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REVIEW ARTICLE

Efficacy and Safety of NSAIDs in Infants: A Comprehensive Review of the Literature of the Past 20 Years

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in infants, children, and adolescents worldwide; however, despite sufficient evidence of the beneficial effects of NSAIDs in children and adolescents, there is a lack of comprehensive data in infants. The present review summarizes the current knowledge on the safety and efficacy of various NSAIDs used in infants for which data are available, and includes ibuprofen, dexibuprofen, ketoprofen, flurbiprofen, naproxen, diclofenac, ketorolac, indomethacin, niflumic acid, meloxicam, celecoxib, parecoxib, rofecoxib, acetylsalicylic acid, and nimesulide. The efficacy of NSAIDs has been documented for a variety of conditions, such as fever and pain. NSAIDs are also the main pillars of anti-inflammatory treatment, such as in pediatric inflammatory rheumatic diseases. Limited data are available on the safety of most NSAIDs in infants. Adverse drug reactions may be renal, gastrointestinal, hematological, or immunologic. Since NSAIDs are among the most frequently used drugs in the pediatric population, safety and efficacy studies can be performed as part of normal clinical routine, even in young infants. Available data sources, such as (electronic) medical records, should be used for safety and efficacy analyses. On a larger scale, existing data sources, e.g. adverse drug reaction programs/networks, spontaneous national reporting systems, and electronic medical records should be assessed with child-specific methods in order to detect safety signals pertinent to certain pediatric age groups or disease entities. To improve the safety of NSAIDs in infants, treatment needs to be initiated with the lowest age-appropriate or weight-based dose. Duration of treatment and amount of drug used should be regularly evaluated and maximum dose limits and other recommendations by the manufacturer or expert committees should be followed. Treatment for non-chronic conditions such as fever and acute (postoperative) pain should be kept as short as possible. Patients with chronic conditions should be regularly monitored for possible adverse effects of NSAIDs.

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Key Points

This review summarizes the efficacy and safety of the non-steroidal anti-inflammatory drugs (NSAIDs) that are available to treat pain in infants (children < 2 years of age).

Most information is available for ibuprofen, ketoprofen, and ketorolac.

Most indications comprise fever and (peri- and) postoperative pain, for which these drugs have proven efficacy.

Safety concerns are bleeding risks and gastrointestinal or renal events.

We also summarize the use of NSAIDs for special indications, e.g. in the fields of pediatric inflammatory rheumatic diseases and pediatric cardiology.

1 Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in infants (children < 2 years of age), children, and adolescents worldwide [1, 2]. Ibuprofen is one of the most frequently administered NSAIDs in infants and children for relief of pain and fever [3–5]. In several European countries, high rates of NSAID use among children < 4 years of age have been observed [6]. There is a lack of comprehensive data on the use of NSAIDs in infants, despite sufficient evidence of the beneficial effects of NSAIDs in children and adolescents.

Reviews have been published on the use of NSAIDs in children with an overview on NSAID risks and benefits in children of different age groups and with a focus on postoperative pain [7, 8]. We previously assessed the safety and efficacy of ibuprofen in infants younger than 6 months of age and concluded that the present safety and efficacy data support its use in infants older than 3 months with a body weight of at least 5–6 kg [9].

Based on their chemical structure and properties, NSAIDs can be classified into the following categories: (1) propionic acid derivatives (ibuprofen, dexibuprofen, naproxen, ketoprofen, flurbiprofen); (2) heteroaryl acetic acid derivatives—(2a) acetic acid derivatives (diclofenac, ketorolac, tolmetin) and (2b) indole and indene acetic acid derivatives (indomethacin); (3) anthranilic acid derivatives/fenamates (mefenamic acid, niflumic acid); (4) enolic acid derivatives/oxicams (meloxicam); (5) salicylates (acetylsalicylic acid); (6) diarylheterocyclics/coxibs (celecoxib, rofecoxib, parecoxib); (7) alkanones; and (8) sulfoanilides (nimesulide) [10]. Only a fraction of these drugs is used in infants and children.

NSAIDs decrease prostaglandin synthesis by inhibiting cyclooxygenase (COX) activity. 'Classical' NSAIDs, such as propionic acid derivatives and acetic acid derivatives, inhibit both isoforms: COX-1 and COX-2. Specific drugs were developed to preferentially block COX-2, which are mainly coxibs, as well as meloxicam and nimesulide. While it is reported that the therapeutic anti-inflammatory effect of NSAIDs is mediated through COX-2 inhibition and that the renal, gastric, hematologic, and cardiovascular adverse effects are caused through COX-1 inhibition, this concept has been revised due to the overlap in function, making the biological activity and interrelation of both enzymatic isoforms far more complex [11, 12]. Prostaglandins synthesized by both enzymatic isoforms not only contribute to many physiological processes such as regulating vascular tone and platelet function, but also to pathological processes such as inflammation [12, 13].

The present review focuses on relevant studies, which were published after the year 2000, and summarizes the current knowledge on safety and efficacy of various NSAIDs in infants, although only a few studies were exclusively performed in infants and the majority of studies also included children older than 23 months [14]. The PubMed database was searched systematically for articles published in English from January 2000 until 22 May 2020 to identify clinical trials using NSAIDs in infants. The search strategy included at first the general search string '(("infant"[Mesh]) AND "anti-inflammatory agents, non-steroidal"[Mesh]) AND "treatment outcome"[Mesh]'. In order to conduct a more diligent search, all of the drugs described in this review were combined with the two search strings '*drug* AND efficacy AND (infant OR infants)' and '*drug* AND safety AND (infant OR infants)'. Additional literature was retrieved from the references of published studies and reviews. Studies were included if they contained original data on the pharmacokinetics (PK), efficacy, and safety of the abovementioned NSAIDs in infants. Original publications on the development of PK models using previously published data were also included.

Studies published before the year 2000 were included if they provided data pertinent to the results of studies discussed in this review. Studies on the use of NSAIDs in preterm infants for closure of a persistent ductus arteriosus were excluded from this review, as well as studies primarily conducted in older children and adolescents. Studies on the use of metamizole (dipyrone) in infants were excluded from this analysis because metamizole is not an NSAID, although still incorrectly classified as such.

2 Pharmacokinetics of Non-steroidal Anti-inflammatory Drugs (NSAIDs) in Infants

Currently used NSAIDs in infants and young children for which recent efficacy and/or safety data are available include ibuprofen, dexibuprofen, ketoprofen, flurbiprofen, naproxen, diclofenac, ketorolac, indomethacin, mefenamic acid, meloxicam, celecoxib, parecoxib, rofecoxib, acetylsalicylic acid, and nimesulide. These drugs are discussed in detail in the following paragraphs and an overview of the PK (including relevant drug-metabolizing enzymes) of currently used NSAIDs in infants and children is given in Table 1.

2.1 Ibuprofen

Ibuprofen is the most widely used NSAID in infants worldwide for relief of fever and pain. It exerts its therapeutic

effect when the inactive R(−) isomer is unidirectionally converted into the active S(+) isomer [15]. Ibuprofen undergoes rapid absorption, followed by a high plasma protein binding, with the R isomer having a higher protein binding affinity compared with the S isomer. It undergoes oxidative metabolism via cytochrome P450 (CYP) 2C9 and CYP2C8 in the liver and is mostly renally excreted [16]. Ibuprofen is administered orally in both tablet and suspension forms but can be administered intravenously and in suppository form. PK data have been previously summarized [11, 17–36], and since completing the current review, it is evident that PK data remain scarce for the infant population; therefore, studies that included infants combined with young children were included. In summary, most studies demonstrated similar PK data in patients with ages ranging from < 3 months to 15 years. For oral, rectal, and intravenous doses of 10 mg/kg ibuprofen, area under the curves (AUCs) were similar in all studies, with increases relative to dose. Similarly, maximum concentration (C_{max}) values were consistent for rectal and oral ibuprofen, relative to dose, and, as expected, C_{max} values were higher for intravenous administration. Time to reach C_{max} (T_{max}) values were similar for oral and rectal administration, and T_{max} was reached much faster for intravenous administration. Half-life ($t_{½}$) was similar for oral and intravenous administration and slightly longer for rectal administration, however the study populations were much younger (1–52 weeks of age), which may explain an increased half-life because of not yet mature clearance (CL). Similarly, CL was consistent across most studies, with a much higher CL observed in older children compared with infants and younger children. The large variation observed with volume of distribution (V_d) and CL between oral and intravenous administration was due to differences in age groups, as was demonstrated with an increase of V_d and CL with age due to differences in body size. Single dosing of 20 mg/kg rectal ibuprofen resulted in similar concentrations in infants (1 week–12 months) and adults, when administered based on weight. No dose adjustments are therefore needed in infants aged 1 week to 12 months. When CL-informed dosing was evaluated in all ages (neonates to adults), it was found that maturation occurred rapidly, with 90 and 98% of adult values reached at 1 month of life in term neonates and at 3 months of life, respectively. This supports the findings demonstrating that young children have similar PK data as adults. However, higher interindividual variability in drug metabolism of infants has been reported compared with older children [34]. Moreover, children with lower body weight had increased C_{max} values and higher CL [35]. Overall, ibuprofen administered at 10 mg/kg for both oral and intravenous routes and 20 mg/kg for the rectal route is well tolerated in infants and children when based on weight. However, oral administration is preferred over rectal administration due to the risk of erratic absorption, for several reasons including expelled suppositories, and intravenous administration is also well tolerated, if required. PK data for ibuprofen dosing in infants can be reviewed in our previously published work [12].

Despite advances in physiology based PK (PBPK) and population PK (pop-PK) modeling and simulation, only two groups have focused on ibuprofen in the pediatric setting. A PBPK model developed for the prediction of ibuprofen concentrations was able to accurately predict AUC, C_{max}, and T_{max} [37]. Moreover, it was shown that predicted ibuprofen AUC and C_{max} were higher in CYP2C9 poor metabolizers, suggesting that lower doses should be used in these poor metabolizers. Another study, using PBPK modeling, was able to predict ibuprofen concentrations [17] and was used to validate physiological parameters in a generic pediatric brain PBPK model to predict AUC plasma and cerebrospinal fluid (CSF) concentrations of drugs that undergo passive transfer. This model also achieved observed and predicted ibuprofen AUC to be very similar (ratios of 0.94–1.05) [18]. This demonstrates a promising shift in approaches whereby pharmacometric modeling and simulation can be used to further enhance our understanding by using existing information to accurately simulate and identify important clinical outcomes.

2.2 Dexibuprofen

Dexibuprofen is the pharmacologically active dextrorotatory enantiomer of racemic ibuprofen. From studies in adults investigating the stereoselective properties of ibuprofen, it was suggested that dexibuprofen might possess a stronger pharmacological activity than racemic ibuprofen when administered at an equal dose while exerting a better safety profile [19–21]. Similarly, to ibuprofen, dexibuprofen is rapidly absorbed, is metabolized via CYP2C9 and CYP2C8, and undergoes conjugation to form glucuronides prior to being renally excreted [19]. To date, no pediatric PK data are available in the literature, therefore we do not recommend prescribing this drug to infants until further data are available.

2.3 Ketoprofen

Ketoprofen is widely used for the treatment of inflammatory and musculoskeletal conditions, pain, and fever in children [22]. It is well absorbed from the gastrointestinal tract [23], and the drug is highly bound to plasma proteins such as albumin, conjugated via glucuronic acid in the liver and largely excreted by the kidneys [24]. The PK of ketoprofen have been studied by Kokki et al. and can be found in Table 1.

Table 1 Pharmacokinetics of ibuprofen, ketoprofen, flurbiprofen, naproxen, diclofenac, and parecoxib used in infants and children. Overview of studies published after 2000 [17, 25–28, 33, 34, 38, 39, 41, 42, 46, 51, 52, 63, 64, 67, 71, 72, 273, 274, 277–280, 317, 318]

	No. of patients	Age (range)	Body weight [kg]	Dose [mg/kg]	Compartment absorption elimination	PK parameters								References
						F [%]	AUC [mg·h/L]	C_{max} [mg/L]	T_{max} [h]	$t_{½}$ [h]	V_d/F [L/kg]	CL/F [L/h]	Metabolism	
Ibuprofen	9	4.2 ± 1.9 weeks (1–7 weeks)	4.4 ± 0.6	19.0 ± 1.6 RECT	NA	NA	299 ± 69	49.2 ± 20.7	1.9 ± 1.2 h	4.6 ± 5.1	NA	NA	CYP2C8 CYP2C9 UGT2B7	[278]
	8	16.1 ± 6.9 weeks (8–25 weeks)	6.7 ± 1.4	19.2 ± 1.1 RECT	NA	NA	248 ± 153	75.6 ± 44.6	1.6 ± 0.7 h	1.9 ± 0.5	NA	NA		
	7	41.4 ± 7.8 weeks (26–52 weeks)	9.4 ± 1.7	19.8 ± 1.1 RECT	NA	NA	339 ± 136	87.9 ± 36.6	1.6 ± 0.3 h	2.1 ± 0.7	NA	NA		
	7	34 ± 6.6 weeks	70.1 ± 13.3	19.5 ± 1.5 RECT	NA	NA	334 ± 123	63.8 ± 20.4	3.3 ± 0.8	2.2 ± 0.4	NA	NA		
	18	6.2 years (0.6–15.3 years)	23 (7.6–49.3)	5–10 (single doses) 60 125 250 mg RECT	NA	NA	57 122 90	23.3	1.3 h (0.3–2.1)	NA	NA	1.90 0.97 1.35		[279]
	28	58.2 ± 51.3 months (5.0–180.5 months)	20.1 (7.2–64.0)	9.5 ± 1.6 (3.4–11.4) PO	1-compartment First order	NA	NA	NA	NA	NA	0.418 (36)	1.72 (19)		[17]
	11	6–18 months	9.5 ± 1.6	7.6 ± 0.3 PO	NA	NA	78.1	24.4 ± 6.6	2–4.1	1.6 ± 0.4	0.2 ± 0.09	1.83 ± 0.17		[277]
	44	3 months–12 years	NA	5 PO	1-compartment	NA	71.12 ± 5.94	19.03 ± 1.37	1.60 ± 0.13	1.65 ± 0.22	0.182 ± 0.017	1.48 ± 0.15		[273]
	49		NA	10 PO		NA	115.76 ± 5.55	34.35 ± 2.18	1.54 ± 0.12	1.48 ± 0.11	0.217 ± 0.026	1.65 ± 0.12		
	49	2.5 years (3 months–10.4 years)	NA	8 PO	NA	NA	102.6 (35.2)	35.8 ± 16.7	0.7 ± 0.5	1.6 ± 0.7	NA	NA		[274]
	1	< 6 months	30.2 (19.5)	10 IV	NA	NA	51.18	49.83	0.167	1.8	1.05	0.62		[317]
	5	6 months to < 2 years		10 IV	NA	NA	71.15 (34.67, 95.20)	59.24 (38.37, 92.02)	0.234 (0.167, 0.500)	1.78 (1.06, 2.35)	2.80 (2.04–3.57)	1.17 (0.84–1.96)		
	12	2 to < 6 years (min, max)		10 IV	NA	NA	79.19 (19.00, 109.50)	64.18 (15.91, 96.31)	0.309 (0.167, 0.767)	1.48 (0.79, 2.87)	3.7 (1.85, 5.41)	1.97 (1.09, 4.74)		
	25	6 to < 16 years		10 IV	NA	NA	80.67 (40.00, 161.30)	61.89 (31.03, 93.32)	0.212 (0.167, 667)	1.55 (0.79, 2.54)	10.3 (2.63, 23.9)	4.88 (1, 12.5)		

