Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

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

Vorgang: 2024-B-321-z Nintedanib

Stand: Februar 2025

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

Nintedanib **[zur Behandlung fortschreitender fibrosierender interstitieller Lungenerkrankungen (ILDs) bei Kindern und Jugendlichen]** **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.	• Langzeit-Sauerstofftherapie • Lungentransplantation • Pulmonale Rehabilitation • Physikalische Therapie (i.S. der Heilmittel-RL)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	• Nintedanib *(D-568 – Beschluss vom 04. Februar 2021)*
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:	
Nintedanib L01XE31 Ofev®	<u>Anwendungsgebiet laut Positive Opinion vom 13.12.2024:</u> Ofev is indicated in children and adolescents from 6 to 17 years old for the treatment of clinically significant, progressive fibrosing interstitial lung diseases (ILDs).
Methylprednisolon H02AB04 Methylprednisolon Jenapharm®	<u>Bronchial- und Lungenkrankheiten</u> […] – Interstitielle Lungenerkrankungen, wie akute Alveolitis, Lungenfibrose, zur Langzeittherapie chronischer Formen der Sarkoidose in den Stadien II und III (bei Atemnot, Husten und Verschlechterung der Lungenfunktionswerte)
Prednisolon H02AB06 generisch	Pneumonologie: […] – interstitielle Lungenerkrankungen wie akute Alveolitis (DS: b), Lungenfibrose (DS: b), Bronchiolitis obliterans organisierende Pneumonie (BOOP) (DS: b ausschleichend), ggf. in Kombination mit Immunsuppressiva, chronische eosinophile Pneumonie (DS: b ausschleichend), zur Langzeittherapie chronischer Formen der Sarkoidose in den Stadien II und III (bei Atemnot, Husten und Verschlechterung der Lungenfunktionswerte) (DS: b) […]
Prednison H02AB07 generisch	Pneumonologie: […] – interstitielle Lungenerkrankungen wie akute Alveolitis (DS: b), Lungenfibrose (DS: b), Bronchiolitis obliterans organisierende Pneumonie (BOOP) (DS: b ausschleichend), ggf. in Kombination mit Immunsuppressiva, chronische eosinophile Pneumonie (DS: b ausschleichend), zur Langzeittherapie chronischer Formen der Sarkoidose in den Stadien II und III (bei Atemnot, Husten und Verschlechterung der Lungenfunktionswerte) (DS: b) […]

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2024-B-321-z (Nintedanib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	29. Januar 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

6MWT	Six Minute Walk Test
ABA	Abatacept
AEMPS	Spanish Agency of Medicines
AI-ILD	Autoimmune-related ILD
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
AZA	azathioprine
CF	Cyclophosphamide
CsA	Cyclosporine A
CYP	Cyclophosphamide
DMARD	Disease-modulating anti-rheumatic drugs
ECRI	ECRI Guidelines Trust
ETC	Etanercept
fHP	fibrotic hypersensitivity pneumonitis
FVC	Forced Vital Capacity
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GLC	Glucocorticoids
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HP	Hypersensitivity pneumonitis
HR	Hazard Ratio
HRCT	High-resolution chest computed tomography
IFX	Infliximab
ILD	Interstitial lung diseases
IPF	Idiopathic pulmonary fibrosis
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LIP	Lymphocytic interstitial pneumonia
LoE	Level of Evidence
MMF	Mycophenolate
MTX	Methotrexate
NICE	National Institute for Health and Care Excellence
NSIP	Non-specific interstitial pneumonia
OP	Organising pneumonia

OR	Odds Ratio
PDN	Prednisone
PF-ILD	Progressive Fibrosing Interstitial Lung Diseases
PFT	Pulmonary function tests
RA-ILD	Rheumatoid arthritis-related interstitial lung disease
RR	Relatives Risiko
RTX	Rituximab
SIGN	Scottish Intercollegiate Guidelines Network
SSc-ILD	Systemic Sclerosis-associated Interstitial Lung Disease
TCZ	Tocilizumab
TOFA	Tofacitinib
TRIP	Turn Research into Practice Database
uILD	unclassifiable interstitial lung disease
UIP	Usual interstitial pneumonia
WHO	World Health Organization

1 Indikation

Treatment in children and adolescents from 6 to 17 years old of clinically significant, progressive fibrosing interstitial lung diseases (ILDs).

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 *interstitielle Lungenerkrankung* 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.startpage.com*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 02.01.2025 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 1996 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 3 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Es wurden keine systematischen Reviews identifiziert.

3.3 Leitlinien

Methodikerhinweis: Keine der hier dargestellten LL entspricht der im AWG genannten Population der Kinder und Jugendlichen zwischen 6-17 Jahren, sondern spiegeln die Erwachsenen ab 18 Jahren wider. Aufgrund fehlender Evidenz in Hinblick auf die relevante Population der 6-17-Jährigen wurden die LL für die Erwachsenen dargestellt.

Narvaez J et al., 2022 [2].

SER-SEPAR recommendations for the management of rheumatoid arthritis-related interstitial lung disease. Part 2: Treatment

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft teilweise zu (keine Patientenvertretung);
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft teilweise zu (Konsensprozesse nicht beschrieben)
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert: trifft nicht zu.

Recherche/Suchzeitraum:

- A search for published scientific evidence was conducted and successively expanded until October 2020.
- PubMed (MEDLINE), EMBASE, and Cochrane Library

LoE/GoR

- The strength of the recommendations was graded using the Scottish Intercollegiate Guidelines Network (SIGN) criteria
- For questions where the evidence was insufficient, recommendations were formulated based on consensus of the expert group.

  (Methodikeranmerkung: keine Spezifizierung zur Operationalisierung der verwendeten Empfehlungsgrade (A-D, √)).

Sonstige methodische Hinweise

- Die Operationalisierung der dargestellten Empfehlungsgrade (A-D, √) wurde nicht weiter spezifiziert.

Empfehlungen

Table 1
SER-SEPAR recommendations for the treatment of interstitial lung disease associated with rheumatoid arthritis.

Recommendations	Grade of recommendation
For the treatment of patients with rheumatoid arthritis-associated interstitial lung disease, multidisciplinary therapeutic management is recommended	√
If interstitial lung disease is present at RA debut, an individualised assessment for the use of MTX is recommended, as there is a risk of drug-induced acute pneumonitis, albeit low	A
In these cases, the drafting group considers that the best strategy to minimise risks is to use another conventional synthetic DMARD whenever possible	√
In patients with RA, when ILD is diagnosed or worsens during the first year of MTX treatment, MTX should be temporarily discontinued until it is clear whether or not there is a causal relationship	√
In patients with RA on methotrexate for more than one year who are diagnosed with interstitial lung disease, the drug can be maintained as there is no evidence to justify discontinuation	D
In patients with RA-ILD who are not of Asian descent, leflunomide can be considered a safe drug	√
In patients with rheumatoid arthritis and interstitial lung disease requiring biologic therapy, abatacept or rituximab should be used interchangeably as safer options	D
In patients with rheumatoid arthritis and interstitial lung disease, in case of contraindication or inadequate response to abatacept and rituximab, the use of an IL-6 inhibitor or a targeted synthetic DMARD can be considered	D
In patients with rheumatoid arthritis being treated with anti-TNF and stable interstitial lung disease, there is inconclusive evidence to recommend discontinuation if the drug has achieved good control of joint symptoms	√
In patients with rheumatoid arthritis-associated interstitial lung disease with an inflammatory radiological pattern (NSIP, OP, LIP, etc.) in whom GLC treatment is considered necessary, their use is always recommended at the lowest dose and for the shortest possible time	√
The drafting group considers that the available evidence is insufficient to issue a conclusive recommendation on the use of immunosuppressants in the treatment of rheumatoid arthritis-associated interstitial lung disease	D
If it is decided to use them, the drafting group suggests the use of mycophenolate because of its better safety profile	√
Although evidence of efficacy of biologic DMARDs in the treatment of rheumatoid arthritis-associated interstitial lung disease is scarce, real-life data suggest that both abatacept and rituximab could be useful in stabilising or improving lung function, particularly in patients with a non-fibrotic radiological pattern	D
In the subgroup of patients with rheumatoid arthritis-associated interstitial lung disease with a progressive fibrosing phenotype, the use of nintedanib is recommended, while maintaining background rheumatoid arthritis treatment	B

DMARDs: slow-acting disease-modulating anti-rheumatic drugs; IL: interleukin; LIP: lymphocytic interstitial pneumonia; NSIP: non-specific interstitial pneumonia; OP: organising pneumonia.

