Zur Erstellung des Updates der S2e-Leitlinie 166/001: *Idiopathisches Nephrotisches Syndrom im Kindesalter: Diagnostik und Therapie* wurde eine sorgfältige Medline-Recherche durchgeführt, die zwischen August 2019 und Mai 2020 wiederholt aktualisiert wurde. Folgende Suchbegriffe wurden verwendet: „nephrotic syndrome“, „pediatric“ kombiniert mit übergeordneten Suchbegriffen wie „diagnostics“, „management“, „therapy“, „complications“ und entsprechend den Inhalten der Leitlinie mit „steroids“, „cyclosporine“, „tacrolimus“, „mycophenolate mofetil“, „mycophenolic acid“, „cyclosphosphamide“, „rituximab“, „levamisol“, „vaccination“, „infection“, „frequently relapsing“, „infrequent relapses“, „steroid-dependent“, „thromboembolism“, „cardiovascular disease“, „lund edema“, „long-term follow-up“, „psychosocial aspects“, „transition“. Mehr als 11.500 Treffer wurden in einem ersten Schritt unter besonderer Beachtung des Erscheinungsjahrs nach 2016 gefiltert. Im weiteren Verlauf wurden insbesondere RCT´s sowie prospektive klinische Studien, sowie für einzelne Unterthemen bei fehlender höhergradiger Evidenz retrospektive Studien beachtet. Letztendlich wurde die Referenzliste der Leitlinie im Zuge des aktuellen Updates um folgende 20 Referenzen ergänzt.

Referenz	**Studientyp Zielstellung**	**Teilnehmer** (Anzahl und Charakteristika)	**Intervention vs. Kontrolle**	**Zielgröße(n)**	**Hauptergebnis** (Intervention vs. Kontrolle)	**Evidenzgrad** (Oxford CEbM, 2009)
Abeyagunawardena, Thalgahagoda et al., Pediatr Nephrol, 2017	Placebo-controlled crossover trial Short courses of daily prednisolone during upper respiratory tract infections reduce relapse frequency in childhood nephrotic syndrome	48 patients with idiopathic NS (2 to 18 years of age).	Group A received 5 days of daily prednisolone at 0.5 mg/kg at the onset of an URTI while group B received 5 days of placebo. A crossover was performed during the next year, with group A receiving placebo and group B receiving prednisolone.	To assess the effect of a short course of low-dose corticosteroid therapy during the course of an URTI on relapse frequency in patients with steroid-sensitive NS who have not been taking any treatment for a minimum period of 3 months.	Prescribing a short course of daily corticosteroids during an URTI significantly reduces the frequency of URTI-induced relapse in patients with steroid-responsive NS who are off corticosteroid therapy.	3b
Abeyagunawardena, Karunadasa et al., Pediatr Nephrol, 2017	Clinical case study Efficacy of higher-dose levamisole	Sixty-four participants were enrolled into the study, with the	n.d.	To evaluate the efficacy of LEV prescribed at 2.5 mg/kg daily, which is double	The prescription of daily LEV is effective and safe for maintaining SDNS remission.	4

	(LEV) in maintaining remission in steroid-dependant nephrotic syndrome	oldest being 14.2 years and the youngest 4.5 years (median 7.95 years).		the alternate-day dose.		
Basu et al., JAMA Pediatr, 2018	RCT Is B-cell–depleting therapy more efficacious than calcineurin inhibition in maintaining relapse-free survival in children with corticosteroid-dependent nephrotic syndrome?	A total of 176 consecutive children aged 3 to 16 years with CDNS not previously treated with corticosteroid-sparing agents were screened for eligibility.	The children received either tacrolimus (along with tapering alternate-day prednisolone) for 12 months or a single course of rituximab (2 infusions of 375 mg/m^2).	Twelve-month relapse-free survival in the intention-to-treat population.	In this randomized clinical trial that included 120 children with corticosteroid-dependent nephrotic syndrome, a single course of rituximab therapy was associated with a significantly higher 12-month relapse-free survival rate than daily tacrolimus therapy (90.0% vs 63.3%) during 12 months of follow-up. The mean cumulative corticosteroid dose during the 12-month study period was lower with rituximab compared with tacrolimus (25.8 vs 86.3 mg/kg).	1b
Benz et al., Ther Drug Monit, 2019	Prospective clinical trial Generation and validation of a LSS to estimate MPA exposure.	23 children with nephrotic syndrome in remission (mean age (±SD):12.3± 4.26 years).	n.d.	LSS to estimate MPA exposure to facilitate therapeutic drug monitoring in children with nephrotic syndrome.	An algorithm based on three PK sampling time points during the first 2 hours after MMF dosing (estimated AUC_{0-12}= $8.7+4.63*C_0+1.90*C_1+1.52*C_2$) was able to predict MPA-AUC with a low percentage prediction error (3.88%) and a good correlation of determination (r^2=0.90).	2b