Table 1 (continued)

	No. of patients	Age (range)	Body weight [kg]	Dose [mg/kg]	Compartment absorption elimination	PK parameters								References
						F [%]	AUC [mg·h/L]	C_{max} [mg/L]	T_{max} [h]	$t_{½}$ [h]	V_d/F [L/kg]	CL/*F* [L/h]	Metabolism	
Ketoprofen	10	9–86 months	18.9 (8–31)	1 PO	NA	NA	4.9	7.4	NA	NA	NA	NA	CYP3A4 CYP2C9 UCT2B7	[29]
	10	> 2.5–7 years	19 (12–27)	0.5 PO	NA	NA	4.9 (0.9)	3.1 (0.6)	0.5	1.9 (0.6)	NA	NA		[27]
	10	8–20 months	10 (8.5–11.5)		NA	NA	5.6 (1.1)	3.0 (0.7)	0.5	2.0 (0.7)	NA	NA		
	6 4	16–69 months 54-66 months	12–17 18–23	0.74–1.39 12.5 mg 25 mg PO	NA	100% compared with IM	11.4 (1.9)	5.4 (1.6)	0.5	1.3 (0.3)	NA	0.09 (0.02)		[28]
	10	10–94 months	10–34	1 IM	NA	NA	11.6 (2.0)	5.7 (1.2)	0.5	1.6 (0.4)	NA	0.09 (0.02)		
	10	33–79 months	16–24	25 mg RECT	NA	NA	11.2 (1.4)	5.3 (1.3)	< 1	1.8 (0.6)	0.12 (0.03)	0.09 (0.01)		[25]
	18	7–93 months	7–36	1 2 min IV	NA	NA	15.4 (4.4)	15.5 (3.5)	NA	1.5 (0.5)	0.07 (0.01)	0.07 (0.02)		
	18	7–193 months	22 (9–47)	1 loading dose and 4 mg/kg/24 h IV	NA	NA	47.6 (1.11) [31.1–65.4]	2.0 (0.5)	NA	1.3 (0.22) (0.8–1.7)	0.16 (0.03)	0.09 (0.02)		[26]
Flurbiprofen	37	4.7 (0.25–13) years	19 (7–76)	1 PO	3-compartment First order	81 (71–90)	NA	9	0.5	NA	8.11	0.96	CYP2C9	[33]
	27	5.6 (0.25–13) years	20 (8–55)	0.65 10 mins IV		NA	NA	10	NA	1.4 min	10	1.2		
	4	7.5 (6-8) years	18.6 ± 3.6	50 mg PO R 48 h later	NA	NA	72.4 (11.6) 77.3 (13.1)	20.0 (2.3) 15.8 (1.6)	1 (0.3) 0.7 (0.1)	2.71 (0.27) 3.22 (0.19)	2.82 (0.35) 3.25 (0.56)	0.026 (0.001) 0.025 (0.002)		[34]
	4	12 years	33.9 ± 1.7	75 mg PO R 48 h later	NA	NA	72.9 (12.8) 57.7 (8.5)	15.5 (2.4) 11.6 (1.8)	1.5 (0.4) 1.0 (0.2)	3.07 (0.16) 3.15 (0.24)	4.87 (0.64) 6.28 (0.92)	0.033 (0.005) 0.043 (0.009)		
Naproxen	53	0.25–12 years	5–69	10 PO	2-compartment First order	NA	NA	64	2.3	NA	12.5	0.62	UGT2B7 CYP2C9 CYP1A2	[39]

Table 1 (continued)

	No. of patients	Age (range)	Body weight [kg]	Dose [mg/kg]	Compartment absorption elimination	PK parameters								References
						F [%]	AUC [mg·h/L]	C_{max} [mg/L]	T_{max} [h]	$t_{½}$ [h]	V_d/F [L/kg]	CL/*F* [L/h]	Metabolism	
Meloxicam	18	8.4 ± 3.7 years	27.19 ± 11.80	0.25	NA	NA	28% lower than adults (no value available)	34% lower than adults (no value available)	NA	13	NA	NA	CYP2C9 (major) CYP3A4 (minor)	[63]
	7	3.4 (2–6) years	15.6 (12.5–22)	0.25 PO	NA	NA	24.8	1.2	2	13.4	2.87	2.49		[64]
	11	10.8 (7–14) years	34.0 (19–50.3)		NA	NA	34.4	1.81	2	12.7	4.07	3.59		
	16	35.5 (22–45) years	NA		NA	NA	30.0	28	2	19	14.0	8.1		
Diclofenac	26	4.5 ± 1.5 years	20.5 ± 4.1 (mean, SD)	Initial dose 2 RECT followed by 1 RECT tid	1-compartment First order First order	Suppository compared with enteric-coated tablet: 1.26	NA	NA	0.83	0.613	22.8 [l.70] (L/h/70 kg)	44.82 (L/h/70 kg)	CYP3A4 CYP2C8 CYP2C9 UCT2B7	[41]
	70	3 (1–12) years	17 (9.4–37)	1 PO	Single disposition compartment Duel First order	NA	3368 (879) nmol l-1 h	NA	NA	1.06	4.84 (L/h/70 kg)	53.98 (L/h/70 kg)		[42]
	10	5 (4–6) years	20 (18–22)	0.5 5 or 15 min IV	NA	NA	NA	4.75	NA	1.28	0.90	0.46		[46]
	244	8.6 (4.0–16.0) years	35.7 (15–93)	0.1/0.5/2.0 PO	1-compartment First order First order	NA	NA	NA	NA	NA	23.4 (L/h/70 kg)	53.5 (L/h/70 kg)		[38]

Table 1 (continued)

	No. of patients	Age (range)	Body weight [kg]	Dose [mg/kg]	Compartment absorption elimination	PK parameters								References
						F [%]	AUC [mg·h/L]	C_{max} [mg/L]	T_{max} [h]	$t_{½}$ [h]	V_d/F [L/kg]	CL/*F* [L/h]	Metabolism	
Ketolerac	8	0.37 (0.30–0.41) years	5.98 (5.58–6.66)	0.5 or 1.0 3.865 (3.27–4.36) 10 mins IV	S-ketorolac: 3-compartment R-ketorolac: 2-compartment	NA	NA	NA	NA	NA	4.03 (11) 4.43 (11)	3.97 (6) 1.45 (6)	CYP2C8 CYP2C9 UCT2B7	[51]
	25	0.91 (0.82–1.09) years	9.4 (8.5–10.6)	0.5 or 1.0 5.83 (3.59–6.92) 10 mins IV		NA	NA	NA	NA	NA				
	20	29 (23.8–38.3) years	70.5 (59.8–76.8)	0.5 23.91 (19.41–27.42) 30 mins IV		NA	NA	NA	NA	NA				
	11	26 (23.5–33.5)	75 (72–79)	20 13.56 30 mins IV		NA	NA	NA	NA	NA				
	16	32 (29.5–34.3)	62 (58.6–67.3)	30 20.345 30 mins IV		NA	NA	NA	NA	NA				
	8	2.5–6	5.4–7.6	1 or 0.5 IV	NA	NA	S-ketorolac 183 ± 167 75 ± 26 R-ketorolac 711 ± 612 375 ± 224	S-ketorolac 2.0 ± 11 1.1 ± 0.6 R-ketorolac 4.1 ± 1.8 2.5 ± 1.4	NA	S-ketorolac 67 min R-ketorolac 197 min	S-ketorolac 0.45 ± 0.33 R-ketorolac 0.27 ± 0.17	S-ketorolac 5.1 ± 4.3 R-ketorolac 0.95 ± 0.54		[52]

Table 1 (continued)

	No. of patients	Age (range)	Body weight [kg]	Dose [mg/kg]	Compartment absorption elimination	PK parameters								References
						F [%]	AUC [mg·h/L]	C_{max} [mg/L]	T_{max} [h]	$t_{½}$ [h]	V_d/F [L/kg]	CL/*F* [L/h]	Metabolism	
Parecoxib	18	9.2 (4.8–15.1)	39.1 (15–83.8)	0.25 IV	3-compartment parent (parecoxib) and one-compartment metabolite (valdecoxib) with first-order elimination	NA	NA	NA	0.5	NA	4.21 (metabolite: valdecoxib 51.0)	19.1 (metabolite: valdecoxib 9.53)	CYP3A4 CYP2C9 UGT2B7	[72]
	18	9.76 (4.5–14.1)	41.9 (19.7–63.4)	1										
	23	9.06 (4.1–14.8)	37.6 (15–54.2)	2 IV										
	38	6.9 (1.1–12.7)	29.6 (9.7–84.2)	1 IV	3-compartment First order First order	NA	NA	NA	NA	4.4 min	5.1 (metabolite: valdecoxib 62)	21 (metabolite: valdecoxib 8.6)		[71]
Rofecoxib	8	8.9 (3–14) years	NA	1 PO (50 mg max)	NA	NA		582	4	14.8	NA	1.34		[318]
Celocoxib	11	39.5 ± 14.5	NA	250 mg/m^2	NA	NA	7709 ± 3176	1234 ± 528	3	3.7 ± 1.1	7.9 ± 7.8	1.4 ± 1.0		[67]

AUC area under curve, C_{max} maximum concentration, *CL/F* apparent clearance, *CYP* cytochrome P450, *F* bioavailability, *IM* intramuscular, *IV* intravenous, *max* maximum, *min* minimum, *NA* not available, *PO* oral, *PK* pharmacokinetics, *RECT* rectal, *SD* standard deviation, T_{max} time to reach C_{max}, $t_{½}$ half-life, *tid* three times daily, *UGT* uridine 5′-diphosphate-glucuronosyltransferase, V_d/F apparent volume of distribution

Different ketoprofen formulations such as oral tablets, oral syrup, rectal suppositories, and intravenous and intramuscular solutions produce similar PK in infants, children, and adults. One study observed that the same milligram/kilogram body weight dose of rectal and intravenous formulations of ketoprofen may be used in both children and adults [25]. Similar doses of continuous intravenous infusions in children aged 7 months to 16 years have also been recommended because of similar PK between a loading dose and continuous intravenous infusion of ketoprofen in adults compared with small children [26]. Ketoprofen syrup had similar PK in infants aged 6–24 months compared with children aged 2–7 years [27]. Moreover, PK were similar in children aged 10–69 months when ketoprofen was administered orally or intramuscularly [28]. Ketoprofen can be measured in the CSF shortly after administration, however several studies have reported that distribution of ketoprofen in the CNS is limited [29, 30].

Overall, administration of oral, rectal, and intravenous formulations of ketoprofen has been shown to have similar PK and are well tolerated in infants and children for the treatment of fever and pain. AUC values were similar for oral administration (4.9–5.6 mg·h/L) at doses ranging from 0.5 to 1 mg/kg across several studies, and increased AUC values were observed for higher doses as well as for intravenous and intramuscular administration (11.6–15.4 mg·h/L). C_{max} values were similar across all routes of administration, with one study showing a lower C_{max} of 2 mg/L and two studies showing higher C_{max} values of 7.4 and 15.5 mg/L, respectively, due to differences in doses. T_{max} and $t_{½}$ were also consistent between all studies across various routes of administration, i.e. 0.5 h and 1.3–2 h, respectively. V_d ranged from 0.12 to 0.16 L/kg, with one study showing 0.07 L/kg. CL was observed to be the same across all studies and administrations, i.e. 0.07–0.09 L/h. However, PK data in infants younger than 6 months and neonates are sparse and therefore caution is required in these populations.

2.4 Flurbiprofen

Similarly, to ketoprofen, flurbiprofen is highly bound to plasma albumin, metabolized by CYP2C9, and conjugated via glucuronic acid in the liver and largely renally excreted [31, 32]. Flurbiprofen has not been sufficiently studied in infants or young children. Two studies have reported PK data in this population. One study used either 1 mg/kg oral or 0.65 mg/kg intravenous flurbiprofen in infants and children 0.25–13 years of age, showing similar PK data [33]. It was found that flurbiprofen concentrations in the CSF were sevenfold higher than unbound plasma concentrations, suggesting potent CNS analgesic and antipyretic action. Relative to dose, another study demonstrated that similar flurbiprofen PK were observed between 50 mg oral syrup and 75 mg suppositories (48 h later). Overall, the PK were similar to adults [34]. Weight alone was a useful covariate for PK prediction in children aged 3 months–13 years. This study was also used to validate the physiological parameters in a generic pediatric brain PBPK model to predict CSF concentrations of drugs that undergo passive transfer. The model achieved, observed, and predicted flurbiprofen AUC ratios of 1 [18], further supporting the use of pharmacometric modeling and simulation in this area [38]. It should also be noted that study cohorts typically include fewer infants than children and therefore the results may be less accurate for infants. Studies in adults reported bleeding complications when used concomitantly with anticoagulants [35]. Currently, we therefore discourage the use of flurbiprofen in both infants and children until more safety and efficacy data become available [18].

2.5 Naproxen

Naproxen is used for the treatment of pain and juvenile rheumatoid arthritis. The drug is rapidly absorbed in the upper gastrointestinal tract and is highly bound to plasma albumin. Naproxen is metabolized by CYP2C9 and also conjugated via glucuronic acid in the liver, and is largely renally excreted [31, 36]. PK data in the pediatric population are nearly non-existent, with only one study currently describing PK data (Table 1). This study also revealed that body weight is the most relevant covariate to determine dosing with naproxen in infants aged 3 months and older [39]. This study was also used to validate the physiological parameters in a pediatric plasma and CSF PBPK model, and the model achieved observed and predicted AUC ratios of 1 [35], again showing the sophistication of pharmacometric modeling and simulation.

2.6 Diclofenac

Diclofenac is an acetic acid derivative with pronounced antirheumatic, anti-inflammatory, analgesic, and antipyretic effects. Diclofenac is well-absorbed in the gastrointestinal tract, highly bound to albumin in the plasma, and diffuses in and out of the synovial fluid. This drug is largely metabolized by CYP2C9, followed by glucuronidation, and eliminated by urinary and biliary excretion [31, 40]. When compared with adults, diclofenac shows age-related changes in CL being highest in infants aged 1–3 years (1 L/h/kg) compared with older children (4–7 years, 0.88 L/h/kg; 8–12 years, 0.79 L/h/kg) and adolescents (12–16 years, 0.70 L/h/kg) [41]. One study developed a pop-PK model, based on adult and pediatric data, to determine the recommended dose for a new diclofenac suspension (50 mg/5 mL) for acute

pain in pediatric patients. Based on their simulations, the authors achieved, observed, and predicted AUC ratios of 1.0, 1.08, and 1.18 for children aged 1–3, 4–6, and 7–12 years, respectively [42]. Moreover, the highest plasma concentration variability occurred during the absorption phase and allometric size models predicted changes in CL and V_d with age [42]. A PK meta-analysis in children and adults revealed that single doses of 0.3 mg/kg intravenous, 0.5 mg/kg rectal, and 1 mg/kg oral diclofenac provide adequate analgesia in infants and children aged 1–12 years and was equivalent to 50 mg doses in adults [43]. Similarly, diclofenac 1 mg/kg with acetaminophen 15 mg/kg achieve equivalent analgesia as acetaminophen 30 mg/kg (combination therapy may use lower doses of both drugs) [38, 42, 43]. Diclofenac was more rapidly absorbed and showed a higher bioavailability and earlier maximum concentration after rectal compared with oral administration [41]. It was also shown that diclofenac penetrates the blood–brain barrier (BBB) rapidly and sufficient CSF concentrations for COX inhibition (range 0.5–4.7 µg/L) are sustained for 4 h after intravenous dosing (1 mg/kg) in 31 children aged 3 months–12 years [44]. However, no correlation between plasma and CSF diclofenac concentrations could be established. Median diclofenac plasma concentration at the time of pain return was 104 (range 70–272) µg/L. Therefore, a higher initial dose is required, or a repeated dose should be administered 3–4 h after the initial dose. Another study demonstrated 50–70% less opioid analgesic use (compared with the control group) when the dose was changed to 1.5 mg/kg intravenously followed by 2 mg/kg rectally twice daily [45]. Overall, oral, rectal, and intravenous diclofenac are well tolerated, and while the use of intramuscular diclofenac is no longer recommended due to pain and risks of infection/inflammation at the injection site, the rectal route allows drug administration to vomiting children or patients without any oral intake. PK data of oral and rectal diclofenac in children are presented in Table 1 [38, 41–43, 46, 47].