Hintergrund:

In clinical practice, GLCs are commonly used in the treatment of RA-ILD, in combination or not with a csDMARD or immunosuppressant. There are no RCTs that have evaluated the efficacy of GLCs in this complication, and therefore the evidence sup-porting their use is based primarily on clinical experience and real-life data. The drafting group endorses their use in ILD patterns with a relevant inflammatory component: non-specific interstitial pneumonia (NSIP), organising pneumonia, lymphoid interstitial pneumonia, as well as in respiratory bronchiolitis associated with ILD, and in desquamative interstitial pneumonia if no improvement after smoking cessation or when it occurs in non-smoking patients. Its use in fibrotic patterns (usual interstitial pneumonia [UIP] and fibrosing NSIP) is questionable, except in acute exacerbations. Because of their adverse effect profile, the drafting group recommends the use of GLCs at the lowest dose and for the shortest duration possible. Prolonged treatment with prednisone (PDN)doses >7.5 mg/day increases the risk of serious infections and worsens cardiovascular risk and mortality in patients with RA.[78–82] A strategy to reduce iatrogenesis would be to apply new knowledge on the mechanisms of action of GLCs in daily clinical practice. It is currently known that they exert their anti-inflammatory action via two pathways: a classic genomic and a non-genomicpathway.[83,84] The genomic pathway has a slow onset of action, a persistent effect (which is responsible for the adverse effects of GLCs), and is 100% active at PDN doses of 30 mg/day. Therefore, if we give doses higher than 30 mg/day (the classic 1 mg/kg/day) we only manage to increase toxicity without substantially increasing its anti-inflammatory effect. In contrast, the non-genomic pathway exerts a much more intense and rapid anti-inflammatory action. This pathway begins to activate appreciably at 100 mg/day of methylprednisolone, with a maximum effect above 250 mg/day. Intravenous pulse therapy above 100–250 mg/day for 3 days has greater efficacy and lower toxicity than prolonged treatment with high-dose PDN. Based on this knowledge, it is now recommended not to exceed 30 mg/day of PDN, regardless of the patient's clinical picture. If necessary due to initial severity or acute exacerbation, methylprednisolone pulses (125 mg or 250 mg per day for 3 days, or500 mg/day in the most severe cases) will be considered, which are more effective and faster (generally in less than 24 h) than prolonged treatment with doses of 1 mg/kg/day. Cyclophosphamide (CF), azathioprine (AZA), mycophenolate (MMF) and cyclosporine A (CsA) have also been used in the treatment of RA-ILD. The studies that have evaluated the efficacy of these immunosuppressants are of very low methodological quality (clinical cases, case series, and some observational studies) (level of evidence 3),[85–97] and therefore the available evidence is insufficient to make a conclusive recommendation on their use. If it is decided to use an immunosuppressant, MMF appears to have the best safety profile. In a multicentre study that analysed mortality over the last 25 years in a cohort of 290 patients with RA-ILD versus290 age- and sex-matched controls with RA without this complication, mortality, both overall and respiratory, was higher in patients treated with CF or AZA than in those treated with MMF.[98] No RCTs evaluating the efficacy and safety of biologic DMARDs or tsDMARDs in the treatment of RA-ILD have been conducted to date. Published experience with biologic DMARDs is generally limited to observational studies with RTX[39,40,44,70–72] and ABA[38,43,68,69,99,100] (level of evidence 2 or 3). In addition to having no control group, the limitations of these studies include the fact that not all patients included had active ILD,

as evidenced by the lack of a protocolised assessment with RFT in some of the cases. Despite these limitations, the real-life observational studies are consistent and suggest that both ABA and RTX, in addition to being safe, also appear to be potentially useful in the treatment of RA-ILD, stabilising and even improving respiratory function parameters and HRCT findings in at least two-thirds of patients, including cases whose ILD had worsened despite previous treatment with GLC and csDMARDs or immunosuppressants and patients with chronic fibrosing ILD with a progressive phenotype.[39] Clinical cases[61,62] and a retrospective observational study[42] have been published with TCZ. In this study, which included 28patients treated with TCZ (23 in monotherapy), improvement or stabilisation in RFT was observed in 76% of cases (20% improvement) and in radiological changes on HRCT in 92.8% at the end of 30 months' follow-up (median) (level of evidence 3). Indirectly supporting the possible beneficial effect of non-anti-TNF biologic agents (RTX, ABA, and TCZ) in the treatment of RA-ILD, another study in Spain demonstrates that there is less lung progression with these drugs than that observed with anti-TNF.[41] Published experience with tsDMARDs is limited to a few clinical cases of RA-ILD treated with TOFA without evidence of pulmonaryworsening.[76] Of the two antifibrotic drugs marketed for the treatment of idiopathic pulmonary fibrosis (IPF) (nintedanib and pirfenidone), only nintedanib has so far been approved by the Spanish Agency of Medicines (AEMPS) for the treatment of RA-ILD with a progressive fibrosing phenotype.[101] Approval for this indication is based on data from the phase III INBUILD RCT,[102] which evaluated the efficacy of the drug in different types of progressive fibrosing IPD other than IPF, including a group of patients with SAD-ILD, mostly with RA or scleroderma (level of evidence 1++). Of the patients, 69.5%received SLN at doses <20 mg/day and 78% received concomitant treatment with csDMARDs (MTX, LEF, or antimalarials) and/or bio-logic DMARDs (ABA, TCZ, ETC, IFX, or adalimumab). In addition, at 6months into the trial, salvage therapy with AZA, MMF, cyclosporine A, tacrolimus, RTX, CF, or PDN >20 mg/day was allowed in case of pulmonary or baseline disease worsening.[102–104] At the end of52 weeks of treatment, nintedanib was able to slow the decline in forced vital capacity (FVC) in this group of patients by 58%compared to placebo, although there were no significant differences between groups in quality of life as measured by the King's Brief Interstitial Disease (K-BILD) questionnaire, or in the frequency of first acute exacerbation or mortality.[102] The safety profile of the drug was similar to that already known, and no new safety alerts emerged when administered in combination with GLCs, csDMARDs, immunosuppressants, and/or biologic DMARDs.

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Piotrowski WJ et al., 2022 [3].

Guidelines of the Polish Respiratory Society on the Diagnosis and Treatment of Progressive Fibrosing Interstitial Lung Diseases Other than Idiopathic Pulmonary Fibrosis

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert: trifft nicht zu.

Recherche/Suchzeitraum:

- Medline and Cochrane
- The literature search was terminated on 31 December 2021.

