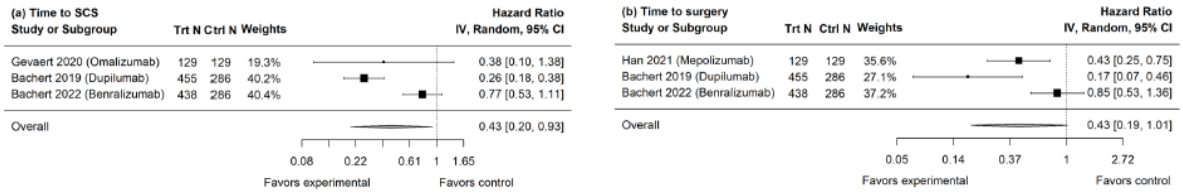


Figure 4. Forest plots showing meta-analyses of: a) a) time to systemic corticosteroids (SCS); and b) time to surgery with biologic use.

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.

Kim DH et al., 2024 [3].

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

Rank MA et al., 2023 [5].

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 [1,4].

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

- Corrigendum: On page 224: Grade for “CRSwNP: Non-Standard Corticosteroid Delivery” should be changed from B to A.

Empfehlungen – Übersicht:

TABLE I-4 Grade A/B evidence-based recommendations for medical management of CRS

Intervention	Grade	Benefit	Harm	Cost	Benefit-Harm Assessment	Policy Level
CRSsNP: Saline Irrigation, Drops, Sprays	B	Improvement in QoL, endoscopic appearance, and role in maintenance therapy. Benefit over control was shown with saline irrigations (≥60 mL) and at 8 weeks duration	Minor and rare adverse effects. Nasal burning and irritation are more reported with hypertonic irrigation; See Table II-1.	Low	Preponderance of benefit over harm	Recommendation: Saline irrigation improves symptoms, QoL and nasal endoscopy. Duration of should be greater than 8 weeks. Hypertonic saline is more effective but may be more irritating than isotonic saline. There is no advantage of heated over room temperature saline. Devices with volume greater than 60 mL bring greater benefits
CRSwNP: Oral Corticosteroids	A	Significant short-term improvements in subjective and objective measures. Duration may last 8-12 weeks in conjunction with topical INCS	GI symptoms, transient adrenal suppression, insomnia, and increased bone turnover. All established systemic corticosteroid risks exist, particularly with prolonged treatment; See Table II-1.	Low	Preponderance of benefit over harm with short-term treatment with follow-up	Strong recommendation: For short-term management of CRSwNP. Longer term use of is not supported by the literature and carries increased risk of harm
CRSsNP: Intranasal Corticosteroid Spray	A	Improved symptom scores, improved endoscopy scores.	Epistaxis, nasal irritation, headache; See Table II-1.	Low to Moderate	Possible mild benefit over harm	Option: Standard metered dose INCS could be used in treatment of CRSsNP, particularly if primary symptoms are that of rhinitis
CRSwNP: Intranasal Corticosteroid Spray	A	Improved symptoms, endoscopy score, polyp size, QoL, olfaction, airway analysis (NPIF), and polyp recurrence. Magnitude of the clinical effect is small	Epistaxis, nasal irritation, headache; See Table II-1.	Low to Moderate	Benefit outweighs harm	Strong Recommendation: INCS are recommended for CRSwNP before or after sinus surgery. Consideration for twice daily dosing if initial treatment effect is small

(Continues)

TABLE I-4 (Continued)

Intervention	Grade	Benefit	Harm	Cost	Benefit-Harm Assessment	Policy Level
CRSsNP: Corticosteroid Irrigations	A	Improvement in HR-QoL, subjective symptom scores and endoscopic appearance in postoperative patients.	Epistaxis, nasal irritation; See Table II-1. No evidence of adrenal suppression using irrigation delivery	Moderate to High	Preponderance of benefit over harm, with increased cost compared to nasal sprays	Recommended: Post-operative patients Option: Non-surgical/medical management
CRSwNP: Non-Standard Corticosteroid Delivery	B	Corticosteroid Irriga-tions/Atomization/ Nebulization have shown benefit over INCS. Exhalation devices have shown benefit over placebo	Some evidence of systemic absorption with first generation corticosteroids especially with multiple modalities of therapy	Moderate	Benefit outweighs harm compared with oral corticosteroids but caution in patients on multiple topical therapies	If not controlled with INCS, strong recommendation for corticosteroid irrigation; recommendation for atomization/nebulization Option: Exhalation delivery
CRSwNP: Corticosteroid Eluting Implants	A	Reduction in ethmoid obstruction, polyp grade, decreased need for revision ESS, reduced nasal obstruction scores	No findings of increased risk of elevated intraocular pressure or cataracts	Moderate to High	Benefits appear to outweigh harm	Option: Corticosteroid-eluting implants can be considered as an option in a previously operated ethmoid cavity with recurrent nasal polyps
CRSwNP: Dupilumab (Biologic)	A	Decreased polyp size, improved nasal congestion, sinus imaging scores, sense of smell, and asthma control	Conjunctivitis and hyper-eosinophilia	High	Likely benefit over harm in patients with CRSwNP not responsive to medical and surgical standard of care	Recommendation: May be considered for patients with severe CRSwNP who have not improved despite other medical and surgical treatment options