2.7 Ketorolac

Ketorolac is a chiral NSAID that is used for analgesia [48] and the S-enantiomer is responsible for its pharmacological activity [49]. The drug is administered as the water soluble tromethamine salt and is available in tablets or as an intravenous injection. Ketorolac undergoes rapid absorption, with a C_{max} reached between 20 and 60 min. Its oral bioavailability is estimated to range from 80 to 100%. In adults, the drug is highly protein bound (> 99%) and has a V_d (0.1–0.3 L/kg) comparable with those of other NSAIDs. The $t_{½}$ is between 4 and 6 h and is moderate in comparison with other NSAIDs. Ketorolac is primarily metabolized by CYP2C9, followed by glucuronidation and renal excretion. Ketorolac is recovered in the urine mainly in its metabolite form. When intravenous ketorolac PK were studied in children aged 2 months to 16 years, it was found that from infancy CL decreased with age [50]. This study concluded that a dose of 0.5 mg/kg every 6 h was sufficient to keep trough concentrations above 0.37 mg/L, which produced sufficient analgesia postoperatively. This dosing regimen is in agreement with current practice. Recently, it was shown that S-enantiomers produce different concentrations between infants and adults, and therefore requires further research as this difference in S-enantiomer concentration may have an important effect on analgesia since the S-enantiomer is solely responsible for the analgesic effect [51]. When clinical and patient covariates were assessed for effects on PK, it was found that no covariates were statistically significant when accounted for body size [52]. Ketorolac does not readily penetrate CSF in children [33]. PK data can be found in Table 1.

2.8 Indomethacin

Indomethacin is currently used in children for the treatment of inflammation of pain from rheumatic diseases or orthopedic surgery, or pericardial effusion, and for pharmacological closure of a persistent ductus arteriosus, which was however not covered in this review (see inclusion/exclusion criteria) [53, 54]. Indomethacin is metabolized by CYP2C9 in the liver [31]. Pediatric data are summarized in Table 1.

No PK data are currently available for indomethacin in pediatrics. One study reported that 1% of indomethacin entered the CSF, as, on average, 1.9 ng/mL and 2200 ng/mL was found in the CSF and plasma, respectively, when 31 infants and children aged 4–11 months undergoing surgery received 0.35 mg/kg intravenous indomethacin. This small percentage entering the BBB may be due to the high protein binding. Nonetheless, indomethacin does enter the BBB and may also cause adverse central nervous effects, such as agitation, dizziness, vertigo or headache [53].

2.9 Fenamates

The fenamates/fenamic acids mefenamic acid, tolfenamic acid, and niflumic acid have traditionally been used for relief of pain and fever in children in several European countries, and mefenamic acid is still quite popular in Switzerland. Some evidence on their pharmacology in children was generated in the 1970s–1990s but more recent data are lacking [55–62].

2.10 Oxicams

Most of the oxicams are well absorbed into the gastrointestinal tract, highly bound to plasma proteins, metabolized by CYP2C9, and renally excreted. When meloxicam PK

were assessed in juvenile rheumatoid arthritis, the C_{max} and AUC were observed to be 34 and 28% lower in children aged 2–6 years compared with older children, respectively; however, $t_{½}$ was similar in all patients [63]. Another study investigated a meloxicam suspension (0.25 mg/kg with 15 mg maximum dose) in children with juvenile rheumatoid arthritis and observed similar PK data as in adults, and therefore recommended doses normalized to body weight [64]. No recent studies on piroxicam PK data in children were found, whereas studies prior to the year 2000 are available [65]. No PK data were found for lornoxicam use in children and therefore we do not recommend using this drug in infants [63].

2.11 Coxibs

Coxibs, such as celecoxib, parecoxib, valdecoxib, rofecoxib, and etoricoxib, are specific inhibitors of COX-2. These COX-2 inhibitors are primarily metabolized by CYP2C9 and, to a lesser extent, by CYP3A4. The majority of the coxibs are mostly prescribed for the treatment of pain in juvenile rheumatoid arthritis in children [66]. When celecoxib PK were evaluated in children, they were found to be vastly different to adult data. It was found that CL was increased twofold and $t_{½}$ was half of that seen in adults [67, 68]. This difference in PK data may explain the difference in pain relief; it was reported that adults endured longer pain relief compared with children [69], which may be a result of the increased CL and shortened $t_{½}$ in children. Other than the PK data reported by the rofecoxib manufacturer, very few studies have assessed rofecoxib PK data in the pediatric population. The manufacturer reported that apparent CL for an oral dose of 0.6 mg/kg (maximum 25 mg) rofecoxib in children aged 2–11 years and 25 mg in children aged 12–17 years achieved a similar AUC to that of healthy adults and higher than that of adults with rheumatoid arthritis [70]. This company also reported that apparent oral CL increased with age and body weight. Another study reported that similar PK data were obtained in children aged 3–14 years as in adults. No PK data were available for infants. Parecoxib is not currently used in children, however due to acceptable safety profiles in adults, parecoxib PK have been evaluated in children for the treatment of postoperative pain [71]. Parecoxib is only available intravenously and acts as a prodrug and is rapidly hydroxylated via CYP3A4 and CYP2C9 to the active metabolite valdecoxib [71, 72]. Therefore, the PK are only reported for valdecoxib, with two studies that have reported nearly identical PK data (Table 1). The first study demonstrated that parecoxib 0.9 mg/kg in a 2-year-old, 0.75 mg/kg in a 7-year-old, and 0.65 mg/kg in a 12-year-old child achieved the equivalence of a 40 mg dose in an average adult. This study also concluded that doses do not need to exceed 1 mg/kg, as no additional analgesia is achieved [72]. The second study generated PK data that were used to develop a pop-PK model to investigate pediatric dose prediction and duration of action. Intravenous doses of 1 mg/kg with a maximum of 40 mg in children aged 2–12.7 years simulated similar AUCs to that of adults who were administered 40 mg intravenous parecoxib. A much faster $t_{½}$ was predicted in children compared with adults, however when the model predicted $t_{½}$ in adults, the $t_{½}$ was consistent with the literature, demonstrating a high-quality pop-PK model. This study also found that elimination CL and V_d increased with age. Etoricoxib is not currently approved for children, however in cases where it is used, it is recommended that it should not be used in children weighing < 40 kg and for not more than 5 days [73].

2.12 Salicylates

Salicylates, like salicylic acid and acetylsalicylic acid, are not widely used in infants and young children for analgesia and antipyresis, mainly because of concerns related to the possible development of Reye syndrome. However, acetylsalicylic acid is widely used as an anti-aggregant, for example after some cardiac surgeries and in the context of Kawasaki syndrome and pediatric inflammatory multisystem syndrome (PIMS). Thus, there need to be other triggers (e.g. viral infection) for Reye syndrome in addition to treatment with salicylates, and hence no increased incidence of Reye syndrome was noted when acetylsalicylic acid was used in patients with Kawasaki disease. PK evidence in children was generated in the 1970s [74].

2.13 Sulfoanilides

Nimesulide is a preferential COX-2 inhibitor with potent analgesic, anti-inflammatory, and antipyretic activities. Some evidence on its pharmacology in children was generated in the 1990s, but more recent data are lacking [75–79].

3 Efficacy of NSAIDs

NSAIDs have proven efficacy in several conditions in infancy. Usual dose recommendations of NSAIDs for the indications of fever and pain are summarized in Table 2.

3.1 Fever

Fever is probably the most frequent symptom prompting the use of NSAIDs in infants. The indication for antipyretic use in children is to improve the child's comfort rather than focusing on the decrease in body temperature or even reaching normothermia [80]. Acetaminophen and NSAIDs are the

most commonly administered drugs in infants and children with fever.

A recent Cochrane review analyzed 30 studies with a total of 4256 children aged 6 months–7 years to assess the efficacy of prophylactic antiepileptics and antipyretics regarding the prevention of recurrent febrile seizures [81]. Two studies were included that studied prophylactic ibuprofen and diclofenac, respectively, including 461 infants and children aged 4 months–4 years [82, 83]. Offringa et al. could not find a benefit of any of these prophylactic treatments and discouraged the use of prophylactic NSAIDs [81]. Another study in infants aged 6–24 months ($n = 165$) with fever also demonstrated that ketoprofen syrup is as effective and well tolerated as acetaminophen and ibuprofen [84] (see Table 3).

3.2 Acute Pain

Besides non-pharmacological measures, analgesics such as acetaminophen or NSAIDs are the first-line therapy for acute pain. Despite the popularity of opioids in the treatment of acute pain in the pediatric emergency department, NSAIDs should still play a relevant role in treating acute pediatric pain [85]. Ibuprofen, naproxen, diclofenac, and ketorolac are used for mild to moderate pain in pediatric emergency departments, although, in most countries, not all of these medications have marketing authorization for infants [86, 87].

3.3 Postoperative Pain

A considerable amount of knowledge on the safety of NSAIDs for postoperative pain has been generated in recent years. NSAIDs are regularly part of postoperative analgesic regimens [8, 88, 89]. Kokki provided a comprehensive review on postoperative pain management in children, including dose recommendations for ibuprofen, ketoprofen, flurbiprofen, diclofenac, and ketorolac [8] (see Table 2). He emphasized the need for more research in children and infants, especially in infants younger than 6 years. However, he concluded that in infants aged 6 months or older, ketoprofen doses every 4–8 h, up to a maximum of 5 mg/kg over a 24-h period for 2–3 days, provide sufficient analgesia after adenoidectomy and tonsillectomy, with more rescue medication required for the latter [22].

Perioperative NSAID administration reduces the need for opioid analgesics. This opioid-sparing effect has been proven in several clinical trials as well as in children, and has been proven by meta-analyses [90–92]. Studied NSAIDs in children include ibuprofen, ketoprofen, naproxen, diclofenac, ketorolac, indomethacin, celecoxib, and rofecoxib. Most benefit was reported when multiple doses of NSAIDs were administered. NSAID administration also decreased postoperative nausea and vomiting, which is attributed to the opioid-sparing effect [91].

Several NSAIDs are available as a solution for injection enabling intravenous dosing, which is a relevant advantage for postoperative analgesic therapy. Although some manufacturers still provide dosing recommendations for intramuscular dosing, intravenous dosing should favor intramuscular dosing because intramuscular dosing is painful and may lead to erratic absorption or site infection, while intravenous dosing allows a complete and rapid absorption as well as a quick onset of action. Furthermore, administration of intramuscular NSAIDs can rarely lead to the so-called Nicolau syndrome, a severe, potentially fatal reaction [93].

In a study in 52 infants and children undergoing correction of craniosynostosis, intravenous NSAID administration (ketorolac) compared with oral administration (ibuprofen) led to significantly less postoperative nausea (odds ratio [OR] 14.0, 95% confidence interval [CI] 1.40–71.69; $p = 0.010$) and vomiting (OR 3.61, 95% CI 1.11–1.76; $p = 0.033$) [94]. Both drugs had been combined with either intravenous or oral acetaminophen, while a non-narcotic postoperative analgesic regimen was followed.

A well-studied condition in infants and children is the management of pain after tonsillectomy, for which several NSAIDs such as ibuprofen, ketoprofen, diclofenac, ketorolac and celecoxib have shown to be effective [95, 96]. Kelly et al. prospectively investigated respiratory parameters during sleep after tonsillectomy in 91 children (mean age ~ 5 years) receiving either morphine/acetaminophen or ibuprofen/acetaminophen [97]. The children who were receiving ibuprofen showed less desaturation events during sleep postoperatively compared with the morphine group, which was concluded as improvement compared with presurgery. The combination ibuprofen/acetaminophen was effective and there was no increased tonsillar bleeding, while morphine exerted an increased risk for respiratory events [97]. In the study by Murto et al. assessing pain after adenotonsillectomy, children receiving celecoxib had a significant reduction in pain scores during postoperative days 0–1 and a lower acetaminophen consumption compared with placebo [69].

NSAIDs also contribute to postoperative pain management in fast-track pediatric cardiac surgery programs, as was proven for ibuprofen, diclofenac, and ketorolac [98–100].

In summary, NSAIDs play a relevant role in postoperative pain management in children and infants. When combined with acetaminophen, even non-opioid analgesic regimens are possible. NSAIDs reduce postoperative opioid requirements, leading to less postoperative nausea and vomiting rates, which makes them especially suitable for pain management after day-case surgery.

Table 2 Recommended doses of different NSAIDs for pain and fever [8, 9, 41–43, 86, 87, 213]

Drug	Route of administration	Age and/or weight	Single dose	Frequency per day	Maximum single dose (mg)	Maximum daily dose (mg or mg/kg)	References
Ibuprofen	IV/PO/RECT	General recommendation	7.5–10 mg/kg	3–4	800	30–40 mg/kg, max. 2400 mg	[8]
	IV	6 months–12 years	10 mg/kg	3–4	400	1200 mg	[213]
		12–17 years	10 mg/kg		600		
	PO	3 months–12 years	5–10 mg/kg	3–4	50 to 60–75	180 mg	[86, 87, 213]
		1–4 years	7.5–10 mg/kg		75–125	375–500 mg	
		4–7 years			150	450 mg	
		7–10 years			200	600 mg	
		10–12 years			300	1200 mg	
		> 12 years			400	1200–2400 mg	
		< 60 kg	6–10 mg/kg		600	2400 mg	
		≥ 60 kg	400–800 mg		800		
	RECT	> 3 months and > 6 kg	7.5–10 mg/kg	3–4	60–75	2400 mg	[9]
		> 6 months	7.5–10 mg/kg		600		
Flurbiprofen	IV/RECT/PO	>3 months	1	2–3		5 mg/kg	[8]
Ketoprofen	IV	≥3 months	0.5 to 1–2 mg/kg (1 mg/kg loading dose followed by 4 mg/kg/24 h for up to 72 h)	3–6		5 mg/kg	[8, 22]
	PO	≥ 6 months	0.5–1 mg/kg				
		≥ 1 year	1 to 2–5 mg/kg (3–5 mg/kg/day for 2–5 days and then as required)				
	RECT	≥ 6–36 months	12.5–25 mg				
		3–13 years	25–50 mg				
		≥ 3 months and 5–10 kg	12.5 mg				
		10–25 kg	25 mg				
		> 25 kg	50 mg				
Diclofenac	IV/RECT/PO	General recommendation	1 mg/kg	2–3	50–75	2–3 mg/kg, max. 150 mg	
	IV	< 12 years	0.3 mg/kg	1–2, max. for 2 days			[41–43]
	IV/IM	> 2 years	0.3–1 mg/kg				
	PO	> 1 years	1 mg/kg	2–3	50		
	PO	< 12 years	1 mg/kg	2–3			
	PO/RECT	> 6 months	0.3–1 mg/kg	3			
	RECT	> 6 years	0.5–1 mg/kg	2			[8, 87]
	RECT	< 12 years	0.5 mg/kg	2			