LoE/GoR

- Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology
- The quality of evidence was assessed as high, moderate, low, and very low.
- The strength of recommendations was assessed as strong or conditional

Sonstige methodische Hinweise

Empfehlungen: Treatment of Progressive Fibrosing Interstitial Lung Diseases

3.2. Treatment Module

Module		Pico Question	Recommendation	Quality of Evidence	Strength of Recommendation
TREATMENT	1	Should patients with an ILD in the course of systemic autoimmune diseases be managed by a multidisciplinary team?	We recommend that an opinion of a multidisciplinary team should be considered in the management of patients with interstitial lung disease in the course of systemic autoimmune diseases.	Very low	Strong
	2	Should a patient with a progressive fibrosing interstitial lung disease (PF-ILD) other than IPF be treated with first-line therapy dedicated to the diagnosed underlying disease?	We suggest that a patient with a progressive fibrosing interstitial lung disease (PF-ILD) other than IPF should be treated with first-line therapy dedicated to the diagnosed underlying disease.	Very low	Conditional
	3	In a patient with a progressive fibrosing interstitial lung disease (PF-ILD) other than IPF, should anti-fibrotic therapy with nintedanib be used in the event of ineffectiveness of the therapy recommended for the treatment of the underlying disease?	We recommend that in a patient with a progressive fibrosing interstitial lung disease (PF-ILD) other than IPF, anti-fibrotic therapy with nintedanib should be used in the event of ineffectiveness of the therapy recommended for the treatment of the underlying disease.	Low	Strong
	4	In a patient with a progressive fibrosing interstitial lung disease (PF-ILD) other than IPF, should anti-fibrotic therapy with pirfenidone be used in the event of ineffectiveness of the therapy recommended for the treatment of the underlying disease?	No recommendations were made for or against the use of anti-fibrotic therapy with pirfenidone if treatment of the underlying disease has failed in a patient with a progressive fibrosing interstitial lung disease (PF-ILD) other than IPF.	Very low	Not issued
	5	Is it possible to use an anti-fibrotic agent as a first-choice therapy (without the need for previous immunomodulatory treatment) in certain clinical situations (UIP or fibrotic NSIP pattern)?	We suggest using an anti-fibrotic agent as the first-choice treatment in certain clinical situations.	Very low	Conditional
	6	Can a patient with a progressive fibrosing interstitial lung disease (PF-ILD) other than IPF receive simultaneous treatment with a disease-modifying drug and anti-fibrotic therapy?	We suggest that in a patient with a progressive fibrosing interstitial lung disease (PF-ILD) other than IPF, one should consider simultaneous treatment with a disease-modifying drug and anti-fibrotic therapy.	Very low	Conditional

TREATMENT	7	Should progression noted during treatment with an anti-fibrotic agent in a patient with a progressive fibrosing interstitial lung disease (PF-ILD) other than IPF be a reason for discontinuation of anti-fibrotic therapy?	No recommendations were made for or against the termination of anti-fibrotic therapy in the case of noted progression during treatment of a progressive fibrosing interstitial lung disease (PF-ILD) other than IPF.	Very low	Not issued
	8	Should the same principles of non-pharmacological and palliative treatment and eligibility for lung transplantation be applied in a patient with an interstitial lung disease other than IPF with progressive fibrosis as in a patient with IPF?	We recommend that the same principles of non-pharmacological and palliative treatment and eligibility for lung transplantation should be applied in a patient with an interstitial lung disease other than IPF with progressive fibrosis as in a patient with IPF.	Very low	Strong

Hintergund:

- Zu Empfehlung 3.2.2:

A progressive interstitial pulmonary fibrosis phenotype other than IPF occurs in different disease entities, such as HP, AI-ILD, iNSIP, and uILD [65,82]. Fibrosis in PFILD is often preceded by or related to activation of various inflammatory and fibrotic pathways that may lead to fibroblast activation and differentiation into myofibroblasts, producing an extracellular matrix, which results in the remodeling of the lung parenchyma and leads to pulmonary fibrosis [83]. In the treatment of these ILDs, glucocorticosteroids or immunosuppressants (e.g., cyclophosphamide, azathioprine, mycophenolate mofetil, rituximab) are used. The impact of immunosuppression on PF-ILD is largely unknown, except for ILD in systemic sclerosis (SSc-ILD) [84]. Randomized clinical trials of SSc-ILD showed that cyclophosphamide-treated patients achieved a slower decline in FVC after one year of treatment compared to the placebo group, and a study assessing the efficacy of two years of mycophenolate mofetil (MMF) treatment vs. cyclophosphamide treatment showed that the effects of the two drugs were comparable, with lower toxicity of MMF [85,86]. Immunomodulatory treatment of the underlying disease may be of major importance, particularly in autoimmune diseases, which should take into account not only respiratory effects, but also the overall disease activity and inflammatory processes in other organs and tissues [87]. In the treatment of HP, the first necessary step is to identify and eliminate the causal antigen, which has a positive impact on the course of the disease and prognosis [4,34]. Early immunomodulatory treatment in patients with fibrosing NSIP or HP may be associated with improved respiratory function and a favorable long-term prognosis [19,20]. MMF and azathioprine are considered first-choice drugs in patients with fibrosing HP who present with disease progression despite previous glucocorticoid therapy [83]. A study evaluating the effect of MMF or azathioprine on lung function in patients with chronic HP demonstrated that both drugs were well tolerated and reduced the need for prednisone, and that annual treatment significantly improved $T_{L,CO}$ [88]. However, it should be noted that other studies showed opposite results [89,90].

Evidence quality: very low

Strength of recommendation: conditional

(voting results: strongly for—12 votes, conditionally for—12 votes, abstain from voting— 5 votes, conditionally against—0 votes, strongly against—0 votes)

- Zu Empfehlung 3.2.3.:

Treatment of ILDs other than IPF with a predominant component of inflammation from the point of view of the disease pathobiology is currently based on immunomodulatory therapy (glucocorticoids or immunosuppressants) and elimination of known causal factors in occupational or environmental diseases [4,91]. In practice, decisions on optimal immunomodulatory treatment are driven mainly by the diagnosis of the underlying disease and its course. Nevertheless, a considerable percentage of patients will, despite the use of immunomodulatory therapy recommended for the treatment of the underlying disease, develop PF-ILD, regardless of the initial diagnosis of an ILD. In these cases, from the point of view of pathobiology, the dominant factor is the process of fibrosis, rather than inflammation, and at the same time, this determines the progression of the disease, although the specific mechanisms responsible for the development of this phenotype are not known [92]. In this situation, immunomodulatory treatment is likely ineffective in terms of ILD control and is unable to prevent further worsening of the patient's clinical condition. A recently completed randomized phase III INBUILD clinical trial demonstrated the efficacy and safety of anti-fibrotic therapy with nintedanib in the population of patients with PF-ILDs other than IPF [16]. The benefits of nintedanib were also demonstrated in both the overall study population and in subgroups of patients with UIP and non-UIP radiological patterns [16]. Even though the INBUILD study did not have the power to

provide evidence in favor of nintedanib in specific diseases in a broad spectrum of PF-ILDs, its results suggest that nintedanib reduces the rate of progression of ILDs measured by the decline in FVC in patients with PF-ILDs, regardless of the initial ILD diagnosis [18]. At the same time, additional analyses of the study showed that concomitant use of glucocorticoids at the initiation of nintedanib treatment or the addition of other immunomodulatory therapies during treatment did not adversely affect the benefits of nintedanib in reducing the rate of decline in FVC [81], and the benefits were consistent regardless of the progression criterion used in the identification of the PF-ILD [93] or baseline FVC [94].