(Continues)

TABLE I-4 (Continued)

Intervention	Grade	Benefit	Harm	Cost	Benefit-Harm Assessment	Policy Level
CRSsNP: Macrolide Antibiotics	B	Reduction in endoscopy and symptom scores	Gastrointestinal side effects, ototoxicity, hepatotoxicity, cardiotoxicity, and drug-drug interactions; See Table II-1.	Low	Benefits appear to outweigh harm	Option: Macrolides are an option for patients with CRSsNP. Optimal drug, dosage, and treatment duration are not known
CRSwNP: Macrolide Antibiotics	B	May improve symptom and endoscopic scores in CRSwNP. Macrolides appear to be comparable to INCS in selected patients	Gastrointestinal side effects, ototoxicity, hepatotoxicity, cardiotoxicity, and drug-drug interactions; See Table II-1.	Low	Benefits appear to outweigh harm	Option: Macrolides are likely beneficial in CRSwNP. Optimal drug, dosage, and treatment duration are not known
CRSwNP: Non-Macrolide Antibiotics (<3 weeks)	B (-)	Potential reduction in polyp size with doxycycline without change in symptoms	GI upset, skin rash, insomnia, and headache; See Table II-1. Potential delay of more effective interventions	Variable	Preponderance of harm over benefits	Recommendation against: Should generally not be prescribed for CRSwNP except in acute exacerbations
CRSs/wNP: Topical Antibiotics	A (-)	Systematic reviews and RCTs failed to show benefit from the use of topical antibiotics in CRS	Nasal congestion, irritation, epistaxis. Theoretical possibility of systemic absorption aminoglycosides. Possibility of bacterial resistance	Moderate to High	Relative harm over benefit	Recommendation against: Topical antibiotics are not recommended for CRSs/wNP
CRSs/wNP: Topical Antifungals	A (-)	No apparent benefit from use of topical antifungals	Potential for local irritation, epistaxis and headache less common	Low to Moderate	Minimal risk of harm but no apparent potential for benefit	Strong recommendation against: Topical antifungals are not recommended for CRSs/wNP

(Continues)

TABLE I-4 (Continued)

Intervention	Grade	Benefit	Harm	Cost	Benefit-Harm Assessment	Policy Level
CRSwNP: Anti-Leukotrienes	A	Improvement in symptoms comparable to INCS. May have limited benefit as an adjunct to INCS	Limited risks. Montelukast associated with neuropsychiatric events. Zileuton associated with elevated liver enzymes requiring monitoring; See Table II-1.	Moderate	Balance of benefits and harm	Option: Montelukast is an option for CRSwNP patients either instead of or in addition to INCS
CRSs/wNP: Xylitol Irrigation	B	Symptomatic improvement in the 2 small RCTs in postoperative patients	Occasional local discomfort, stinging	Low	Preponderance of mild benefit over harm	Option postoperatively in CRSsNP and CRSwNP patients.
CRSs/wNP: Colloidal Silver	B (-)	No benefit for the use of in clinical studies	Potential increase in serum silver levels	Low to High	No benefit in light of potential harm	Recommendation against: CAg may have anti-bacterial properties *in-vitro* but lacks efficacy in clinical studies
CRSwNP: Furosemide	B	Reduced recurrence of nasal polyps following ESS over placebo nasal spray	No studies have been performed to assess systemic safety with nasal delivery	Low	Benefits likely outweighs harm when used on a rotating basis as studied	Option: Topical furosemide after ESS and in combination with an INCS may reduce the recurrence of nasal polyps
CRSwNP (AERD): ASA Desensitization	A	Reduced post-op polyp re-recurrence, increased QoL and reduced symptoms. Reduced need for systemic corticosteroids and surgical revisions	GI bleeding, increased morbidity in renal disease and clotting dysfunction at high maintenance doses. <3% GI side effects with low-dose protocols	Low to Moderate (Including cost of desen-sitization)	Clear benefit over harm	Recommendation: Aspirin desensitization should be considered in AERD after surgical removal of NPs to prevent recurrence.

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 4 of 12, April 2025) am 11.04.2025

#	Suchschritt
1	[mh ^Sinusitis]
2	[mh ^Rhinitis]
3	[mh Rhinosinusitis]
4	(rhinosinusitis OR rhino-sinusitis OR nasosinusitis OR "naso-sinusitis" OR pansinusitis OR "pan-sinusitis" OR sphenoiditis):ti,ab,kw
5	((Sphenoid* OR maxilla* OR chronic OR paranasal) AND sinusitis):ti,ab,kw
6	[mh "Nasal Polyps"]
7	((nose* OR nasal* OR nasi OR intranasal* OR paranasal* OR rhinosin* OR rhinitis OR sinus* OR sinonasal* OR nasosinusal*) AND polyp*):ti,ab,kw
8	(CRSwNP OR CRSwp):ti,ab,kw
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10	#9 with Cochrane Library publication date from Apr 2020 to present, in Cochrane Reviews
11	#10 with Cochrane Library publication date from Apr 2023 to present, in Cochrane Reviews
12	#10 NOT #11

Leitlinien und systematische Reviews in PubMed am 11.04.2025

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

verwendete Suchfilter für systematische Reviews:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 15.01.2025.