Table 2 (continued)

Drug	Route of administration	Age and/or weight	Single dose	Frequency per day	Maximum single dose (mg)	Maximum daily dose (mg or mg/kg)	References
Ketorolac	IV/RECT/PO	General recommendation	0.3 to 0.5–1 mg/kg	3–4	1 mg/kg	2 mg/kg, max. 60–90 mg	[8]
	IV	> 1 year	0.5 mg/kg	3	0.5–1 mg/kg		[86, 87]
		≥ 1 month to < 2 years	0.5 mg/kg	3–4	0.5–1 mg/kg		
		2–16 years	0.5–1 mg/kg	4	15 mg		
		> 16 years	0.5–1 mg/kg	4	30 mg		
		6 months–16 years	0.5–1 mg/kg (initial dose), then 0.5 mg/kg	4, max. for 2 days		60 mg	
	PO	≥ 50 kg	20 mg (initial dose), then 10 mg	4–6		40 mg	
	PO	16–18 years	10 mg (initial dose), then 10–30 mg	4–6, max. for 7 days		40 mg	
Mefenamic acid	PO	> 6 months	7 mg/kg	3	500	1500 mg	
	RECT		12 mg/kg				
Naproxen	PO	> 2 years/< 60 kg	5–7 mg/kg	2 (– 3)	500	15–24 mg/kg, max. 1000 mg	[86]
		≥ 60 kg	250–500 mg				

IV intravenous, *PO* oral, *RECT* rectal, *IM* intramuscular, *max.* maximum

3.4 Pediatric Inflammatory Rheumatic Diseases

Pediatric inflammatory rheumatic diseases (PiRDs) are chronic conditions, including juvenile idiopathic arthritis (JIA), connective tissue diseases, vasculitis, uveitis, systemic lupus erythematosus, and autoinflammatory diseases (AIDs). PiRDs are associated with chronic inflammation, pain, functional impairment, and diminished health-related quality of life [101, 102]. JIA is one of the most common PiRDs, defined as an inflammatory arthritis of unknown etiology during at least 6 weeks with onset before 16 years of age [103, 104]. Treatment options in PiRD patients include NSAIDs, conventional disease-modifying drugs (cDMARDs), and biologic disease-modifying drugs (bDMARDs) or Janus kinase (JAK) inhibitors. Treatment aims are to control signs and symptoms of active disease, prevent structural damage, avoid comorbid conditions and drug toxicities, and to optimize function, growth, development, quality of life, and social participation [105, 106]. PiRD patients typically require long-term treatment over several years, therefore drug safety is highly important.

NSAIDs are often used as first-line or adjuvant therapy in PiRD patients to treat inflammation, fever, and pain and should be available as liquid preparations for children who cannot swallow tablets [107–110]. The higher free fraction of NSAIDs in synovial fluid may account for clinical effects observed with relatively low plasma drug concentrations [111]. Ibuprofen concentrations fluctuated less in synovial fluid than in serum [112]. Children treated with a mean ibuprofen dose of 37.1 mg/kg/day reached a mean ibuprofen peak concentration of 65 µmol/L in synovial fluid 5–6 h after drug intake [112]. After 12 h, ibuprofen synovial fluid concentrations were still higher compared with serum concentrations, which were measured at 20 µmol/L [112, 113]. Naproxen concentrations in synovial fluid and membrane were 74 and 30%, respectively, of that in plasma 15 h after administration [112, 113]. Particularly in JIA patients with oligoarthritis (four or fewer affected joints) and low disease activity without joint contracture or features of poor prognosis, NSAID monotherapy is recommended as first-line treatment [114]; however, NSAID monotherapy for longer than 2 months is inadequate in pediatric patients with active arthritis and treatment escalation is recommended [114]. In the last years, the cytokine modulating effect of bDMARDs

Table 3 Efficacy and safety of the propionic acid derivatives ibuprofen, dexibuprofen, ketoprofen, and naproxen, used in infants and children. Overview of studies published after 2000 [84, 221, 222, 238, 282–284, 319–322]

References	No. of patients exposed to drug; age	Design	Indication, clinical setting and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Ibuprofen						
Bauer et al. [222]	$N = 51$; 1–16 years	Retrospective database review	Postoperative alternating ibuprofen and acetaminophen; brain tumor surgery; average FU ~ 1.4 days	10 mg/kg ibuprofen PO q4–6h alternating every ~ 2 h with 10 mg/kg acetaminophen q4h	Dose regimen exceeded the maximum recommended dose of ibuprofen (30 mg/kg/day) if taken over 24 h; one patient (1.9%) had moderate postoperative hemorrhage in the tumor cavity, and nine patients (17.6%) had a small amount of blood in the tumor resection cavity in postoperative imaging	No significant postoperative hemorrhage
D'Souza et al. [221]	$N = 449$ Total cohort: $N = 2180$, 9.5 ± 3.4 years (mean ± SD)	Retrospective	Postoperative alternating ibuprofen and acetaminophen; intracapsular tonsillectomy	Ibuprofen 5–10 mg/kg PO and acetaminophen vs. with opioids and acetaminophen	Incidence of postoperative bleeding requiring surgical intervention was higher in the NSAID group compared with the opioid group (1.6 vs. 0.5%, $p = 0.01$; OR 3.4, 95% CI 1.1–10.1), same for primary (2 vs. 0.12%, $p < 0.0001$) and secondary postoperative hemorrhage (3.8 vs. 1.1%, $p < 0.0001$; OR 3.5, 95% CI 1.7–7.2)	Bias might have been introduced by ketorolac, which was administered to 39.4% of patients in the NSAID group; 2.5% of patients who received additional ketorolac suffered from primary postoperative bleeding compared with 1.7% of patients in the NSAID group who did not receive ketorolac
Sheehan et al. [238]	12–59 months (range)	Multicenter, prospective, randomized, double-blind, parallel-group trial	Antipyresis or analgesia; at home; 48 weeks	As-needed ibuprofen vs. as-needed acetaminophen PO	Children in the ibuprofen group had a mean of 0.87 exacerbations (95% CI 0.69–1.10) over 46 weeks of follow-up compared with a mean of 0.81 asthma exacerbations (95% CI 0.65–1.02) in the acetaminophen group (relative rate with acetaminophen vs. ibuprofen 0.94, 95% CI 0.69–1.28; $p = 0.67$)	No difference in the incidence of asthma exacerbations (defined as exacerbations that led to treatment with systemic glucocorticoids) or worse asthma control

Table 3 (continued)

References	No. of patients exposed to drug; age	Design	Indication, clinical setting and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Dexibuprofen						
Yoon et al. [282]	$N = 170$ 5 mg/kg: $n = 86$; 47.3 ± 34.0 7 mg/kg: $n = 84$; 43.0 ± 33.1	Multicenter, randomized, double-blind, comparative, controlled (ibuprofen), parallel group	Fever ≥ 38.0°C due to upper respiratory tract infection; 6 h; follow-up 3 days	5 mg/kg 7 mg/kg Single dose PO	No significant difference in maximal decrease of temperature or mean time to reach temperature < 38.0°C between the dexibuprofen and ibuprofen groups No significant difference in adverse events, which included diarrhea, constipation, nausea, vomiting, abdominal pain, decreased oral intake, irritability, facial edema, skin rash, elevated liver enzymes and thrombocytopenia	Dexibuprofen is as tolerable and effective as ibuprofen. Doses of 5 and 7 mg/kg dexibuprofen are comparable with 10 mg/kg ibuprofen for fever control caused by upper respiratory tract infection
Kim et al. [283]	$N = 146$ 2.5 mg/kg: $n = 37$; 2.34 ± 2.02 5 mg/kg: $n = 34$; 2.76 ± 1.74 3.5 mg/kg: $n = 44$; 2.46 ± 1.50 7 mg/kg: $n = 31$; 3.48 ± 2.14 years (mean ± SD)	Multicenter, randomized, double-blind, comparative, controlled (ibuprofen), parallel group	Fever ≥ 38.0°C due to upper respiratory tract infection; 4 h	2.5/5 mg/kg 3.5/7 mg/kg Single dose PO (higher dose for fever ≥ 38.5°C)	No significant difference in mean temperature change after 4 h between the higher dexibuprofen (3.5 or 7 mg/kg) dose group and ibuprofen (5 or 10 mg/kg), but the lower dexibuprofen dose in patients with fever ≥ 38.5°C (5 mg/kg) was less effective in lowering body temperature compared with the control group No significant difference in number of AEs between groups; all 159 AEs deemed probably or definitely not related	Dexibuprofen (3.5 or 7 mg/kg) is as effective and tolerable as ibuprofen for fever caused by upper respiratory tract infection

Table 3 (continued)

References	No. of patients exposed to drug; age	Design	Indication, clinical setting and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Choi at al. [284]	$N = 138$ 3.0 (0–13.0) years [median (range)]	Multicenter, randomized, double-blind, comparative (vs. IV propacetamol), parallel group	Fever ≥ 38.0°C due to upper respiratory tract infection; 6 h; follow-up 3 days	6 mg/kg single dose PO	Body temperature at 0.5, 1, 1.5 and 2 h were significantly lower after propacetamol compared with dexibuprofen. Body temperature < 38.0°C was achieved 0.5 h after propacetamol but 1 h after dexibuprofen Most common adverse events were vomiting ($n = 4$), diarrhea ($n = 7$), abdominal pain ($n = 1$), rash ($n = 5$); no serious adverse events. Laboratory AEs such as elevated liver enzymes and thrombocytopenia deemed as unlikely or not related	IV propacetamol was more effective in lowering body temperature compared with oral dexibuprofen, but t_{max} may occur > 2h after oral dexibuprofen administration, with potential influence on the study results
Ketoprofen						
Messeri et al. [320]	$N = 85$ Ketoprofen group: 9.7 ± 2.5 years (mean ± SD) Control group: 8.8 ± 2.6 years	Multicenter, randomized, single-blind, parallel-group (vs. RECT acetaminophen)	Minor pediatric surgery; inpatients, follow-up 8 h	Body weight-based dosing: < 30 kg: 30 mg RECT > 30 kg : 60 mg RECT q8 (max. two doses)	Ketoprofen was more effective than acetaminophen in reducing postoperative pain ($p = 0.008$), with earlier onset and longer duration (8 h) of the analgesic effect as described by the area under the curve of the visual analog scale. No AEs were observed	Rectal ketoprofen administered at 1–2 mg/kg provided effective pain relief compared with rectal acetaminophen administered at 15–20 mg/kg
Celebi et al. [321]	$N = 301$; 47.8 ± 41.1 months (mean ± SD); Ketoprofen group: $n = 105$; 50.0 ± 41.0 months	Multicenter, randomized, controlled (vs. ibuprofen and acetaminophen), parallel group (vs. PO ibuprofen and acetaminophen)	Fever ≥ 38.0°C (axillary), ≥ 39.0°C (rectally), emergency department, follow-up 4–6 h and 48 h	0.5 mg/kg/dose PO, single dose	There were no differences between age groups for antipyretic effect, taste, and adverse effect for all three drugs	Ketoprofen may be used as alternative to acetaminophen and ibuprofen

Table 3 (continued)

References	No. of patients exposed to drug; age	Design	Indication, clinical setting and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Kokki and Kokki [84]	$N = 165$ Age 6–24 months: 0.25 mg/kg: $n = 36/41$; 14 ± 5 months (range 7–23) 0.5 mg/kg: $n = 39/41$; 13 ± 5 months (range 6–21) 1 mg/kg: $n = 40/42$; 14 ± 5 months (range 6–24) Control group: $n = 35/41$; 14 ± 4 months (range 6–24)	Age 2–6 years: 0.25 mg/kg: $n = 37/43$; 45 ± 13 months (range 24–71) 0.5 mg/kg: $n = 33/40$; 45 ± 12 months (range 25–70) 1 mg/kg: $n = 39/43$; 43 ± 14 months (range 24–71) Control group: $n = 33/38$; 45 ± 14 months (range 26–70)	Multicenter, randomized, single-blind, comparator-controlled (vs. PO acetaminophen), phase II Fever ≥39.0°C (rectally), emergency department, follow-up 24–48 h	Randomized dosing (single dose PO): 0.25 mg/kg vs. 0.5 mg/kg vs. 1 mg/kg vs. acetaminophen	In the ketoprofen groups, the mean maximal temperature decreases in the younger/older age groups were 1.6/1.6 °C, 2.0/1.9 °C and 1.9/2.2 °C with doses of ketoprofen 0.25, 0.5 and 1 mg/kg, respectively, compared with 1.8/1.8 °C with acetaminophen 15 mg/kg. In the older children, ketoprofen provided antipyretic efficacy in a dose-dependent manner	Ketoprofen was found to have a significant antipyretic efficacy in children. The lowest dose of ketoprofen syrup that provided a meaningful antipyretic effect in both groups was 0.5 mg/kg. At this dose, the antipyretic efficacy was equal to that of acetaminophen 15 mg/kg. Based on these data, a dose of 0.5 mg/kg of ketoprofen was selected for future evaluation in phase III studies in the symptomatic management of fever in children
Senel et al. [322]	$N = 316$; 34.8 ± 30.7 months (mean ± SD) Ketoprofen group: $n = 158$, 35.9 ± 31.7 months	Open-label, randomized (vs. PO acetaminophen)	Fever ≥ 37.8 < 41 °C; emergency department; follow-up 4 h	0.5 mg/kg/dose PO, single dose	A higher proportion of patients in the ketoprofen group achieved a temperature below 37.8 °C during 4 h (95% CI 3.03–12.99, $p < 0.001$). Ketoprofen was more likely to achieve a temperature below 37.8 °C compared with acetaminophen (OR 6.25, 95% CI 3.03–12.99, $p < 0.001$). Ketoprofen was superior in fever reduction at temperatures ≥ 39 °C ($p < 0.001$). Mean temperature reductions at 15, 30 and 60 min were larger in the ketoprofen group ($p < 0.001$). Ketoprofen was superior to acetaminophen for shorter fever duration in the first 4 h ($p < 0.001$)	It seems reasonable to use ketoprofen first-line if in need of rapid fever reduction

Table 3 (continued)

References	No. of patients exposed to drug; age	Design	Indication, clinical setting and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Naproxen						
Korpela et al. [319]	$N = 30$; 1.6 (0.8–5.9) years [median (range)]	Randomized, double-blind, active (acetaminophen) and placebo-controlled, parallel group	Postoperative pain (adenectomy); day-case surgery; ≥ 2 h; follow-up 1 day	10 mg/kg PO, single dose	Rescue IV fentanyl requirements were lower in patients who received naproxen compared with placebo or acetaminophen (83 vs. 97%, $p < 0.05$). Significantly fewer patients in the naproxen group required four or more fentanyl doses (9/30 vs. 3/30)	Oral naproxen (10 mg/kg), compared with acetaminophen, reduces the need for rescue analgesic after adenectomy

AEs adverse events, *RECT* rectal, *PO* oral, *SD* standard deviation, *FU* follow-up, *qxh* every *x* hours, *NSAID* non-steroidal anti-inflammatory drug, *OR* odds ratio, *CI* confidence interval, *IV* intravenous, t_{max} time to reach maximum concentration, *max.* maximum

or JAK inhibitors have enabled 'treat-to-target' T2T strategies and have markedly improved clinical outcome, which might explain why NSAID monotherapy is nowadays less common compared with the 1990s [115]. In pediatric and adolescent patients with chronic recurrent multifocal osteomyelitis without spine involvement, NSAIDs seem to still be the first-line treatment [116]. Furthermore, NSAIDs are used in periodic fever syndromes. NSAIDs are recommended as a symptomatic on-demand therapy during inflammatory attacks in AIDs in addition to maintenance therapy with colchicine and/or bDMARDs [117, 118]. For anterior uveitis, often associated with JIA, topical and systemic NSAID monotherapy has no demonstrable effect [119, 120]. In addition to established treatment regimens for uveitis/iridocyclitis, NSAIDs may play an adjunctive role by permitting corticosteroid dose reduction [119, 120].