Evidence quality: low
Strength of recommendation: strong
(voting results: strongly for—16 votes, conditionally for—10 votes, abstain from voting—2 votes, conditionally against—1 vote, strongly against—0 votes)

- Zu Empfehlung 3.2.4.:

Pirfenidone is the first approved treatment for IPF [95–97]. Given its multifactorial anti-fibrotic effect, a similar effect may also be expected in patients with other ILDs with the progressive fibrosis phenotype. We have the results of several randomized clinical trials. The RELIEF study enrolled patients with progressive pulmonary fibrosis in AI-ILD, NSIP, fHP and asbestos exposure [98]. Most patients received standard treatment with glucocorticoids alone or in combination with an immunosuppressant. The study was terminated early due to too slow enrollment of eligible patients. The analysis of available data showed that patients receiving pirfenidone had a significantly lower FVC decline than patients receiving a placebo (difference between the groups of 1.69%, p = 0.042). No significant differences in progression-free survival were demonstrated, while a higher proportion of patients on pirfenidone maintained stable functional parameters (FVC decline of less than 5% over 48 weeks). The beneficial effects of pirfenidone were also observed with regard to $T_{L,CO}$ and distance in 6MWT [98]. The second phase (II), a multicenter, international, randomized, double-blind, placebo-controlled study, investigated the efficacy of pirfenidone in patients with unclassifiable ILDs with the progressive fibrosing phenotype [17]. The primary endpoint was a change in FVC after 24 weeks of treatment as assessed by daily home spirometry. It was not achieved due to technical difficulties, irregularities, and lack of consistency in performing this examination by patients at home. However, the evaluation of office spirometry (secondary endpoint) showed a smaller decline in FVC in pirfenidone-treated patients as compared with the placebo (17.8 mL vs. 113.0 mL/24 weeks). Fewer patients in the pirfenidone group experienced FVC declines greater than 5 and 10% over the study duration. No differences in progression-free survival or quality of life were observed. Although the aforementioned studies did not meet formal requirements, they indicate the efficacy of pirfenidone in inhibiting pulmonary fibrosis progression, as in the case of IPF. No new safety signals were observed—the adverse event profile was consistent with the one observed in the studies in IPF patients [17,98]. Pirfenidone is currently being studied in patients with SSc-ILD, rheumatoid-arthritis-associated interstitial lung disease (TRAIL-1), sarcoidosis with pulmonary fibrosis, fHP, and pneumosilicosis [99].

Evidence quality: very low
Strength of recommendation: not issued
(voting results: strongly for—1 vote, conditionally for—12 votes, abstain from voting—14 votes, conditionally against—2 votes, strongly against—0 votes)

- Zu Empfehlung 3.2.5.:

Currently, no studies are available that directly assess the efficacy of immunomodulatory treatment compared to anti-fibrotic therapy in patients with PF-ILDs. Treatment decisions in this group of patients are, therefore, difficult and should be supported by a discussion in a multidisciplinary team, considering close collaboration with a rheumatologist in the case of AI-ILD. Antifibrotic therapy as a first-choice therapy should be considered in patients with an IPF-like phenotype, i.e., patients with a UIP pattern in lung HRCT or histopathological examinations and presenting worsening respiratory symptoms, FVC decline ≥ 10% within 12 months, and especially in those patients for whom immunosuppressive therapy would be associated with greater potential adverse effects [83,100]. The presence of the UIP pattern in patients with RA-associated ILD or fibrotic HP is associated with a worse prognosis than in the case of other patterns visible in HRCT and histology [100,101]. A comparison of the placebo groups from the INPULSIS and INBUILD studies showed that the FVC decline was similar between IPF and PF-ILD patients with a similar pattern of UIP in HRCT [3]. Immunosuppressive therapy in patients with IPF was associated with poorer survival compared with the placebo [102,103]. Some retrospective studies also suggested the deleterious effects of immunosuppressive therapy in fHP [89,90]. Patients with fibrosing NSIP have a poorer prognosis than patients with the cellular disease [104]. Immunomodulatory treatment (glucocorticoids, MMF, azathioprine, cyclophosphamide, rituximab) is the treatment of choice in NSIP patients according to the previous recommendations [104,105].

Antifibrotic agents were evaluated in randomized clinical trials in patients with PF-ILD and SSc-ILD, some of which included patients with fibrotic NSIP [16,23,37]. Studies with nintedanib have shown that it slowed the rate of decline in FVC by 57% in PF-ILD, with 19% being patients with NSIP, and by 44% in SSc-ILD, where NSIP was the predominant form of ILD [16,23]. Treatment with nintedanib, the only agent currently approved for the treatment of PF-ILD, should be considered in the case of fibrosis progression in patients with NSIP when immunosuppressive therapy is contraindicated.

Evidence quality: very low

Strength of recommendation: conditional

(voting results: strongly for—7 votes, conditionally for—12 votes, abstain from voting—6 votes, conditionally against—4 votes, strongly against—0 votes)

- Zu Empfehlung 3.2.6.:

Immunosuppressive therapy remains the basis for the management of patients with PF-ILDs—in particular, autoimmune diseases, such as rheumatoid arthritis or systemic sclerosis. Glucocorticosteroids and certain immunosuppressive agents, such as MMF and azathioprine, are also used in the treatment of HP, NSIP, or uILD [14,106]. Despite such treatments, approximately 18 to 32% of patients with ILD other than IPF are estimated to develop a progressive fibrosing phenotype [14]. The results of randomized clinical trials in recent years show a beneficial effect of anti-fibrotic drugs on slowing the rate of progression of PF-ILDs [16,23,98]. Combining immunosuppressive and anti-fibrotic therapy may be a beneficial therapeutic option, taking into account the potential for both therapies to influence different pathogenic pathways involved in the development and progression of PF-ILDs. The safety of a combination treatment with pirfenidone and MMF, as well as nintedanib and MMF, was established in clinical trials in patients with uILD and SSc-ILD [17,23]. The SENSCIS study enrolled patients with SSc-ILD taking MMF at a stable dose in the previous 6 months, methotrexate, or ≤10 mg prednisone, and ultimately, around half of the patients were treated with MMF. It was observed that in the placebo group, the decline in FVC was lower in patients receiving MMF, suggesting a potentially beneficial effect of MMF. In addition, patients treated with both nintedanib and MMF had the slowest rate of FVC decline, suggesting a potential role for combination therapy in SSc-ILD [23]. In the INBUILD trial, immunosuppressant use was not allowed at randomization and for the next 6 months, except for prednisone at a dose of ≤20 mg/day. Post-study analysis showed that the use of glucocorticoids at baseline or the initiation of immunomodulatory treatment during the study had no impact on the beneficial effects of nintedanib in patients with PF-ILDs [81]. An SLS-III trial evaluating the efficacy and safety of the combination therapy with pirfenidone and MMF versus MMF alone in patients with SSc-ILD is ongoing [99].

Evidence quality: very low

Strength of recommendation: conditional

(voting results: strongly for—6 vote, conditionally for—17 votes, abstain from voting—5 votes, conditionally against—1 vote, strongly against—0 votes)

- Zu Empfehlung 3.2.7.:

The results of the INBUILD study showed that anti-fibrotic therapy with nintedanib slowed the rate of FVC loss in a population of patients who developed progressive fibrosis (PF-ILD) in interstitial diseases other than IPF (non-IPF ILD) [16]. Moreover, an additional post hoc analysis of the study's results in the overall patient population that evaluated the predicted categorical absolute changes in FVC percentage (FVC%) over a 52-week study period showed that the percentage of patients experiencing clinically meaningful declines in FVC% (FVC decline ≥5%) was lower in the nintedanib group compared with that in the placebo group [107,108]. Currently, there are no data on the efficacy of nintedanib in patients with PF-ILDs beyond 52 weeks or data indicating the benefit of continuing antifibrotic treatment in patients with PF-ILDs who experience disease progression during such treatments. Data on the prognostic significance of FVC decline in the non-IPF ILD population are scarce. At the same time, studies in the IPF population have shown that FVC decline is a weak predictor of future FVC decline despite its association with mortality [109–111]. Published analyses of pooled data from registration trials for anti-fibrotic agents in IPF provided evidence that continued pirfenidone therapy benefited patients with IPF who had significant on-treatment disease progression (defined as a decline in FVC of ≥10% over 6 months of treatment), with a risk reduction with respect to further FVC decline or death [110]. A similar analysis of pooled data from the INPULSIS I and II studies suggested the benefit of continued treatment with nintedanib in patients with IPF despite disease progression [111].