Calderon-Margalit et al., New Engl J Med, 2019	Historical cohort study ESRD associated with a history of childhood kidney disease.	1,521,501 Israeli adolescents who were examined before compulsory military service in 1967 through 1997.	n.d.	ESRD in follow-up	During 30 years of follow-up, ESRD developed in 2490 persons. A history of any childhood kidney disease was associated with a hazard ratio for ESRD of 4.19 (95% confidence interval [CI], 3.52 to 4.99). In case of childhood glomerular disease the hazard ration for ESRD was 3.85 (2.77–5.36).	2c
Christiansen et al., Am J Med, 2014	Population based cohort study Risk and prognosis of cancer in patients with nephrotic Syndrome.	All individuals diagnosed with nephrotic syndrome between 1980 and 2010 without a preceding cancer history (N= 4293 of all ages).	n.d.	5-year mortality for patients with cancer after nephrotic syndrome.	The 5-year mortality after cancer was 68.5% in patients with cancer with nephrotic syndrome and 63.4% in the cancer comparison cohort (adjusted hazard ratio, 1.20; 95% CI, 1.02-1.42).	1c
Deschênes et al., Pediatr Nephrol, 2019	Educational Review Role of steroids to achieve remission in childhood nephrotic syndrome.		n.d.	First flare Relapse snd steroid dependency Steroid resistancy	Steroids remain the answer to obtain a rapid and full urinary remission of the flares in idiopathic nephrotic syndrome, but their efficiency to prevent a chronic disease after the first flare is closely limited.	3a
Gruppen et al., Kidney Int, 2018	RCT Usefulness of levamisol in prevention of relapses in children with	103 patients (2 to 18 years of age), recruited from 13 sites in 6 countries (The	Levamisol versus placebo.	Time to relapse.	The time to was significantly increased in the levamisole compared to the placebo group (hazard ratio 0.22 [95% confidence	1b

	steroid-sensitive idiopathic nephrotic syndrome.	Netherlands, Belgium, France, Italy, Poland, and India).			interval 0.11–0.43]).	
Kamei et al., J Pediatr, 2018	Prospective clinical trial Immunogenicity and safety of live attenuated vaccines in patients with nephrotic syndrome receiving immunosuppressive agents.	60 patients, median age 8 (1-24) years.	n.d.	The primary endpoint was the seroconversion rate (ie, achievement of virus-specific IgG levels ≥4.0) at 2 months after vaccination.	Seroconversion rates were 95.7%formeasles, 100% for rubella, 61.9% for varicella, and 40.0% for mumps. No patient experienced breakthrough infection. No serious adverse events, including vaccine-associated infection, were observed.	3b
Kari et al., Pediatr Nephrol, 2020	Prospective clinical trial (pilot study) Rituximab versus cyclophosphamide as first steroid-sparing agent in childhood frequently relapsing and steroid-dependent nephrotic syndrome.	46 children (>1 and <18 years of age) diagnosed with idiopathic frequently relapsing (defined as two or more relapses within 6 months after the initial response, or four or more relapses over a12-month duration) and/or steroiddependent (defined as two consecutive relapses	The recruited children were allocated either to the oral cyclophosphamide (3 mg/kg/day for 8 weeks) or intravenous rituximab treatment (two doses of 375 mg/m2/dose, 2 weeks apart) and were monitored for relapses and side effects for 12 months.	Cessation of oral prednisolone within the first 3 months after completion of the treatment course in patients who maintained remission or the dose of alternate-day oral prednisolone to maintain remission.	Both treatmentswere associated with a significant ($p < 0.001$) reduction in prescribed dose of oral alternateday steroid from 1.02 to 0.36 mg/kg (cyclophosphamide) and 0.86 to 0.08 mg/kg (rituximab). Importantly, a significantly ($p = 0.003$) higher percentage of patients achieved complete withdrawal of steroid within 3 months of commencing study treatment in the rituximab (73.7%) versus cyclophosphamide (29.6%) group.	4