To achieve the anti-inflammatory effect, higher NSAID dosages are necessary as needed for their analgesic effects [109]. Moreover, it seems that the anti-inflammatory effect of NSAIDs is time-dependent. Giannini et al. pointed out that JIA patients treated with ibuprofen show some improvement as early as 2 weeks, with continuous decrease of inflammatory disease activity until week 24 of treatment [121]. Lovell et al. postulated that the mean response time to NSAIDs is approximately 1 month and that an adequate therapeutic trial should be at least 8 weeks [122].

The choice of NSAIDs in very young patients with PiRD is often determined by whether a liquid form is available for exact dosing and administration, particularly when tablet swallowing is not possible [108, 109]. Safety and efficacy studies in PiRD patients focused on NSAIDs are scarce. The available data mainly address the PiRD subgroup JIA. Eccleston et al. performed a Cochrane review to assess the analgesic efficacy and adverse events in children and adolescents with chronic non-cancer pain treated with NSAIDs [123]. They identified seven trials with a total number of 1074 participants aged 2–18 years with JIA treated with NSAIDs for more than 3 months. All studies looked at different comparisons between acetylsalicylic acid, celecoxib, fenoprofen, ibuprofen, indomethacin, ketoprofen, meloxicam, naproxen, and rofecoxib [121, 124–129]. The authors concluded that the number of studies identified was too small for a sufficient data analysis [123].

Tolmetin is a heterocyclic acetic acid derivative. Available data suggest that tolmetin sodium has anti-inflammatory and analgesic effects in JIA and appears to be well tolerated for long-term therapy in JIA [121, 130]. Moreover, ibuprofen suspension has shown efficacy and safety at dosages of 30–40 mg/kg/day in JIA treatment [121, 130]. Naproxen is well-tolerated with long-term efficacy and tolerance, even in younger PiRD patients [131, 132]. It is one of the first-choice NSAIDs in JIA due to its twice-daily administration

(advantage over ibuprofen), its availability as suspension in several countries, and its favorable adverse effect profile [109, 111, 133, 134].

Leak at al. compared naproxen 10 mg/kg/day, tolmetin 25 mg/kg/day, and diclofenac 2 mg/kg/day in 28 children diagnosed with seronegative JIA and assessed a clinical improvement for all three drugs [135]. Adverse effects were mild and typical but occurred less frequently with naproxen and tolmetin than diclofenac [135]. Ibuprofen, diclofenac, naproxen, fenoprofen, and tolmetin were found to be as effective as acetylsalicylic acid but were better tolerated than acetylsalicylic acid due to lower adverse events. Furthermore, they did not have a risk for Reye syndrome [10].

Foeldvari et al. performed a 12-week, multicenter, randomized, double-blind non-inferiority study for celecoxib administered at 3 mg/kg twice daily or 6 mg/kg twice daily, and naproxen 7.5 mg/kg twice daily [124]. Both celecoxib dosing regimens were at least as effective as naproxen and all treatments were generally well tolerated [124].

For rofecoxib (0.3 mg/kg/day up to 12.5 mg/day, or 0.6 mg/kg/day up to 25 mg/day) compared with naproxen (15 mg/kg/day up to 1000 mg/day), Reiff et al. showed comparable clinical effectiveness for JIA patients aged 2–17 years [125].

Ruperto et al. showed comparable short- and long-term safety and efficacy for meloxicam oral suspension (once daily 0.125 or 0.25 mg/kg) compared with naproxen oral suspension (10 mg/kg/day divided in two doses) in the treatment of JIA [126].

Foeldvari et al. found that meloxicam suspension 0.25 mg/kg once daily observed lower concentrations in children aged 2–6 years compared with older children; however, $t_{½}$ (13 h) was similar among all patients [63].

Sobel et al. assessed long-term safety and developmental data for 274 JIA patients aged 2–17 years treated with celecoxib ($n = 55$) and other NSAIDs ($n = 219$) [136]. A total of 410 patient-years were observed showing a similar rate of adverse events between the two groups and overall a low number of severe adverse events with no new safety concerns [136].

In addition, Falkner et al. assessed a comparable safety profile for celecoxib (50 or 100 mg twice daily) in comparison with naproxen (7.5 mg/kg twice daily) in JIA patients aged 2–17 years [137]. Even though indomethacin is a potent anti-inflammatory and antipyretic agent in children with JIA, it is less frequently used [10, 111].

In their review, Eccleston et al. reported adverse events by drug as follows: acetylsalicylic acid, 85/120; fenoprofen, 28/49; ibuprofen, 40/45; indomethacin, 9/30; ketoprofen, 9/30; meloxicam, 113/147; naproxen 102/202, and rofecoxib 43/209 [123]. The most common adverse effects of NSAIDs observed in patients with JIA are gastric irritation and abdominal pain [106, 131, 138, 139].

Due to the risk of dyspepsia and gastric irritation, Lovell et al. investigated the fixed combination of naproxen and esomeprazole and postulated that this treatment is well tolerated in JIA patients aged 12–16 years without new safety signals [140]. Furthermore, pseudoporphyria is often implicated in JIA patients taking NSAIDs, particularly in patients treated with naproxen [141, 142]. The prevalence for pseudoporphyria ranges between 10.9 and 12% [141–143]. Pseudoporphyria occurs mainly in the first 2 years of naproxen treatment, and JIA disease activity is an important risk factor [143]. Furthermore, topical NSAIDs such as diclofenac are well-tolerated and effective in the treatment of inflammatory and painful conditions [144]. For example, diclofenac sodium 4% spray administered 2, respectively 3, times with 40 mg daily can penetrate the skin in substantial amounts and synovial-tissue concentrations are 10- to 20-fold higher (median 40.9 ng/g, respectively 74.9 ng/g) than those of synovial fluid (median 3.0 ng/mL, respectively 2.7 ng/mL) or plasma (median 4.1 ng/mL, respectively 4.2 ng/mL), but until now no studies in PiRD patients exist [145].

In summary, NSAIDs are used in PiRD patients as first-line therapy for a defined time span and as an on-demand therapeutic approach. Several NSAIDs can be used to treat PiRD patients safely and effectively. Dosing recommendations for NSAIDs are heterogeneous (several dosing recommendations are summarized in Table 4). The choice of NSAIDs is based on considerations such as age, individual patient's response, approval, dosing, availability of a pediatric formulation, comedications, and hepatic impairment, and also on disease type, disease activity, and localization of arthritis. Regular monitoring of blood count and renal function in PiRD patients receiving daily long-term NSAIDs is recommended [111].

3.5 Indications in Pediatric Cardiology

Common indications of NSAIDs in infants with congenital heart defects are postoperative pain management, anti-inflammatory treatment in patients with pericardial effusion, pericarditis, or Kawasaki disease, as well as the use of salicylates for anticoagulation. For dose recommendations, see Table 5.

NSAIDs such as diclofenac play an important role in fast-track pediatric cardiac surgery due to their opioid-sparing effect, as was demonstrated in 54 patients with a median age of 5.6 years [98]. Ketorolac reduced morphine requirements after cardiac surgery in 67 infants (median age 22.7 months) within 24 h after its first administration [99]. The safe use of ketorolac has been demonstrated in neonates and infants [146], however special caution is needed when NSAIDs are used in combination. Based on a cohort of 14 young infants, Moffett and Cabrera report that coadministration of ketorolac and acetylsalicylic acid was a significant

risk factor for drug-induced acute kidney injury (AKI) in the postoperative period [147].

NSAIDs are also one of the mainstays in the management of idiopathic pericarditis or pericardial effusion and could be used either alone or in combination with acetylsalicylic acid, colchicine, or corticosteroids, depending on the underlying cause of the effusion [54, 148].

Postoperative pericardial effusion occurs in about 25% of patients after congenital cardiac surgery, but its incidence also depends on the type of surgical procedure [149]. Postpericardiotomy syndrome is an inflammatory reaction of the pericardium and/or the pleura that usually occurs within 1–6 weeks after cardiac surgery and manifests with pericardial effusion and fever. It occurs in 2–30% of patients after cardiac surgery but may also occur after catheter interventions or other conditions with pericardial damage. In children, NSAIDs such as ibuprofen, diclofenac, indomethacin, and acetylsalicylic acid are established treatments for postpericardiotomy syndrome but should not be used as prophylaxis [150, 151].

Acetylsalicylic acid is one of the most frequently used antiplatelet agents in pediatric cardiology. The usual dose is 3–5 mg/kg/day, which may be decreased to 1–3 mg/kg/day if dual antiplatelet therapy is used.

Patients with congenital heart defects are at higher risk of thrombosis, especially when critically ill [152]. About 94 and 77% of patients with hypoplastic left heart syndrome receive acetylsalicylic acid for thromboprophylaxis after stage 1 and stage 2 palliative surgery, respectively [153]. Shunt thrombosis can be fatal in patients with systemic-to-pulmonary shunts. Therefore, therapeutic efficacy of acetylsalicylic acid may be assessed in patients at risk for acetylsalicylic acid resistance. This condition is not yet fully understood; its etiology is multicausal and the interfering mechanisms seem to be alterations in platelet function, platelet interactions, acetylsalicylic acid bioavailability, acetylsalicylic acid efficacy, and genetic polymorphisms [154, 155]. Acetylsalicylic acid responsiveness can be measured but there is no routine laboratory monitoring of acetylsalicylic acid antiplatelet therapy [156–160]. There is a higher risk of thrombosis after surgical and interventional procedures, especially in patients with single-ventricle physiology (25-40%) or systemic-to-pulmonary shunts, and there also is a higher rate of acetylsalicylic acid resistance after such procedures [161]. In a retrospective analysis, standard-dose (≤ 7 mg/kg/day at that institution) was compared with high-dose (≥ 8 mg/kg/day) acetylsalicylic acid in infants < 1 year of age, after surgery for creation of a systemic-to-pulmonary shunt [162]. There was no difference in shunt thrombosis, shunt interventions, and mortality between groups but single-ventricle morphology and postoperative red blood cell transfusion were associated with shunt-related adverse events.

Kawasaki disease is an acute self-limiting febrile vasculitis of the small- and medium-sized arteries, typically in children younger than 5 years of age. Coronary artery aneurysms are a dreaded complication that can be life-threatening. Kawasaki disease is diagnosed based on clinical criteria. Complete Kawasaki disease can be diagnosed in the presence of fever for at least 5 days together with four of the following clinical features: (1) erythema and cracking lips, strawberry tongue, and/or oral/pharyngeal

Table 4 Recommended doses for commonly used NSAIDs in PiRD based on the literature [10, 107, 109, 111, 126]

Drug	Daily drug dose	Frequency per day	Maximum daily dose (mg)	References
Ibuprofen	30–40 mg/kg/day	3–4	2400–3200	[107]
	20–40 mg/kg/day (tablet) 45 mg/kg/day (suspension)			[10] [109] [111]
Naproxen	10 to 15–20 mg/kg/day	2	1000–1100	[10, 107, 109, 111]
Indomethacin	1 to 2–4 mg/kg/day	3–4	150–200	[10, 107, 109, 111]
Diclofenac	2–3 mg/kg/day	1–3	100–150	[109] [111] [10]
Meloxicam	0.125–0.25 mg/kg/day	1	15	[107, 109, 126]
Piroxicam	5 mg (< 15 kg) 10 mg (16–25 kg) 15 mg (26–45 kg) 20 mg (> 46 kg)	1	20	[10]
	0.2–0.4 mg/kg/day	1		[109, 111]
Celecoxib	50–100 mg (10–25 kg) 100–200 mg (25–50 kg)	2	400	[107, 111]
	4–6 mg/kg/day	1–2		[109]

NSAIDs non-steroidal anti-inflammatory drugs, *PiRD* pediatric inflammatory rheumatic disease

Table 5 Recommended doses for different NSAIDs for applications in pediatric cardiology [54, 150, 151, 157, 163, 168–170, 323–326]

Drug	Drug dose	Frequency per day	Indication	References
Ibuprofen	30–50 mg/kg/day	3–4	Pericarditis	[54]
Indomethacin	1–2 mg/kg/day	2–4	Pericarditis	[54]
ASA	20–50 mg/kg/day for 1–6 weeks, alternatively 60 mg/kg/day for 7 days from day 3	1	Postsurgical pericardial syndrome	[150, 151, 323]
ASA	80–100 mg/kg/day	4	Acute Kawasaki disease	[163, 168, 324]
	30–50 mg/kg/day	3–4		[169, 170]
	3–5 mg/kg/day	1		[325]
ASA	3–5 mg/kg/day	1	Afebrile Kawasaki disease	Over 6–8 weeks; if no coronary artery abnormalities can be detected, after initial acute-phase acetylsalicylic acid treatment [163, 168–170, 324]
ASA	1–5 mg/kg/day	1	Antiplatelet therapy	[324, 326]
	1–3 mg/kg/day	1	Dual antiplatelet therapy	When combined with other antiplatelet agents
	3–10 mg/kg/day	1	Antiplatelet therapy, high risk for thrombosis	[157]

NSAIDs non-steroidal anti-inflammatory drugs, *ASA* acetylsalicylic acid

edema; (2) bilateral conjunctivitis; (3) rash; (4) erythema and edema of the hands/feet (acute) or desquamation (subacute); and (5) cervical lymphadenopathy [163]. Its diagnosis warrants the immediate initiation of treatment to abrogate systemic and tissue-level inflammation and to prevent thrombosis in developing coronary aneurysms [164]. Therefore, intravenous immunoglobulins (IVIGs) should be instituted as early as possible after diagnosis is established, as IVIGs administered early are effective in reducing the prevalence of the development of coronary artery abnormalities [165–167]. Concomitant acetylsalicylic acid is recommended every 6 h intravenously in a total daily dose of 80–100 mg/kg/day in the US, whereas a dose of 30–50 mg/kg/day is routinely used in Japan and West Europe [163, 168–171], without differences in coronary outcome [172]. There are no data to suggest that either dose of acetylsalicylic acid is superior [163]. Furthermore, it seems that some centers in Canada routinely treat their patients with lower doses of acetylsalicylic acid (3–5 mg/kg/day). In the current literature, the role and dose of acetylsalicylic acid in the treatment of the acute phase of Kawasaki disease is discussed controversially, as previously performed studies report no benefits/differences of low-dose acetylsalicylic acid (3–5 mg/kg/day) compared with high-dose acetylsalicylic acid (30–50 mg/kg or 80–100 mg/kg/day) if administered in conjunction with IVIGs [173–175]. Other studies state that low-dose acetylsalicylic acid (3–5 mg/kg/day) was associated with three times higher odds of intravenous retreatment compared with high-dose acetylsalicylic acid (80–100 mg/kg/day), with no significant difference in duration of hospital stay or incidence of coronary artery aneurysms [171]. Despite these findings, the use of acetylsalicylic acid in Kawasaki disease is a widely accepted practice, albeit with varying dose regimens [176]. After the acute phase of Kawasaki disease in the US, West Europe and Japan, acetylsalicylic acid should be reduced to a dose of 3–5 mg/kg/day and may be discontinued after 6–8 weeks if coronary aneurysms have been excluded by echocardiography [163, 168–170]. Patients with coronary artery aneurysms need lifelong antiplatelet therapy.