Evidence quality: very low

Strength of recommendation: not issued
(voting results: strongly for—4 votes, conditionally for—6 votes, abstain from voting—9 votes, conditionally against—8 votes, strongly against—2 votes)

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Lee AS et al., 2021 [1].

Consensus Guidelines for Evaluation and Management of Pulmonary Disease in Sjogren's

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz, hinsichtlich der Fragestellung zur Therapie von progressiven fibrosierenden interstitiellen Lungenerkrankungen bei 6-17-Jährigen, wird die LL ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft teilweise zu (keine PatV.);
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft teilweise zu (keine Angaben zu Interessenskonflikten, sondern nur zur Finanzierung);
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft teilweise zu (nur MEDLINE/PubMed genannt);
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft teilweise zu (keine Angaben zur externen Begutachtung);
- Regelmäßige Überprüfung der Aktualität gesichert: trifft nicht zu.

Recherche/Suchzeitraum:

- MEDLINE/PubMed
- between January 1, 1990, and February 1, 2020

LoE/GoR

Rating for Total Body of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (e.g., balance of benefits versus harms) and further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Intermediate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect, however it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change the magnitude and/or direction of this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. Reliance on consensus opinion of experts may be reasonable to provide guidance on the topic until better evidence is available.

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Sonstige methodische Hinweise

- Die vorliegende Leitlinie ist konsensbasiert und demnach lediglich ergänzend dargestellt.
- Der Hintergrundtext (und die dort enthaltenen Referenzen) wurde aufgrund fehlender Relevanz (keine Infos zu Therapieoptionen) nicht extrahiert.

Empfehlungen

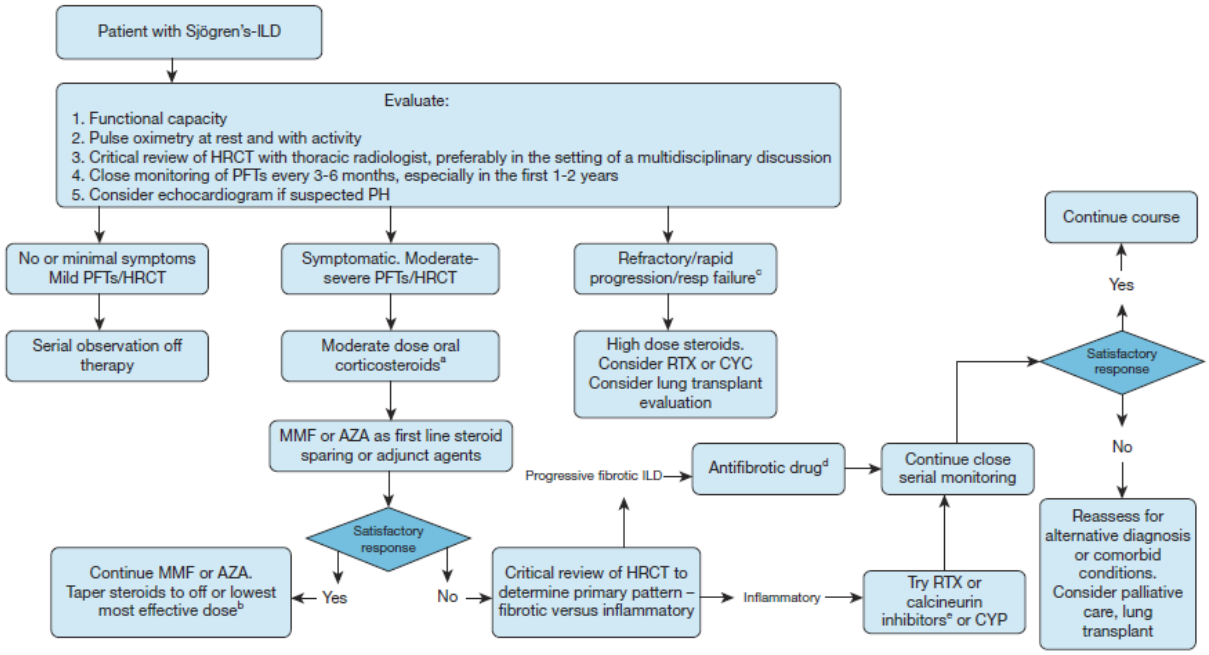

Figure 1: Evaluation and management of patients with Sjögren's who exhibit symptoms and/or physical examination signs of interstitial lung disease. Details regarding PFTs and HRCT examinations are given in Figure 1. [a]The dose and duration of corticosteroids in Sjögren's-ILD is not standardized. The panel proposes a dose not to exceed 60 mg daily of prednisone with a slow taper over weeks-months. In rapidly progressive ILD, or acute respiratory failure, consider pulse dose IV corticosteroids or high-dose oral corticosteroids up to 60 mg daily of prednisone. [b]In patients who are not able to successfully taper off corticosteroids, or experience unfavorable adverse effects, or in patients where the length of corticosteroid therapy is predicted to be long-term, steroid-sparing agents should be initiated as maintenance therapy. [c]Condition rapidly deteriorates and requires hospitalization. [d]Nintedanib is approved by the US Food and Drug Administration for progressive fibrotic lung disease phenotype. [e]Calcineurin inhibitors can be considered in patients who are intolerant to the initial maintenance therapy; no evidence to support the superiority in patients who fail the first-line therapy. AZA = azathioprine; CYP = cyclophosphamide; HRCT = high-resolution CT; ILD = interstitial lung disease; MMF = mycophenolate mofetil; PFTs = pulmonary function tests; PH = pulmonary hypertension; RTX = rituximab.

Recommendations: ILD—nonpharmacological and other management

Recommendation	Strength of Evidence	Strength of Recommendation
1. Vaccination: All Sjögren's patients must be immunized against influenza and pneumococcal infection (Prevnar and Pneumovax) in accordance with Centers for Disease Control and Prevention guidelines.	HIGH	STRONG
2. Pneumothorax and cystic lung disease: Because a Sjögren's patient with cystic lung disease might have an increased risk of pneumothorax, patients and caregivers/family must be educated about signs and symptoms of pneumothorax and instructed to seek immediate medical attention if they experience signs or symptoms.	INTERMEDIATE	STRONG
3. Pulmonary rehabilitation and ILD: In a symptomatic Sjögren's patient with ILD and impaired pulmonary function, referral for pulmonary rehabilitation is recommended.	INTERMEDIATE	STRONG
4. Oxygen and ILD: In a Sjögren's patient with suspected ILD and clinically significant resting hypoxemia (defined by resting oxygen saturation $< 88\%$, $Pao_2 < 55$ mm Hg or < 60 mm Hg with complication of chronic hypoxemia such as cor pulmonale), long-term oxygen therapy is recommended.	INTERMEDIATE	STRONG
5A. Air travel and ILD: In a Sjögren's-ILD patient considering air travel, the need for supplemental oxygen should be evaluated by a physician.	INTERMEDIATE	MODERATE
5B. Air travel and ILD: In a Sjögren's patient with ILD, discouraging air travel is not recommended unless the patient develops signs and symptoms of pneumothorax or new onset/unexplained chest pain or dyspnea prior to boarding.	INTERMEDIATE	STRONG
6. Lung transplant and ILD: In a Sjögren's patient with ILD whose condition is advanced with resting hypoxia or whose lung function is rapidly deteriorating, lung transplant evaluation is recommended.	INTERMEDIATE	STRONG