		while tapering corticosteroid therapy, or within 14 days of stopping steroid) nephrotic syndrome, who received only steroid treatment with or without levamisole.				
Korsgaard et al., Pediatr nephrol, 2019	Retrospective study Long-termoutcome of childhood steroid-sensitive nephrotic syndrome (SSNS).	39 adult patients with childhood onset SSNS. The patients were followed for at mean duration of 14.4 (range 7.8–19.3) years with a mean age of 22.8 (range 18.0–30.9) years at last day of follow-up.	n.d.	Clinical outcome.	A total of 31% (12/39) had active disease in adulthood. Univariate analysis showed that more severe forms of SSNS (e.g., steroid dependent/ frequent relapsing (SD/FR) nephrotic syndrome) in childhood were associated with active disease in adulthood.	4
Midtvedt et al., Transplantation, 2017	Population-based retrospective cohort study Exposure to mycophenolic acid (MPA) and Fatherhood.	230 immunosuppressed renal transplanted men fathered 350 children (155 on MPA/195 not on MPA).	With of without MPA.	Clinical outcome of children.	There were no significant increased risks of malformation (3.9% vs. 2.6%, P = 0.49) in MPA exposed versus unexposed cohorts of children.	3b
Querfeld et al., Monatsschr Kinderheilkd, 2017	Leitlinienbericht zur AWMF-LL 166/001 „Idiopathisches nephrotisches Syndrom im Kindesalter“	n.d.	n.d.	n.d.	Siehe Leitlinie.	S2e

Rensen et al., Cochrane Database of Systematic Reviews, 2017	Systematic Cochrane Review Hypothalamic-pituitary-adrenal (HPA) axis suppression after treatment with glucocorticoid therapy for childhood acute lymphoblastic leukaemia.	n.d.	n.d.	n.d.	Siehe Review.	1a – 2a
Sinha et al., Kidney Int, 2019	RCT Efficacy and safety of mycophenolate mofetil versus levamisole in frequently relapsing nephrotic syndrome.	207 patients, ages 6 to 18 years, with frequently relapsing or steroid-dependent nephrotic syndrome screened, 58 were excluded. Of 149 included, 76 were randomized to receive MMF and 73 were randomized to treatment with levamisole.	Participants were randomized in a 1:1 ratio to receive therapy with MMF (750-1000 mg/m2 daily) or levamisole (2-2.5 mg/kg on alternate days) for 1 year.	Efficacy and safety of 12 months of treatment with levamisole with MMF in reducing the frequency of relapses in patients with frequently relapsing nephrotic syndrome	Therapy with MMF was not superior to levamisole in terms of the proportions of participants with sustained remission (40.8% vs. 34.2%), frequent relapses (14.5% vs. 16.4%), or treatment failure, a composite outcome of frequent relapses, steroid resistance, or significant steroid toxicity (15.8% vs. 20.6%).	1b
Schijvens et al., BMJ Open, 2017	Protocol of a national, doubleblind, randomised, placebo-controlled, non-inferiority intervention study.	n.d.	n.d.	n.d.	n.d.	n.d.