A more recent application of diclofenac is the use for prostaglandin-induced periostitis in infants receiving prostaglandin therapy to maintain a patent arterial duct. The use of diclofenac against prostaglandin adverse effects seems contradictory and there have been case reports of intrauterine duct closure after maternal intake of diclofenac [177, 178]. However, clinical practice shows efficacy of diclofenac in that indication, but prospective and controlled studies are lacking.

3.6 Other Indications

Other indications for acetylsalicylic acid in infants include stroke prevention but this is not discussed in this review [179–183].

4 Safety of NSAIDs in Infants

Adverse drug reactions to NSAIDs can be renal, gastrointestinal, hematologic, or immunologic. While most reactions are mild in nature, there have been reports of clinically significant morbidity and mortality after NSAID use [184]. The safety of NSAID use, especially in infants, is discussed in the following sections.

4.1 Renal Safety

Potential renal adverse effects of NSAIDs are acute renal failure, tubular interstitial nephritis, and papillary necrosis, with the latter especially being associated with long-term use. The mechanisms by which NSAIDs exert renal toxicity have been described elsewhere in detail [185].

Acute kidney failure may already occur in children after short-term drug use (~ 5 days), especially when predisposing risk factors such as dehydration, prediagnosed kidney disease (renal transplantation), and concomitant therapy with other nephrotoxic drugs are present [185, 186]. Kidney damage through NSAIDs occurs through two different mechanisms, which include (1) altered renal hemodynamics by vasoconstriction of the afferent glomerular arteriole leading to reduced renal perfusion, local hypoxia and acute tubular necrosis, and (2) tubular interstitial nephritis mediated by locally increased production of leukotrienes [187]. AKI in children occurs more frequently in critically ill children (27%) rather than in non-critically ill children (5%), and critically ill children are also at a higher risk of drug-induced AKI [188–190]. Drug-induced AKI among children is most frequently due to NSAIDs, antibiotics, or chemotherapeutics [187]. Several case reports and small case series have been published with a total of approximately 50 patients [185, 191–210]. NSAID use was rather short in most patients (< 1 week) and mostly (~ 75%) at recommended doses, but at least 50% of patients showed signs of decreased oral intake of fluids during NSAID use. The individual substances were ibuprofen ($n = 18$), niflumic acid ($n = 7$), naproxen ($n = 5$), ketorolac ($n = 4$), rofecoxib and diclofenac ($n = 3$ each), sulindac ($n = 2$), flurbiprofen and ketoprofen ($n = 1$ each), and drug combinations with ibuprofen or diclofenac ($n = 7$). In some cases, patients were taking other drugs with potential nephrotoxicity at the same time, e.g. antibiotics.

In their retrospective analysis, Misurac et al. found an incidence of NSAID-induced AKI of 2.7% (2.1% acute tubular necrosis, 0.6% acute interstitial nephritis) among 1015 pediatric patients admitted for AKI to one US hospital [193]. When patients with multifactorial causes of AKI were excluded, the incidence was 6.6%. The patients had been taking ibuprofen (67%), naproxen (11%), ketorolac (7%), ibuprofen/naproxen (7%), and ibuprofen/ketorolac (7%). The administered doses had been appropriate for 65% of the patients with NSAID-induced AKI, if dosing data were available. Younger patients (< 5 years) were more likely to receive renal replacement (100 vs. 0%), intensive care unit (ICU) admission (75 vs. 9%), and needed longer inpatient care (10 vs.7 days). Time to recovery was a median of 15 days (range 1–180 days), and no patients had an ongoing need for renal replacement therapy.

NSAIDs may also cause clinically non-apparent kidney injury. Levels of the biomarker urinary neutrophil gelatinase-associated lipocalin (NGAL) were assessed in young children (median age 2.5–3.2 years) after cardiopulmonary bypass (CPB) with no apparent signs of AKI, who were stratified by NSAID administration [211]. At 60–72 h after CPB, urinary NGAL levels were more than fivefold higher in patients receiving NSAIDs, suggesting urinary NGAL as an early non-invasive marker of NSAID-induced subclinical kidney injury.

Prediagnosed kidney disease is the most relevant contraindication for NSAID therapy [9, 193]. The combination therapy with other potentially nephrotoxic drugs is a relative contraindication for administering NSAIDs, but alternative treatments should be evaluated if possible in order to reduce the risk of renal damage [7, 10, 193, 212]. Dehydration, caused by fever, vomiting, and/or diarrhea, is a risk factor for renal failure and therefore signs of volume depletion, such as poor oral intake and decreased urine output, should be recognized and corrected when prescribing NSAIDs [213].

4.2 Gastrointestinal Safety

The most common adverse effects of NSAIDs occur in the gastrointestinal tract and presenting symptoms include nausea, dyspepsia, abdominal pain, diarrhea or constipation, flatulence, and vomiting. Potentially life-threatening, but very rare, adverse events in children are peptic ulcers, gastric hemorrhage, or gastric perforation.

The risk of upper gastrointestinal complications such as hematemesis, melena, or endoscopically confirmed gastroduodenal lesion during therapy with NSAIDs, oral corticosteroids, and antibiotics was assessed in a case–control study (486 cases) in children aged 15–71 months [214]. An association between the short-term use (1–8 days) of NSAIDs and an increased risk for upper gastrointestinal complications was found. The adjusted OR for ibuprofen was 3.7 (95% CI 2.3–5.9) compared with niflumic acid (OR 1.6, 95% CI 0.8–3.2), ketoprofen (OR 2.6, 95% CI 1.2–5.6), acetylsalicylic acid (OR 2.5, 95% CI 0.9–7.4), and NSAIDs overall (OR 2.9, 95% CI 2.1–4.0). ORs for other NSAIDs (e.g. indomethacin) were not reported separately. The true incidence of upper gastrointestinal complications could not be calculated due to the study design, but overall risk was

estimated to be low (2.4 per 10,000 children). However, the population investigated in this case–control study did not reflect the typical pediatric patient population receiving NSAID treatment, because children with upper gastrointestinal complications were compared with a control group of children with neurological disorders.

A more recent study assessed gastrointestinal complications in 51 children aged 5 months to 15 years (including 11 children < 3 years of age) after short-term use of the NSAIDs ibuprofen (68.6%), ketoprofen (9.8%), acetylsalicylic acid (7.8%), flurbiprofen, ketorolac, naproxen, niflumic acid, and nimesulide, mainly for pain and fever [215]. Hematemesis was the most frequent symptom (33.3%), followed by abdominal pain (31.3%), anemia (25%), melena (7.8%), and nausea and vomiting (1.9%). Upper gastrointestinal endoscopy confirmed gastric (62%), duodenal (33%), and esophageal lesions (15%), with the proximal lesions being more prevalent in children < 3 years of age. Risk factors were concomitant drug use (37.3%, mainly antibiotics and corticosteroids), associated comorbidities (23.5%), active *Helicobacter pylori* gastritis (19.6%), and a family history of peptic ulcer disease (9.8%) or *H. pylori* infection (5.8%). About 9.8% of patients were taking gastroprotective drugs such as proton pump inhibitors (PPIs) or H_2 receptor antagonists, but NSAID therapy had a longer duration in these patients. It was further remarkable that NSAIDs were inappropriately used in 47% of patients regarding the correct weight-based dose, the number of daily doses, or the recommended age.

In summary, chronic comorbidities, the concomitant use of other medications with known gastrointestinal adverse effects (e.g. corticosteroids), *H. pylori* infection, a history of peptic ulcer, and long-term or high-dose NSAID therapy are also risk factors for gastrointestinal adverse events in children, as seen in adults [215–217]. Therefore, infants and children should also be assessed for additional risk factors and gastroprotective drug treatment with antacids, H_2 blockers, or PPIs. Furthermore, *H. pylori* eradication should be considered in infants and children as it is already recommended for pediatric patients with PiRD during long-term treatment [218].

4.3 Hematologic Safety

NSAIDs also inhibit platelet COX, thereby blocking the formation of thromboxane A_2 and impairing thromboxane-dependent platelet aggregation, leading to an increased risk for bleeding complications, e.g. in patients after major surgery.

Postoperative bleeding after tonsillectomy was assessed in a recent Cochrane review including 15 studies involving 1101 children aged up to 16 years [219]. The review revealed a non-significant increase in the risk of bleeding requiring surgical intervention (OR 1.69, 95% CI 0.71–4.01). Furthermore, the frequency of perioperative bleeding events requiring non-surgical intervention was not significantly altered (OR 0.99, 95% CI 0.41–2.40). Due to the rareness of relevant bleeding after tonsillectomy requiring surgical intervention, the review was limited by the insufficient data to exclude or confirm a significantly increased bleeding risk because of an insufficient number of studies and individuals studied. Ketorolac has been attributed to an increased risk of bleeding but the meta-analysis found no statistical significant difference in postoperative bleeding events requiring either surgical or non-surgical intervention when compared with other NSAIDs [219].

Riggin et al. conducted a meta-analysis of 18 studies (participants: 1747 children, 1446 adults) and found no increased risk of bleeding in those using NSAIDs after tonsillectomy [220]. NSAID use in children was not associated with an increased risk of bleeding, most severe bleeding, secondary bleeding, readmission or surgical intervention (OR 1.06, 95% CI 0.65–1.74), with the bleeding risk even lower than in the population overall (OR 1.30, 95% CI 0.90–1.88). No significant differences were described for the individual NSAIDs.

A more recent retrospective study compared a postoperative analgesic regimen of ibuprofen 5–10 mg/kg and acetaminophen with opioids and acetaminophen in 2180 children (449 in the ibuprofen + acetaminophen group) with a mean age of 9.5 ± 3.4 years undergoing intracapsular tonsillectomy [221]. The incidence of postoperative bleeding requiring surgical intervention was higher in the NSAID group compared with the opioid group (1.6 vs. 0.5%, $p = 0.01$; OR 3.4, 95% CI 1.1–10.1), as were the rates of primary (2 vs. 0.12%, $p < 0.0001$) and secondary postoperative hemorrhage (3.8 vs. 1.1%, $p < 0.0001$; OR 3.5, 95% CI 1.7–7.2). Bias might have been introduced by ketorolac that was administered to 39.4% of patients in the NSAID group, and 2.5% of patients who received additional ketorolac experienced primary postoperative bleeding compared with 1.7% of patients in the NSAID group who did not receive ketorolac. Pain scores were not evaluated during the study but the rate of emergency department visits or admissions for pain did not differ between groups.

Liu and Ulualp retrospectively analyzed 583 patients aged 1–18 years (mean 7 ± 3 years) receiving alternating ibuprofen/acetaminophen post tonsillectomy. They reported that 9.6% of patients reported inadequate pain control and 4.1% of patients experienced postoperative bleeding that in 1.5% of patients required surgical intervention [96].

A retrospective database review evaluated postoperative bleeding after alternating ibuprofen and acetaminophen after brain tumor surgery in 51 patients aged 1–16 years [222]. Patients were postoperatively treated with 10 mg/kg ibuprofen every 4–6 h, alternating every ~ 2 h with 10 mg/kg acetaminophen administered every 4 h. Besides the fact that this dosing regimen exceeded the maximum recommended dose of ibuprofen (30 mg/kg/day) if taken over 24 h, only one patient (1.9%) had moderate postoperative hemorrhage in the tumor cavity, and nine patients (17.6%) had a small amount of blood in the tumor resection cavity in postoperative imaging studies performed, on average, 1.4 days after surgery.

These studies are in line with the review by Romsing et al. who compared preoperative, intraoperative and postoperative NSAID safety in children undergoing a variety of surgeries [223]. The timing of NSAID administration did not seem to affect postoperative hemorrhage. A higher bleeding risk was reported for ketorolac and indomethacin based on four studies that reported a significantly higher bleeding risk for NSAIDs compared with the control groups [223–227].

In particular, neonates and young infants are at a significantly increased risk for postoperative bleeding after ketorolac therapy [228]. Aldrink et al. report associations between age, serum creatinine, and enteral feeding regarding the bleeding risk during ketorolac therapy (see Table 6).

It has been observed in adults that ibuprofen and other NSAIDs lead to a relevant pharmacodynamic drug–drug interaction regarding the inhibition of platelet aggregation by acetylsalicylic acid [229]. This phenomenon has been observed for ibuprofen, indomethacin, naproxen, and tiaprofenic acid, but not for diclofenac, sulindac, meloxicam, celecoxib, etoricoxib, and rofecoxib [229–231]. Ibuprofen and naproxen inhibited the anti-thrombocyte effect of acetylsalicylic acid, even below the non-response threshold, in a recent adult ex vivo study [231]. Therefore, it is recommended for adults that ibuprofen and other NSAIDs with this interaction potential should not be combined. This pharmacodynamic interaction has not been described in infants to date but may play a role in infants with congenital heart disease (e.g. with stents or vascular grafts). Based on the few available studies in adults, it should be considered whether diclofenac would be an alternative with less interaction potential, but the pharmacodynamic interaction between NSAIDs and acetylsalicylic acid should be studied in children before any conclusions for infants can be made.

In summary, physiological hemostasis can be impaired depending on the type of surgery. However, NSAIDs seem to affect postoperative bleeding but the data still remain inconclusive. NSAIDs can be considered as well tolerated postoperative analgesics among children undergoing surgery but attention should be paid to the type and duration of surgical procedure, bleeding complications already present intraoperatively, and the choice of NSAID for postoperative pain management, including postoperative monitoring for pain and bleeding complications. Based on the available data, we recommend using NSAIDs with a reportedly higher bleeding risk, such as acetic acid derivatives, only in the clinical setting where appropriate postoperative surveillance is possible.

4.4 Immunologic Safety

4.4.1 NSAID-Induced Hypersensitivity

Hypersensitivity reactions are frequently reported adverse effects and may present as non-specific allergic reactions, various skin reactions such as pruritus or urticaria, angioedema or anaphylaxis, and respiratory tract reactivity. Hypersensitivity reactions towards NSAIDs can be classified based on two mechanisms: (1) cross-intolerance hypersensitivity reactions, which are more frequent, and (2) selective hypersensitivity reactions [232].

Cross-intolerance hypersensitivity reactions comprise NSAID-exacerbated respiratory disease, NSAID-exacerbated cutaneous disease, and NSAID-induced urticarial angioedema, which usually occur within 6 h after drug exposure. These reactions are caused by a non-immunologic mechanism due to COX-1 inhibition, leading to an imbalance of arachidonic acid metabolism through both the lipoxygenase and COX pathways. By inhibiting the COX pathway, arachidonic acid metabolites are diverted to the lipooxygenase pathway, leading to an increase in the synthesis of proinflammatory leukotrienes [232, 233]. This cross-intolerance may occur for every NSAID, including acetylsalicylic acid, independent of its structural class. This is of particular interest since NSAIDs are a unique class of drugs in that they are defined primarily by their mechanism of action and not by their physicochemical properties. In fact, as described above, there is notable chemical heterogeneity among the different compounds.