Recommendations: ILD—pharmacological interventions

Recommendation	Strength of Evidence	Strength of Recommendation
1A. Symptomatic/moderate-severe ILD—systemic corticosteroids: In Sjögren's patients with symptomatic ILD with moderate to severe impairment on lung function, imaging, or in gas-exchange and especially in organizing pneumonia, systemic steroids should be considered as a first-line treatment at a dosage based on the clinical context and disease severity, with standard dosage being 0.5-1.0 mg/kg.	INTERMEDIATE	MODERATE
1B. Cautions for systemic corticosteroids: In a Sjögren's patient with ILD or a related disorder, providers must be aware of the following risks/potential harms: Potential short-term side effects[a]: • Glucose intolerance • Avascular necrosis • Mineralocorticoid effect, leading to potential fluid retention and/or hypertension • Myopathy • Psychological, including hyperactivity, insomnia, psychosis • Pancreatitis • Hypertension • Truncal obesity • Acne • Hematopoietic, including leukocytosis • Ecchymosis • Acanthosis nigricans Potential long-term side effects: • Osteoporosis • Diabetes • Adrenal insufficiency • GI symptoms, including peptic ulcer, hepatic steatosis • Ophthalmological, including glaucoma, cataract • Hyperlipidemia • Congenital malformation in utero exposure (very rare) • Growth suppression (only in pediatrics)	HIGH	STRONG
2A. Symptomatic/moderate-severe ILD—MMF or azathioprine: In a Sjögren's patient with symptomatic ILD with moderate to severe impairment as determined by lung function testing, imaging, or gas-exchange, MMF or azathioprine should be considered when long-term steroid use is contemplated and steroid-sparing immunosuppressive therapy is required.	INTERMEDIATE	MODERATE
2B. Cautions for azathioprine: In a Sjögren's patient with ILD or related disorder and considering use of azathioprine, patients and health-care providers must be aware of potential risks for drug-induced pneumonitis, GI upset, hepatotoxicity, bone marrow suppression, rash, and hypersensitivity syndrome. Testing for thiopurine methyltransferase activity or genotype before initiating azathioprine is recommended to reduce the risk of severe, life-threatening leukopenia due to complete lack of thiopurine methyltransferase activity.[a]	HIGH	STRONG
2C. Cautions for MMF: In a Sjögren's patient with ILD or related disorder and considering use of MMF, patients and health-care providers must be aware of potential side effects, including nausea, diarrhea, hepatotoxicity, and bone marrow suppression.[a]	HIGH	STRONG
3. Symptomatic/moderate-severe ILD—maintenance therapies: Following initial treatment for Sjögren's patients with ILD who are symptomatic and in whom PFTs or HRCT demonstrated moderate-severe impairment, first-line maintenance drugs should be either MMF or azathioprine.	LOW	MODERATE
4A. Symptomatic/ moderate-severe ILD—second-line therapies: If initial treatment with MMF or azathioprine is insufficient or not tolerated in Sjögren's patients with ILD who are symptomatic and in whom PFTs or HRCT demonstrated moderate-severe impairment, subsequent second-line maintenance drugs may include rituximab and calcineurin inhibitors, cyclosporine, or tacrolimus.	LOW	WEAK

4B. Cautions for rituximab: In a Sjögren's patient with ILD considering use of rituximab, patients and health-care providers must be aware of the following potential risks/harms, although rare[a]:
• Pneumonitis
• Worsening of ILD
• Infusion reactions
• Tumor lysis syndrome in those with NHL
• Bacterial, viral, or fungal infections including:
  • Hepatitis B reactivation with possible fulminant hepatitis
  • Progressive multifocal leukoencephalopathy
• Hypogammaglobulinemia
• Cytopenias
• Severe mucocutaneous reactions
• Bowel obstruction and perforation
• Cardiac arrhythmias and angina
• In pregnancy and nursing, risk vs benefit must be carefully considered
• Avoid live vaccines with rituximab
	HIGH	STRONG

5. Symptomatic/moderate-severe Sjögren's-ILD—antifibrotic drugs[b]: The use of antifibrotic therapy such as nintedanib should be tried as a second-line maintenance therapy either alone or in combination with immunomodulatory agents in Sjögren's patients with progressive fibrotic ILD who are symptomatic and in whom PFTs or HRCT demonstrated moderate-severe impairment.	LOW	MODERATE
6. Rapidly progressive or exacerbating ILD—IV steroids: In Sjögren's patients with ILD who are rapidly progressive or present with acute respiratory failure, a trial of high-dose corticosteroids (such as IV methylprednisolone) is recommended. Alternative etiologies, such as infections or lymphoproliferative disorders, must be considered.	INTERMEDIATE	STRONG
7A. Symptomatic/refractory, rapidly progressive, or exacerbating ILD—cyclophosphamide: In a Sjögren's patient with ILD who has acute or subacute hypoxic respiratory failure requiring hospitalization, despite initial therapies, rituximab or cyclophosphamide should be considered in addition to high-dose corticosteroids.	LOW	MODERATE
7B. Cautions for cyclophosphamide: In Sjögren's with ILD when cyclophosphamide is considered, the significant risks must be assessed[a] and *Pneumocystis jirovecii* prophylaxis provided. Risk of bladder cancer can be greatly reduced with IV vs oral route.	INTERMEDIATE	STRONG
8. Drug-induced lung disease: Clinicians and patients must be aware of pulmonary complications associated with medications used in Sjögren's and related CTDs, particularly when patients are progressive or refractory to therapies. Complications may include infections, malignancies, bronchospasm, and drug-induced ILD, and may require bronchoscopy, biopsy, and/or withdrawal of the medication. In addition to medication withdrawal, corticosteroids may be used if significant symptoms and respiratory impairment are present. While the risk is low for most agents (approximately 1%), health-care providers should keep in mind that medications used to treat Sjögren's have been associated with drug-induced ILD, including: • TNF-alpha inhibitors • Sulfasalazine • Cyclophosphamide • Rituximab • Leflunomide • Methotrexate • Sulfonamides	INTERMEDIATE	STRONG

CTDs = connective tissue diseases; HRCT = high-resolution CT; ILD = interstitial lung diseases; MMF = mycophenolate mofetil; NHL = non-Hodgkin lymphoma; PFTs = pulmonary function tests; TNF = tumor necrosis factor.

[a]Refer to the US Food and Drug Administration label for additional information.

[b]The antifibrotic, nintedanib, was US Food and Drug Administration-approved for progressive fibrotic ILD just as these recommendations went to consensus. This factor, in addition to the authors' awareness of minimal experience with antifibrotics in autoimmune disease, precluded inclusion of a Recommendation listing cautions for antifibrotics. Please consult the Physicians' Desk Reference for potential risks and side effects.