#	Suchfrage
	Leitlinien
1	Sinusitis[mh:noexp]
2	Rhinitis[mh:noexp]
3	"Rhinosinusitis"[mh]
4	rhinosinusitis[tiab] OR rhino-sinusitis[tiab] OR nasosinusitis[tiab] OR naso-sinusitis[tiab] OR pansinusitis[tiab] OR pan-sinusitis[tiab] OR sphenoiditis[tiab]
5	(Sphenoid*[tiab] OR maxilla*[tiab] OR chronic[tiab] OR paranasal[tiab]) AND sinusitis[tiab]
6	Nasal Polyps[mh]

#	Suchfrage
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] OR nasosinusal*[tiab]) AND polyp*[tiab]
8	CRSwNP[tiab] OR CRSwp[tiab]
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10	(#9) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
11	(#10) AND ("2020/04/01"[PDAT] : "3000"[PDAT])
12	(#11) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews
13	(#9) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[mh] OR "network meta-analysis"[pt] 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"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
14	(#13) AND ("2020/04/01"[PDAT] : "3000"[PDAT])
15	(#14) NOT "The Cochrane database of systematic reviews"[Journal]
16	(#15) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
17	#16 NOT #12
18	(#17) AND ("2023/04/01"[PDAT] : "3000"[PDAT])

#	Suchfrage
19	#17 NOT #18

Iterative Handsuche nach grauer Literatur, abgeschlossen am 11.04.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- 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.: 2025-B-104

Verfasser	
Name der Institution	DGHNO, DEGAM
Datum der Erstellung	29. April 2025

Indikation

…ist 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), bei denen durch eine Therapie mit systemischen Kortikosteroiden und/oder durch einen chirurgischen Eingriff keine ausreichende Krankheitskontrolle erreicht wird

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 2024 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 Schwangerschaft 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 ausreichende 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.: 2025-B-104

Verfasser	
Name der Institution	Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ)
Datum der Erstellung	6. Mai 2025
Indikation	
…ist 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), bei denen durch eine Therapie mit systemischen Kortikosteroiden und/oder durch einen chirurgischen Eingriff keine ausreichende Krankheitskontrolle erreicht wird	
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.)*	
Der Behandlungsstandard bei Patientinnen und Patienten mit diagnostizierter CRSwNP ist die intranasale Therapie mit Kortikosteroiden, hierfür findet sich auch eine entsprechende Evidenz. Daneben finden eine Kurzzeitbehandlung mit Antibiotika (Doxycyclin 100 mg täglich für einen Zeitraum von drei Wochen) bei ausgeprägtem Leidensdruck oder eine Therapie mit oralen Kortikosteroiden Anwendung in der medikamentösen Behandlung des Krankheitsbildes. Bei Verordnung oraler Kortikosteroide sind unerwünschte Arzneimittelwirkungen zu beachten, der therapeutische Effekt dieser systemischen Kortikosteroidbehandlung ist vielfach nur kurzzeitig (1). Eine S2k-Leitlinie (Update 2022) empfiehlt in schweren Krankheitsfällen Antibiotika, orale Kortikosteroide, operative Eingriffe und gegebenenfalls Biologika (monoklonale Antikörper) (2).	
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.)*	
Ein wesentlicher Gesichtspunkt für die Basistherapie von Patienten mit CRSwNP sind mögliche Begleiterkrankungen wie Asthma bronchiale, atopische Dermatitis, eosinophile Oesophagitis und Allergien; diese Komorbiditäten sind ähnlich Th2-vermittelt und kommen hochprävalent bei an CRSwNP Erkrankten vor. Ferner sind bereits erfolgte Operationen (mikroendoskopische Nasennebenhöhlenoperationen) in der Therapieplanung zu berücksichtigen; insbesondere bei Zustand nach mehrfachen Voroperationen besteht im Falle weiterer operativer Eingriffe eine erhöhte Komplikationsgefahr, zum anderen zeigen Nachuntersuchungen, dass auch nach vollständiger Operation in mehr als 70 % der operierten Patienten nach zehn bis zwölf Jahren eine Rezidivpolyposis nachweisbar ist (3, 4). Finden sich bei Patientinnen und Patienten mit beidseitiger CRSwNP nach erfolgter Nasennebenhöhlenoperation drei der nachfolgenden Kriterien, besteht eine Indikation für Biologika: signifikant beeinträchtigte Lebensqualität, Verlust des Riechvermögens, Diagnose eines	

komorbiden Asthma bronchiale, Bedarf an oralen Kortikosteroiden, Evidenz für Typ-2-Inflammation (European Position Paper on Rhinosinusitis and Nasal Polyps) (5).

Die vorliegende Stellungnahme bezieht sich auf Erwachsene.

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