In contrast, selective, or compound-specific, hypersensitivity reactions are caused by a single agent and cross-reactivity is rare. These include selective NSAID-induced urticaria, angioedema, and anaphylaxis, which are not directly related to COX inhibition. These reactions are likely immunoglobulin (Ig) E-mediated and occur within 1 h of drug intake, and delayed-type hypersensitivity (type IV) reactions which are cell-mediated and usually manifest within up to 48 h after drug intake [232]. Previous drug exposure towards the culprit drug is a prerequisite for selective hypersensitivity reactions. This also explains why compound-specific hypersensitivity is more common among NSAIDs than for

Table 6 Efficacy and safety of the acetic acid derivatives diclofenac and ketorolac used in infants and children. Overview of studies published after 2000 [42, 95, 100, 146, 228, 244, 288–290, 327–332]

Reference	No. of patients exposed to drug; age	Design	Indication, clinical setting, and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Diclofenac						
Tawalbeh et al. [288]	$N = 41$; 3–14 years (range)	Controlled (acetaminophen), prospective	Acute postoperative pain (adenotonsillectomy); inpatients; 24 h–1 week	1–3 mg/kg; RECT; divided in two doses, administered 8 h apart	Oral intake higher after diclofenac (595 vs. 390 mL, $p = 0.02$), with 7% of patients in the diclofenac group having no oral intake at 6 h compared with 15% of patients in the acetaminophen group. Earlier solid intake after diclofenac (9.5 ± 5.97 h, range 3–24 h vs. 16.5 ± 3.97 h, range 12–30 h, $p < 0.001$). Significantly less earache in 24 h after diclofenac (5% vs. 26%) AE: fever > 38°C (diclofenac 2.5% vs. acetaminophen 15%); less frequent episodes of nausea and vomiting after diclofenac compared with acetaminophen (2.5 vs. 31%, $p = 0.05$). Serious adverse event: 1 readmission per group, unrelated to drug	Significant effect on post-tonsillectomy pain; diclofenac allowed earlier oral intake, suggesting an anti-inflammatory effect
Standing et al. [42, 244]	$N = 301$; 6.3 (0.9–12.9) years	Observational, prospective	Acute postoperative pain; pediatric surgical wards; ~ 1 week	~ 1 mg/kg; no. of doses: 1 (1–22) dose [median (range)]	Adverse events: incidence of rash was 0.8% (95% CI 0.016–2.3); minor CNS disturbance 0.5% (0.95% CI 0.06–1.9), rectal irritation with suppositories 0.3% (95% CI 0.009–1.9), and of diarrhea was 0.3% (95% CI 0.007–1.5). No serious adverse event	Serious adverse events occurred in < 0.8% of children; the incidence of diclofenac-induced bronchospasm in asthmatic children was < 2.7%

Table 6 (continued)

Reference	No. of patients exposed to drug; age	Design	Indication, clinical setting, and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Vons et al. [95]	$N = 89$; 54 (39–69) months [median (IQR)]	Prospective cohort study	Postoperative pain (adenotonsillectomy); day case surgery; 7 days	BW < 25 kg: 12.5 mg; BW > 25 kg: 25 mg, rectal	After adenotonsillectomy, daytime activities normalized after 7 days during treatment with diclofenac and acetaminophen (20–30 mg/kg rectal). Diclofenac treatment was discontinued earlier (mean 3.8 days) vs. acetaminophen (4.5 days). Diclofenac was administered by 97% of parents on the first postoperative day, decreased via 89, 88, 81, 53, to 9% on the sixth postoperative day and was discontinued thereafter. No postoperative bleeding reported	Children still suffer from significant pain for up to 2 days after adenotonsillectomy with a specific technique
Lee et al. [289]	$N = 116$; 41 ± 27 months (mean ± SD) Total: $n = 300$	Observational, retrospective (chart review)	Fever ≥38.0 °C; emergency department; ~ 1 h	~2 mg/kg, single dose, IM	Average time until antipyresis 69.1 ± 23.8 min. Average temperature reduction after 1 h, 1.1 ± 0.6°C. Infants ≤ 24 months had a more rapid onset of antipyresis compared with children ≥ 60 months (64.5 ± 23.9 vs. 80.4 ± 25.1 min). No allergic reactions or asthma reported	Effective antipyresis was achieved with 2 mg/kg diclofenac IM Infants had a more rapid onset of antipyresis

Table 6 (continued)

Reference	No. of patients exposed to drug; age	Design	Indication, clinical setting, and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Sharif et al. [290]	$N = 40$; 3.17 ± 1.41 years (mean ± SD); range 1–6 years	Double-blind, randomized, controlled (acetaminophen)	Fever > 38°C for < 4 days; 1 h	1 mg/kg, single dose, rectal	Temperature reduction after diclofenac (1.43 ± 0.69 °C) was significantly greater than after acetaminophen (0.65 ± 0.17 °C) 1 h after drug administration ($p < 0.001$) No drug-related allergic reactions	Diclofenac was more effective in fever reduction than acetaminophen
Ketorolac						
Keidan et al. [327]	$N = 57$ Ketorolac group: $n = 25$ (4.3 ± 2.6) years (mean ± SD), range 1.7–10 years Fentanyl group: $N = 32$ (5.6 ± 2.6) years (mean ± SD), range 2–10 years	Prospective, randomized, double-blind	Intraoperative analgesia for ambulatory adenoidectomy and tonsillectomy, follow-up 48 h	1 mg/kg IV, single dose 2 µg/kg IV, single dose	Incidence of postoperative nausea and vomiting was low and equal in both groups (propofol and dexamethasone were used for prophylaxis). Postoperative pain scores were equal at all stages of follow-up. Agitation scores in the Post-Anesthesia Care Unit were significantly higher in the ketorolac group but this had no effect on the late variables of behavior studied	Ketorolac showed no advantage over fentanyl in reducing the incidence of PONV in children undergoing this ambulatory procedure

Table 6 (continued)

Reference	No. of patients exposed to drug; age	Design	Indication, clinical setting, and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Gupta et al. [328]	$N = 70$: 10 months (2.5–174) [median (range)] Ketorolac group: $n = 35$; 23.1 ± 29.1 months (mean ± SD)	Prospective, randomized, controlled (no comparator)	Postoperative pain after congenital heart surgery; inpatients, follow-up length of hospital stay (median 5 days, range 1–49 days)	0.5 mg/kg/dose (max. 15 mg/dose) q6h IV, over up to 48 h	Bleeding complications, measured as chest-tube drainage, wound bleeding and GI bleeding, were low in both groups. In the ketorolac group, the median chest-tube drainage was 13.3 (range 4–22) mL/kg/day. No patients had significant wound bleeding, and 1 (0.03%) patient had gastrointestinal bleeding. In the control group, the median chest-tube drainage was 16.5 (range 3–24) mL/kg/day. One (0.03%) patient had wound bleeding and no patients had gastrointestinal bleeding	Ketorolac can be used to treat pain after congenital heart surgery without an increased risk of bleeding complications
Gupta et al. [329]	$N = 94$; 8.5 ± 6.1 years (mean ± SD) Matched controls: $n = 94$; 6.7 ± 5.6 years (mean ± SD)	Retrospective case-matched study	Postoperative pain after congenital heart surgery; inpatients	A loading dose of 1 mg/kg was used in 40% of patients, then all patients received 0.5 mg/kg/dose q6h IV; over 18–96 h	No (0%) patients in the ketorolac group and four (4.2%) patients in the non-ketorolac group developed postoperative bleeding requiring surgical exploration. The relative risk for postoperative bleeding that required surgical exploration in the ketorolac group compared with the non-ketorolac group was 0.2 (95% CI 0.02–1.67)	The use of ketorolac after congenital heart surgery in infants and children does not significantly increase the risk of bleeding complications requiring surgical exploration. Ketorolac may serve as a well tolerated and effective supplement to narcotic analgesics in congenital heart surgery

Table 6 (continued)

Reference	No. of patients exposed to drug; age	Design	Indication, clinical setting, and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Moffett et al. [146]	$N = 53$; 93.5 ± 58.5 days (mean ± SD); including 11 neonates (<30 days)	Retrospective	Postoperative pain in neonates and infants after congenital heart surgery; inpatients	A loading dose of 0.93 ± 0.14 mg/kg was used in 7 infants (13%), then all infants received a maintenance dose of 0.44 ± 0.09 mg/kg q6h IV (1 infant q8h); mean number of doses per infant: 5.6 ± 3.4 (range 1–13). Ketorolac dosing was initiated on mean postoperative day 2.9 ± 3.4	No clinically significant differences in hematologic indices, also no clinically significant differences in hematologic indices from baseline in the neonatal subgroup. Bleeding events occurred in four infants (1 neonate). The events included epistaxis ($n = 1$), bleeding after nasopharyngeal suctioning ($n = 1$), superficial skin bleeding after removal of temporary pacing wires ($n = 1$), and hematoma of the wrist ($n = 1$). No event required treatment nor resulted in change of clinical status or laboratory parameters	Ketorolac was safely used to treat moderate pain in neonates and infants after cardiac surgery. Therapy with ketorolac caused a minimal increase in serum creatinine and blood urea nitrogen at 48 h after therapy initiation. Ketorolac was not associated with clinically significant bleeding episodes

Table 6 (continued)

Reference	No. of patients exposed to drug; age	Design	Indication, clinical setting, and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Dawkins et al. [100]	$N = 19$; 3.2 ± 1.9 months (mean ± SD) Matched controls: $n = 19$; 2.8 ± 1.6 months (mean ± SD); all patients < 6 months	Retrospective case–control	Postoperative pain after congenital heart surgery; inpatients	Mean dose 0.5 mg/kg (range 0.4–0.63) q6h–q8h IV; mean number of doses per infant 4.5 ± 2.5 (range 2–12). Mean length of therapy was 3.1 ± 1.6 days (range 1–6)	No difference in serum creatinine, blood urea nitrogen, hemoglobin, hematocrit or platelet count. No difference in coadministered analgesic doses of morphine, fentanyl, acetaminophen or ibuprofen. No difference in acid suppressive medications	No statistically significant changes in preoperative vs. post-treatment renal function or hematologic effects. No statistically significant differences for number of postoperative blood transfusions or additional analgesic administration between groups. Intravenous ketorolac appears to be well tolerated when used in infants < 6 months of age with biventricular circulations following cardiothoracic surgery. Ketorolac as used in this study does not decrease the use of standard analgesic therapy

Table 6 (continued)

Reference	No. of patients exposed to drug; age	Design	Indication, clinical setting, and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Kay et al. [330]	$N = 221$; 6.7 ± 4.2 years (mean ± SD) Ketorolac group: $n = 169$: 7.1 ± 4.2 years (mean ± SD) Control group: $n = 52$; 5.5 ± 4.1 years (mean ± SD)	Retrospective	Perioperative pain therapy for operative fracture care, inpatients, but follow-up until fracture healing	Loading dose 0.5–1.0 mg/kg (maximum dose: 30 mg), followed by 0.5 mg/kg/dose q6h during hospital stay	No difference in length of hospital stay (2.5 ± 2.2 days in the ketorolac group and 2.5 ± 1.6 days in the non-ketorolac group). No difference in overall complication rates between the two groups ($p = 0.928$): 3 blood transfusions needed [2 (1.2%) in the ketorolac group and 1 (1.9%) in the non-ketorolac group]. Wound infection rate was comparable in the two groups (1.9% in the non-ketorolac group and 2.3% in the ketorolac group). No cases of delayed or non-union in either group	Perioperative ketorolac use does not increase the risk of complications after operative fracture care in children ($p = 0.928$). No increased risk with regard to infection or wound complications, and there were no cases of delayed union or non-union
Kay et al. [331]	$N = 327$ Ketorolac group: $n = 299$: 8.4 ± 2.3 years (mean ± SD) Control group: $n = 28$; 9.2 ± 4.5 years (mean ± SD)	Retrospective	Perioperative pain therapy for lower extremity osteotomies, inpatients, follow-up minimum 6 months	0.5 mg/kg/dose q6h during hospital stay	Wound complications occurred in 16/327 patients overall (4.9%), including 13/299 (4.3%) in the ketorolac group and 3/28 (10.7%) in the non-ketorolac group ($p = 0.301$). There was no significant difference in estimated blood loss ($p = 0.584$) or the need for blood transfusion ($p = 0.777$) between the two groups	There was no significant difference in the rate of either osseous or soft tissue complications between the two groups. There were no non-unions in either of the groups, and there was also no difference in wound infections between the two groups

Table 6 (continued)

Reference	No. of patients exposed to drug; age	Design	Indication, clinical setting, and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Aldrink et al. [228]	$N = 57$ Bleeding group: $n = 10$; corrected GA 39.4 weeks (mean days of life 20.7) Non-bleeding group: 42 weeks (mean days of life 31.9)	Retrospective	Postoperative pain therapy after neonatal surgery	0.5 mg/kg/dose q6h (2 infants q6h)	Of 57 patients, 10 (17.2%) had a bleeding event. These patients received ketorolac at a mean of 20.7 days of life, with 70% receiving the drug at < 14 days of age, whereas those without a bleeding event received ketorolac at a mean of 31.9 days ($p = 0.04$). Bleeding events correlated with glomerular filtration rate of < 30 mL/min/1.73 m^2 or concomitant medications in all but one patient. 90% of patients with bleeding events had not been enterally fed, compared with 57% of those without bleeding events ($p = 0.07$)	Infants younger than 21 days and < 37 weeks CGA are at significantly increased risk for bleeding events and should not be candidates for ketorolac therapy
Richardson et al. [332]	$N = 1451$; 4.8 years (0–30) [median (range)] Ketorolac group: $n = 955$	Retrospective	Perioperative pain therapy in neurosurgery, inpatients; Follow-up for 30 days or hospital stay, whichever was longer	Not reported	No significant association between clinically significant bleeding events (OR 0.69, 95% CI 0.15–3.1) or radiographic hemorrhage (OR 0.81, 95% CI 0.43–1.51) and the perioperative administration of ketorolac	Short-term ketorolac therapy does not appear to be associated with a statistically significant increase in the risk of bleeding documented on postoperative imaging in pediatric neurosurgical patients and may be considered as part of a perioperative analgesic regimen

RECT rectal, *AE* adverse event, *CI* confidence interval, *CNS* central nervous system, *IQR* interquartile range, *BW* body weight, *IM* intramuscular, *IV* intravenous, *SD* standard deviation, *max.* maximum, *qxh* every *x* hours, *GI* gastrointestinal, *OR* odds ratio, *CI* confidence interval, *GA* gestational age, *CGA* corrected gestational age

other drug classes with more homogenous physicochemical properties.

There are only scarce data regarding NSAID-induced hypersensitivity reactions in children and infants, besides NSAID-induced asthma, but cross-intolerance occurs more frequently than selective hypersensitivity in children [184, 234, 235]. Zambonino et al. found a higher rate of positive drug provocation tests for ibuprofen compared with other analgesic agents in children with a history of NSAID hypersensitivity (percentage positivity: ibuprofen, 53.4%; acetylsalicylic acid, 37%; metamizole, 14%; acetaminophen, 8.2%). There is evidence that cross-intolerance is associated with atopy. Angioedema was the most prevalent symptom in that study.

Hypersensitivity to NSAIDs can be safely diagnosed by drug provocation tests, but different phenotypes that do not fit into the current classification might exist [232, 234, 236, 237].

4.4.2 Asthma

Although NSAID hypersensitivity reactions, including NSAID-exacerbated respiratory disease, have already been discussed in this review, the following paragraph focuses specifically on NSAID-exacerbated asthma because of its relevance and the general prevalence of asthma in childhood.

For ibuprofen, a recent multicenter, prospective, randomized, double-blind, parallel-group trial in young children has shown that there was no difference in the incidence of asthma exacerbations (defined as exacerbations that led to treatment with systemic glucocorticoids) or worse asthma control between patients taking as-needed ibuprofen or as-needed acetaminophen [233, 238]. The 300 patients aged 12–59 months were prediagnosed with mild persistent asthma and were assigned to receive either ibuprofen or acetaminophen for antipyresis or analgesia for a period of 48 weeks. The children in the ibuprofen group had a mean of 0.87 exacerbations (95% CI 0.69–1.10) over 46 weeks of follow-up compared with a mean of 0.81 asthma exacerbations (95% CI 0.65–1.02) in the acetaminophen group (relative rate with acetaminophen vs. ibuprofen 0.94, 95% CI 0.69–1.28; $p = 0.67$). The true relative rate compared with placebo remains unknown, and the possibility that both ibuprofen use and acetaminophen use may also be associated with increases in asthma exacerbation cannot be excluded because the study did not include a placebo group for ethical reasons [239, 240]. However, similar results have been found in earlier studies, such as the Boston University Fever Study, as well as reviews [241, 242].