Maintenance Therapies for ILD in Sjögren's

Drug	Mechanism of action	Common side effects	Level of recommendation
Mycophenolate	Antimetabolite, inhibition of DNA synthesis	Nausea, diarrhea, hepatotoxicity, bone marrow suppression. Pregnancy risk category D	First line therapy for symptomatic ILD with moderate to severe impairment. Moderate strength of recommendation
Azathioprine	Antimetabolite, inhibition of DNA synthesis	Nausea, diarrhea, hepatotoxicity, bone marrow suppression, rash, hypersensitivity syndrome. Pregnancy risk category D	First line therapy for symptomatic ILD with moderate to severe impairment. Moderate strength of recommendation
Cyclosporin	Calcineurin inhibitor T cell target agent	Nephrotoxicity, neurotoxicity, hypertension, hyperglycemia, hirsutism, gingival hyperplasia. Pregnancy risk category C	Second line therapy for symptomatic ILD with moderate to severe impairment. Weak strength of recommendation
Tacrolimus	Calcineurin inhibitor T cell target agent	Nephrotoxicity, neurotoxicity, hypertension, hyperglycemia, alopecia. Pregnancy risk category C	Second line therapy for symptomatic ILD with moderate to severe impairment. Weak strength of recommendation
Cyclophosphamide	Cytotoxic alkylating agent	Infection, bone marrow suppression, gonadal toxicity, bladder toxicity, malignancy risk. Pregnancy risk category D	First line therapy for symptomatic ILD with refractory, rapidly progressive or exacerbating condition requiring hospitalization. Moderate strength of recommendation
Rituximab	Anti CD20 monoclonal antibody B cell target agent	Infusion reaction, cytopenias, infection, hypogammaglobulinemia, hepatitis B reactivation, progressive multifocal leukoencephalopathy. Pregnancy risk category C	First line therapy for symptomatic ILD with refractory, rapidly progressive or exacerbating condition requiring hospitalization. Moderate strength of recommendation Second line therapy for symptomatic ILD with moderate to severe impairment. Weak strength of recommendation
Nintedanib	Tyrosine kinase inhibitor	Nausea, vomiting, diarrhea, weight loss, hepatotoxicity. Pregnancy risk category D	Second line therapy for symptomatic ILD with moderate to severe impairment with progressive fibrotic lung disease phenotype. Moderate strength of recommendation

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 12 of 12, December 2024) am 23.12.2024

#	Suchschritt
1	[mh "Lung Diseases, Interstitial"]
2	(interstitial NEAR/3 (lung OR pneumon* OR pulmon*)):ti,ab,kw
3	(diffuse NEAR/3 parenchym*):ti,ab,kw
4	((extrinsic AND allergic AND alveolit*) OR (hypersensitiv* NEAR/3 pneumonit*)):ti,ab,kw
5	((bird* OR pigeon* OR budgerigar* OR farmer* OR avian*) NEAR/3 lung):ti,ab,kw
6	((goodpasture* NEAR/3 (syndrom* OR disease*)) OR (lung NEAR/3 purpura)):ti,ab,kw
7	(pneumoconios* OR bagassos* OR anthracos* OR asbestos* OR beryllios* OR byssinos* OR (caplan NEXT syndrome) OR sideros* OR silicos*):ti,ab,kw
8	(radiation NEAR/3 (pneumon* OR fibros*)):ti,ab,kw
9	((sarcoidos* OR fibros*) NEAR/3 (pulmon* OR lung*)):ti,ab,kw
10	{OR #1-#9}
11	[mh "scleroderma, Systemic"]
12	(systemic NEXT (scleroderma* OR scleros*)):ti,ab,kw
13	[mh Dermatomyositis]
14	(dermatomyosit* OR polymyosit*):ti,ab,kw
15	[mh "Arthritis, Rheumatoid"]
16	(rheumatoid NEAR/3 arthrit*):ti,ab,kw
17	[mh "Lupus Erythematosus, Systemic"]
18	(lupus NEAR/3 erythematos*):ti,ab,kw
19	{OR #11-#18}
20	(lung OR pulmon* OR pneumon*):ti,ab,kw AND #19
21	{OR #10, #20}
22	#21 with Cochrane Library publication date from Dec 2019 to present

Leitlinien und systematische Reviews in PubMed am 23.12.2024

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

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

#	Suchschritt
	Leitlinien
1	Lung Diseases, Interstitial[mh]
2	interstitial[tiab] AND (lung[tiab] OR pneumon*[tiab] OR pulmon*[tiab])
3	diffuse[tiab] AND parenchym*[tiab] AND lung[tiab]
4	(extrinsic[tiab] AND allergic[tiab] AND alveolit*[tiab]) OR (hypersensitiv*[tiab] AND pneumonit*[tiab])
5	(bird*[tiab] OR pigeon*[tiab] OR budgerigar*[tiab] OR farmer*[tiab] OR avian*[tiab]) AND lung[tiab]
6	(goodpasture*[tiab] AND (syndrom*[tiab] OR disease*)) OR (lung[tiab] AND purpura[tiab])
7	pneumoconios*[tiab] OR bagassos*[tiab] OR anthracos*[tiab] OR asbestos*[tiab] OR beryllios*[tiab] OR byssinos*[tiab] OR “caplan syndrome”[tiab] OR sideros*[tiab] OR silicos*[tiab]
8	radiation[tiab] AND (pneumon*[tiab] OR fibros*[tiab])
9	(sarcoidos*[tiab] OR fibros*[tiab]) AND (pulmon*[tiab] OR lung*[tiab])
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11	Scleroderma, Systemic[mh]
12	systemic scleroderma*[tiab] OR systemic scleros*[tiab]
13	Dermatomyositis[mh]
14	dermatomyosit*[tiab] OR polymyosit*[tiab]
15	Arthritis, Rheumatoid[mh]
16	rheumatoid[tiab] AND arthrit*[tiab]
17	Lupus Erythematosus, Systemic[mh]
18	lupus[tiab] AND erythematos*[tiab]
19	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
20	lung[tiab] OR pulmon*[tiab] OR pneumon*[tiab]
21	#19 AND #20
22	#10 OR #21
23	(#22) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])

#	Suchschritt
24	((((#23) AND ("2019/12/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])
	systematische Reviews
25	(#10) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
26	(((#25) AND ("2019/12/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))) NOT ("retracted publication"[Publication Type] OR "retraction of publication"[Publication Type] OR "preprint"[Publication Type])
	systematische Reviews ohne Leitlinien
27	(#26) NOT (#24)

Iterative Handsuche nach grauer Literatur, abgeschlossen am 02.01.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **Lee AS, Scofield RH, Hammitt KM, Gupta N, Thomas DE, Moua T, et al.** Consensus guidelines for evaluation and management of pulmonary disease in sjogren's. Chest 2021;159(2):683-698.

2. **Narvaez J, Diaz Del Campo Fontecha P, Brito Garcia N, Bonilla G, Aburto M, Castellvi I, et al.** SER-SEPAR recommendations for the management of rheumatoid arthritis-related interstitial lung disease. Part 2: treatment. Reumatol Clin (Engl Ed) 2022;18(9):501-512.

3. **Piotrowski WJ, Martusewicz-Boros MM, Bialas AJ, Barczyk A, Batko B, Blasinska K, et al.** Guidelines of the Polish Respiratory Society on the diagnosis and treatment of progressive fibrosing interstitial lung diseases other than idiopathic pulmonary fibrosis. Adv Respir Med 2022;90(5):425-450.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

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

Verfahrens-Nr.: 2024-B-321-z

Verfasser	
Name der Institution	1) Gesellschaft für pädiatrische Pneumologie 2) Gesellschaft für Kinderrheumatologie
Datum der Erstellung	28. Januar 2025