Schijvens et al., Kidney Int, 2019	Mini Review Control of relapses in children with nephrotic syndrome.	n.d.	n.d.	Role of therapeutic drug monitoring to optimize therapy with MMF	Using therapeutic drug monitoring to obtain adequate MPA exposure could therefore lead to significantly lower relapse rates. An additional randomized controlled trial with proven adequate MPA exposure is needed to draw a final conclusion about the comparability of MMF and levamisole as steroid-sparing agent in patients with FRNS or steroid-dependent nephrotic syndrome.	5
Suresh et al., Pediatr Transplant, 2019	Expert recommendation on live vaccines after pediatric solid organ transplantion (SOT)	n.d.	n.d.	Outcomes and adverse events with live vaccines after SOT	Recommendations are structured according to the following sections: 1. Pretransplant optimization of vaccination with MMR and VV uptake. 2. Post-transplant patient evaluation and risk stratification prior to considering live vaccination. 3. Considerations specific to the vaccinating agent—MMR and VV. 4. Immunologic evaluation of the SOT recipient prior to live vaccination.	3a

					5. Informed consent prior to live vaccination. 6. Monitoring for adverse events following live vaccination. 7. Current knowledge gaps and future research endeavors.	
Wagner et al., Bundesgesundheitsbl, 2019	Expertenmeinung auf der Grundlage der verfügbaren Evidenz Impfen bei Immundefizienz	n.d.	n.d.	n.d.	Kernaussagen zu folgenden Themen: 1. Infektionsanfälligkeit bei Autoimmunkrankheiten und anderen chronischentzündlichen Erkrankungen 2. Allgemeine Grundsätze für die Impfung von Personen mit Autoimmunkrankheiten, chronisch-entzündlichen Erkrankungen bzw. unter immunmodulatorischer Therapie 3. Spezielle Hinweise zu Immunsuppressiva/ Immunmodulatoren: Anhaltspunkte zur Einordnung des Grades der Immunsuppression und empfohlene zeitliche Mindestabstände zwischen Therapie und Impfungen 4. Spezielle Impfungen	n.d. Verbreitungsorgan und Zusammensetzung der Expertengruppe geben dieser Mitteilung hohe Bedeutung.

					5. Impfen von Säuglingen nach *in-utero*-Exposition bei immunmodulatorischer Therapie der Mutter 6. Impfen von Kontaktpersonen 7. Hinweise zu Reiseimpfungen	
Webb et al., Health Technol Assess, 2019	RCT Sixteen-week versus standard eight-week prednisolone therapy for childhood nephrotic syndrome.	Two hundred and thirty-seven children presenting with a first episode of SSNS (age 1 – 15 years).	The control group (n = 118) received standard course (SC) prednisolone therapy: 60 mg/m2/day of prednisolone in weeks 1–4, 40 mg/m2 of prednisolone on alternate days in weeks 5–8 and matching placebo on alternate days in weeks 9–18 (total 2240 mg/m2). The intervention group (n = 119) received extended course (EC) prednisolone therapy: 60 mg/m2/day of prednisolone in weeks	The primary outcome measure was time to first relapse. The secondary outcome measures were relapse rate, incidence of FRNS and SDNS, other immunosuppressive therapy use, rates of serious adverse events (SAEs) and AEs and the incidence of behavioural change [using Achenbach Child Behaviour Checklist (ACBC)].	There was no significant difference in time to first relapse between the SC and EC groups (hazard ratio 0.87, 95% confidence interval 0.65 to 1.17; log-rank p = 0.3). There were also no differences in the incidence of FRNS (SC 50% vs. EC 53%; p = 0.7), SDNS (44% vs. 42%; p = 0.8) or requirement for other immunosuppressive therapy (56% vs. 54%; p = 0.8). The total prednisolone dose received following completion of study medication was 5475 mg vs. 6674 mg (p = 0.07). SAE rates were not significantly different (25% vs. 17%; p = 0.1) and neither were AEs, except poor behaviour (yes/no), which was less frequent with EC treatment. There were no differences in	1b

			1–4; started at 60 mg/m2 of prednisolone on alternate days in weeks 5–16, tapering by 10 mg/m2 every 2 weeks (total 3150 mg/m2).		ACBC scores. EC therapy was associated with a mean increase in generic health benefit [0.0162 additional quality-adjusted life-years (QALYs)] and cost savings (£4369 vs. £2696).	