Indikation
…indicated in children and adolescents from 6 to 17 years old for the treatment of clinically significant, progressive fibrosing interstitial lung disease (ILDs). Inoffizielle Übersetzung: „...angezeigt bei Kindern und Jugendlichen im Alter von 6 bis 17 Jahren zur Behandlung von klinisch relevanten, fortschreitenden fibrosierenden interstitiellen Lungenerkrankungen (ILD).“
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 der klinisch relevanten, fortschreitenden fibrosierenden interstitiellen Lungenerkrankung (ILD) bei Kindern- und Jugendlichen von 6 bis 17 Jahren Die Lungenfibrose ist ein einheitliches Reaktionsmuster der Lunge bei einer Vielzahl von Erkrankungen. Eine kürzlich erstellte Übersicht hat mehr als 40 Erkrankungen und Erkrankungsgruppen aus dem europäischen und US-amerikanischen Kinderlungenregistern identifiziert, bei denen Lungenfibrosen vermerkt wurden (1). Dies umfasst Erkrankungen wie Surfactantprotein C Dysfunktion, ABCA3 Defizienz, die nicht-spezifische interstitielle Pneumonitis, das Hermansky-Pudlak Syndrom, Aminoacyl t-RNA-Synthethasen-assoziierte Erkrankungen, die juvenile systemische Sklerose, andere collagenvaskuläre Erkrankungen einschließlich der juvenilen Dermatomyositis, die Sarkoidose, chronische Lungenerkrankungen nach Knochenmarktransplantation, COPA Defizienz, TBX4- oder NKX2.1-assoziierte Erkrankungen, Bestrahlungs-, Medikamenten- und toxisch-induzierte Lungenschäden und die chronische exogen allergische Alveolitis. Alle vorliegenden Empfehlungen für Kinder und Jugendliche sind extrem begrenzt durch das Fehlen geeigneter randomisierter kontrollierter klinischer Studien und beruhen auf Expertenmeinung, der Übertragung von Erfahrungen bei erwachsenen auf Kinder und kleinen Fallserien oder Einzelfallberichten (2). Unterstützende Behandlung durch O2-Gabe / mechanische Beatmungsunterstützung, angemessene Kalorienzufuhr, psychosoziale Unterstützung und physiotherapeutische Rehabilitation. Prophylaktische Immunisierungen zur Reduktion des Exazerbationsrisikos. Medikamentös-therapeutisch werden Patienten mit inflammatorischen pulmonalen und systemischen Reaktionen mit Steroiden und potenziell steroidsparenden Immunsuppressiva wie Mycophenolatmofetil (MMF), Azathioprin oder Cyclophosphamid behandelt. Auch intravenöse Immunglobulingaben, Calcineurin-Inhibitoren kommen empirisch zum Einsatz. Janus-Kinase-Inhibitoren (zB Baricitinib, Ruxolitinib) können auch eine wirksame Behandlung von autoinflammatorischen Interferonopathien, wie SAVI, STAT3-GOF und COPA darstellen. Darüber

werden Biologika wie Rituximab bei der Behandlung immunvermittelter ILDs angewendet. Mehrere Studien haben den Einsatz dieser Medikamente, auch in Kombination bei ILD bei systemischer Sklerose bei Erwachsenen und Kindern (Rituximab / MMF) gezeigt; für diese Erkrankung wird separat zusätzlich in 2024-B-320-z geantwortet. Die entzündungshemmenden Mittel Hydroxychloroquin und Azithromycin werden ebenfalls verwendet. Die erste randomisierte, placebokontrollierte Studie bei chILD, die viele kindliche ILD (mittlere forcierte Vitalkapazität etwa 50 % des Solls) untersuchte als Phase-II-Studie Hydroxychloroquin an 35 Kindern. Die Power der Studie war zu klein, um die Wirksamkeit der Behandlung zu dokumentieren. Hydroxychloroquin wurde gut vertragen, die beobachteten Wirkeffekte (effect size sehr klein) legen jedoch nahe, dass die bisherige optimistische Einschätzung der Verwendung von Hydroxychloroquin bei kindlichen ILD weiter evaluiert werden sollte (3).
Eine gezielte Behandlung der vorliegenden fibrosierenden Prozesse der ILD bei Kindern und Adoleszenten ist bisher nicht verfügbar. Bei einzelnen Kindern wurden in den letzten Jahren (aus therapeutischer Ausweglosigkeit) off-label Pirfendon oder Nintedanib angewendet.
Eine doppelblinde, randomisierte, placebokontrollierte klinische Studie zu Nintedanib bei Kindern und Jugendlichen (6-17 Jahre, N=39, 13 Plazebo, 26 Nintedanib) mit klinisch signifikanter fibrosierender ILD wurde 2023 publiziert (4). Die Studie hat zur Definition der Lungenfibrose eine Kombination aus CT-Bildgebungs- und Histologiekriterien verwendet. Die primären Endpunkte, das Sicherheitsprofil und die Pharmakokinetik der Nintedanib-Therapie, entsprachen den von erwachsenen bekannten Ergebnissen. Hauptnebenwirkung waren Durchfälle, die etwa doppelt so häufig in der Verum- wie in der Plazebogruppe auftraten, jedoch klinisch gut behandelbar waren. Wie aufgrund der geringen Fallzahl zu erwarten, zeigten die Ergebnisse keinen signifikanten Unterschied. Die Patienten in der Nintedanib-Gruppe hatten einen mittleren Anstieg der forcierten Vitalkapazität von 0,3±1,3 % nach 24 Wochen im Vergleich zu einem Rückgang von 0,9%±1,8% in der Placebo-Gruppe (nominal p=0,60). Eine Bayes'sche Analyse ergab einen medianen Unterschied von 1,63% (95% Glaubwürdigkeitsintervall -0,69 bis 3,40)(5).
Eine aufgrund der sehr geringen Fallzahl notwendige weitere Beobachtung der Patienten findet in der InPedILD-ON Studie statt. Die Daten dieser offenen Beobachtungsstudie liegen aktuell noch nicht vor.
Die beiden bei Erwachsenen mit ähnlichen Fibrosen zugelassenen antifibrotischen Medikamente Pirfendon und Nintedanib stehen in Deutschland den betroffenen Kindern nicht zur Verfügung. Über Einzelanträge (Pirfenidon) oder Firmen-Patienten-Programmen (Nintedanib) können die Medikamente mit erheblichem Aufwand einigen Patienten zugänglich gemacht werden.

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.)

Die unterstützenden Behandlungen und die prophylaktischen Maßnahmen kommen allen Patienten zugute. Die medikamenösen Therapien werden abhängig von der persönlichen Erfahrung des Behandelnden Arztes systematisch in Abhängigkeit vom Schweregrad und der Akuität der Erkrankung eingesetzt. Prinzipiell werden, nach dem Grundsatz durch die Behandlung nicht zusätzlich zu schaden, Medikamente mit einem besseren Sicherheitsprofil bevorzugt eingesetzt. Längerfristige Behandlungen die mit hoher Wahrscheinlichkeit Nebenwirkungen hervorrufen werden, werden gemieden.
Starke inflammatorische Reaktionen werden eher kurzzeitig und stark behandelt (zB Steroidpulse), chronische inflammatorische Zustände eher langfristig möglichst ohne Steroide mit den o.g. Steroid sparenden Medikamenten behandelt. Man bevorzugt Steroide nur als bridging Therapie zu verwenden.
Eine direkte antifibrotische Behandlung (zB Nintedanib oder Pirfenidon) steht regulär für die Kinder leider noch nicht zur Verfügung, obgleich Lungenfibrosen bei einem erheblichen Anteil der von den

o.g. Diagnosen betroffenen Kindern nachgewiesen werden und dringend erforderlich sind. Tocilizumab ist für Erwachsene für Systemische Sklerodermie assoziierte ILD in der USA zugelassen, es ist besonders in der Kombination mit Mycophenolat Mofetil effektiv und dieses Therapiekonzept wurde von den Kinderrheumatologen für juvenile systemische Sklerodemie übernommen(6), besonders da Tocilizumab für juvenile Patienten ab den 2 Lebensjahr zugelassen ist. Man kann diesen Konzept für den Dermatomyositis assoziierten ILD extrapolieren.

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