A nationwide retrospective analysis of Taiwanese pediatric patients comparing children during anti-asthmatic and NSAID therapy (index group, assessed medications: ibuprofen, diclofenac, mefenamic acid, naproxen, acetylsalicylic acid, flurbiprofen, and ketoprofen) with those during anti-asthmatic therapy only suggested a higher risk of hospitalization for asthma exacerbation in the index group (adjusted relative risk [RR] 1.41, 95% CI 1.30–1.53) [243]. A probable correlation was found between short-term use of acetylsalicylic acid, ibuprofen and diclofenac but no association with long-term NSAID use. In the study by Standing et al., diclofenac was not avoided in asthmatic patients and the incidence of diclofenac-induced bronchospasm in asthmatic children was estimated at < 2.7% [244].

Asthma has also been reported as a significant adverse drug reaction in another retrospective study using data gathered through an adverse drug reaction program at an Australian children's hospital; one patient died due to severe exacerbation of asthma during rofecoxib therapy for joint pain [184].

The SOS project, a population-based analysis of NSAID use in children in four European countries (Germany, Italy, The Netherlands, and the UK) using seven databases calculated incidence rates (IRs) for serious adverse events, such as asthma exacerbation, anaphylactic shock, upper gastrointestinal complications, stroke, heart failure, acute renal injury, Reye syndrome, Stevens–Johnson syndrome, acute liver injury, and acute myocardial infarction [6]. The dataset consisted of 7.7 million children up to 18 years of age with 29.6 million person-years (11.5% relating to infants < 2 years of age) of observation. Asthma exacerbation was the serious adverse event with the highest IR of 82/100,000 person-years.

4.4.3 Bacterial Infections

A possible association between ibuprofen and invasive group A streptococcal infections in children with varicella was reported by Lesko et al., but there was a lack of data supporting a causal relationship in a case–control study including 52 patients with invasive group A streptococcal infections [80, 245]. In contrast, Dubos et al. found that persistence or recurrence of fever ≥ 38.5 °C for ≥ 3 days after the beginning of the varicella infection and the use of NSAIDs (not including acetylsalicylic acid) were independent risk factors associated with severe secondary bacterial skin infections (OR 8.5%, 95% CI 2.3–28.1 and OR 4.8%, 95% CI 1.6–14.4) in multivariate analysis of their data [246]. Infants < 2 years of age had a significantly and independently lower risk than the overall population aged up to 9 years. The association of NSAIDs with potential soft tissue infections in children with varicella led to recommendations to avoid NSAIDs in children with varicella [213].

An epidemiological study reported an increased incidence of severe bacterial infections after exposure to NSAIDs for fever, pain, and inflammation, in the center studied [247]. A number or 32 children were admitted

with bacterial infections after NSAID use over the previous 15 days, requiring surgical therapy in seven patients (22%). In cases where causative agents could be identified (56% of cases), these were *Staphylococcus aureus*, group A streptococci, *Streptococcus pneumoniae,* and *Haemophilus influenza* (non-B type). Previously administered NSAIDs included mainly ibuprofen (94%), morniflumate (6%), and combinations of ibuprofen/acetylsalicylic acid and ibuprofen/morniflumate. A 'possible' causality was concluded for previous NSAID use and severe bacterial infections [247].

A more recent case control study (ChANCE – Children, Antibiotic, NSAIDs and Childhood Empyema) also reported an increased risk of empyema associated with exposure to NSAIDs (OR 2.79, 95% CI 1.4–5.58) administered for antipyresis during a viral infection, which was lowered by concomitant antibiotic treatment [248]. While viral infections are a risk factor for bacterial infections, the involvement of NSAIDs in this process still remains to be studied, but suppression of the body's inflammatory response to infection by NSAIDs is plausible [249].

Similar observations have been made in children and adults. A causal relationship of NSAIDs and complicated pneumonia has been suggested based on weak evidence but has not yet been investigated [250–253]. Besides the inhibition of prostaglandin synthesis, experimental data suggest that NSAIDs exert a depressive effect on neutrophil functions (chemotaxis, adhesion, aggregation, degranulation), which would support the theory that based on a previous attenuation of the immune system by viral infections, NSAIDs may cause a certain extent of immune depression that may allow the invasion of pathogens [254]. This would explain that NSAID administration masks the initial symptoms of pneumonia to a certain extent, delaying diagnosis and treatment. Byington et al. hypothesize that NSAIDs interfere with the infection in its initial stages (modification of neutrophil and alveolar macrophage functionality, alteration of inflammatory processes linked to arachidonic acid derivatives) and symptom control by NSAIDs, delaying the diagnosis of empyema [253, 254].

Little et al. reported in two trials that ibuprofen use was associated with an increase in both reconsultations with progression of symptoms and in complications, and with worse control of severe symptoms [255, 256]. The discussion has even come so far as to say that NSAIDs should not be used at all in acute respiratory infections [249].

Le Bourgeois et al. discussed the pathogenesis of empyema and the role of viral infections in this process and concluded that NSAIDs should not be recommended as first-line antipyretic treatment during acute viral infections in children because of their as yet unknown role in the pathogenesis of complicated bacterial infections [248]. Despite this recommendation, NSAIDs account for the most commonly used antipyretics in children worldwide and are partly sold over-the-counter for this indication [1, 3, 4].

As recommended by pediatric practitioners and as stated in the Summary of Product Characteristics, medical advice should be sought in infants aged 3–6 months if symptoms worsen, or not later than 24 h if symptoms persist, and in infants and children older than 6 months of age if symptoms worsen or the drug is required for more than 3 days, as NSAIDs might also alleviate symptoms of bacterial infections, suppress the physiological immune response, and thus delay the diagnosis. Following these recommendations should ensure that relevant bacterial infections should be detected early.

While Le Bourgeois et al. discouraged the use of NSAIDs as first-line antipyretics in infants with acute viral infections, we cannot give a clear recommendation to avoid them in this population. We would like to emphasize rational drug use in infants and to administer antipyretics for the child's comfort only and not to achieve normothermia. We would also draw attention to the recommendation that NSAIDs for antipyresis are indicated for short-term use only.

4.4.4 Vaccinations

Fever is the most common adverse effect of vaccinations in infancy [257]. In contrast to acetaminophen, ibuprofen was shown to not affect the immunogenicity of a 10-valent pneumococcal conjugated vaccine, and could therefore be considered as the primary antipyretic during vaccination courses in infancy [258]. Furthermore, the immune response to an inactivated influenza vaccine was not blunted when infants and children aged 6–47 months received antipyretics (ibuprofen vs. acetaminophen) vs. placebo [259].

4.4.5 Diabetes

The TEDDY (The Environmental Determinants of Diabetes in the Young) study aims at identifying environmental triggers of type 1 diabetes in children who are genetically at risk [260]. Since NSAIDs have been shown to lower blood glucose, markers for islet autoimmunity were assessed in about 8000 infants and children until 6 years of having received antipyretics (acetaminophen/NSAIDs) while < 2.5 years of age [261]. No relevant hazard ratios could be reported for the seroconversion to persistent islet autoimmunity after NSAID use.

5 Discussion of the Specific NSAIDs, and Overall Conclusion

5.1 Ibuprofen and Propionic Acid Derivatives

In summary, most evidence on safety and efficacy is available for ibuprofen (see Table 3). Orally administered

ibuprofen is reliable and well tolerated for up to 3 days in infants aged 3 months and older with a body weight above 5–6 kg when special attention is given to the hydration of the patient [9, 17, 262–280]. One study reported that infants had an increased risk of adverse events when taking oral ibuprofen compared with acetaminophen alone, but very low risks of adverse events were reported overall; this is consistent with our previous findings and several other large studies [272, 281]. Further details on PK data for ibuprofen dosing in infants can be found in previous works [9, 12, 17, 262–280].

Kokki et al. have extensively studied ketoprofen in relation to its PK, efficacy, and safety in infants and children for the treatment of fever, (peri- and postoperative) pain, and inflammatory conditions [22, 25–30, 84]. They report that intravenous ketoprofen was superior to oral ketoprofen in the perioperative setting, while oral ketoprofen has shown efficacy in the treatment of JIA. Reported adverse events are similar to other NSAIDs. In a dose-finding study in febrile children, an oral dose of 0.5 mg/kg was found to achieve sufficient antipyresis [84]. Ketoprofen is approved for use in children in many countries but should not be used in infants younger than 6 months of age [22].

Dexibuprofen has been investigated in ~ 450 Asian children, showing a similar efficacy and safety profile as ibuprofen [282–284]. There is currently no benefit of dexibuprofen over ibuprofen in children due to the limited available data. Therefore, we do not recommend its use in infants until supporting data are available from adult studies that show the superiority of enantio-selective NSAIDs with a favorable safety profile facilitating such studies in children. Data on the safety and efficacy of flurbiprofen in infants and children are scarce. A pediatric case of anaphylaxis has been recently published [285]. One case of psychiatric adverse effects in a 2-year-old infant has also been reported [286]. UK Poison Information Service data report significantly more CNS toxicity with naproxen overdosing when compared with ibuprofen (adjusted OR 3.12) or diclofenac (adjusted OR 2.37) overdosing [287]. Therefore, naproxen is generally not recommended in children but may be used for specific indications, e.g. in PiRD.

5.2 Diclofenac and Acetic Acid Derivatives

An overview on the efficacy and safety of oral and rectal diclofenac is given in Table 6 [42, 244, 288–290]. It was consistently shown that children and infants will not benefit from doses higher than 1 mg/kg [38, 43]. In the study by Standing et al., diclofenac-induced bronchospasm in asthmatic children was shown to be < 2.7%, therefore caution in this population needs to be taken [244]. Vons et al. reported children undergoing adenotonsillectomy experienced significant pain for up to 2 postoperative days when treated with acetaminophen and diclofenac, and no pain after seven days; however, a different technique (adenoidectomy) and analgesic (acetaminophen) was used in the group that reported better pain relief [95]. Another study reported that children undergoing adenoidectomy experienced fewer sequelae compared with adenotonsillectomy [291], therefore the efficacy of diclofenac may not directly be comparable in the previous study, but rather an effect of the type of intervention.

Lee at al. showed that effective antipyresis was achieved with 2 mg/kg diclofenac administered intramuscularly, and that infants < 24 months of age had a more rapid onset of antipyresis compared with children <60 months of age [289]. Rectal diclofenac provided more effective antipyresis compared with rectal acetaminophen in children aged 1–6 years [290] and can be used for children suffering from vomiting or patients being on nihil per os' status [292]. In the postoperative setting, rectal diclofenac allowed earlier solid intake in children aged 3–14 years after tonsillectomy, suggesting an anti-inflammatory effect compared with acetaminophen [288]. A prospective observational study in children focusing on adverse drug reactions after diclofenac suggested that the common adverse drug reactions of diclofenac in children when used for acute pain are similar to those in adults [244].

Ketorolac has recently experienced a renaissance for use in postoperative pain in children, especially in the US, but was withdrawn from some European markets (or recommended dosages had been reduced) in the 1990s due to increased risks of bleeding.

5.3 Fenamates

Mefenamic acid has been reported to exert renal, gastrointestinal, hematologic, and CNS toxicity (especially convulsions for the latter), when overdosed [293, 294]. Recent analyses from national poison information services confirm a higher risk of CNS toxicity when overdosed compared with other NSAIDs [287, 295]. Swiss data report an incidence of seizures after overdosed mefenamic acid in 51/470 patients (10.9%, 95% CI 8.4–14.0%), with a higher incidence in adolescents (23.9%) than in adults (5.7%) [295]. Kamour et al. found a higher adjusted OR for convulsions when overdosing with mefenamic acid (adjusted OR 81.5, 95% CI 27.8–238.8) compared with overdosing with other NSAIDs, in the UK database. About 19.7% (91/461) of patients who had overdosed with mefenamic acid experienced CNS toxicity, with 9.1% (42/461) experiencing seizures [287].

Regarding the safety of niflumic acid, there were reports in the 1990s regarding renal and cutaneous adverse effects [198, 296], and there has been controversy regarding the risk of mucocutaneous reactions after niflumic acid use in children. Menniti-Ippolito et al. reported an (adjusted) OR of 4.9 (95% CI 1.9–12.8) compared with, for example,

acetaminophen in a case–control study of 22 children aged 10 months–10 years exposed to niflumic acid [297]. Based on a retrospective cohort study of 32,150 children aged 0–14 years, Sturkenboom et al. reported an adjusted RR of niflumic acid for severe and mild mucocutaneous reactions of 0.5 (95% CI 0.23–1.27) and 0.9 (95% CI 0.79–1.11), respectively. Younger children aged ≤ 3 years had a slightly higher adjusted RR of 0.7 (95% CI 0.2–2.2) compared with children aged > 3 years (0.2, 95% CI 0.0–1.6). This is particularly interesting as the study also reported that 57% of children receiving niflumic acid were 3 years of age or younger [298]. The studies are summarized in Table 7 [297, 298].

Fenamates are understudied in children regarding their safety, as the use of fenamates in children has declined over the past decades. There have been reports of kidney failure and gastrointestinal, hematologic, and neurologic complications. The most compelling risk is that of CNS toxicity when overdosed compared with other NSAIDs. Therefore, we discourage the use of these drugs as first-line analgesics/antipyretics in the presence of better studied alternatives, such as ibuprofen [198, 294, 299, 300] (Table 8).

5.4 Oxicams and Coxibs

The use of oxicams and coxibs should be reserved for indications in PiRD. Due to safety concerns, parecoxib was not approved for use in the US, but in the European Union, such as etoricoxib. Valdecoxib and rofecoxib were withdrawn from the US market in 2004/2005 due to an increased risk of adverse cardiovascular events.

There are only a few reports on the efficacy and safety of coxibs in children, which are summarized in Table 9. Furthermore, it was reported that rofecoxib and celecoxib were used to regulate urine output in infants with congenital nephrogenic diabetes insipidus [301, 302]. In these cases, COX-2 inhibitor-mediated effects, such as reduction in renal medullary blood flow and reduced GFR, were used to reduce urinary sodium and water excretion.

Based on the available knowledge, we recommend to avoid the use of coxibs in children, if possible, or to limit their use to specific indications (e.g. pediatric inflammatory rheumatological disease) during appropriate safety monitoring.

5.5 Salicylates

Acetylsalicylic acid should not be the first choice in infants except for specific indications, e.g. in children with heart conditions or Kawasaki disease, but not generally as an antipyretic because of the risk of Reye syndrome.

Acetylsalicylic acid is used for pediatric pain or as antiplatelet agent but its use was discouraged due to the risk of Reye syndrome [303], a rare but potentially fatal disease that is associated with the use of acetylsalicylic acid in young children. It is usually diagnosed by exclusion. Based on viral infection, immune-mediated processes are suspected to cause mitochondrial damage, modified by genetic and exogenous factors such as drugs or toxins, leading to the clinical symptoms of hepatopathy and encephalopathy. No causal relationship has been proven for acetylsalicylic acid and Reye syndrome, and only observational studies showed an association between reduced acetylsalicylic acid sales (81 mg tablets) and a decrease in Reye incidence, but it is not clear whether reduced pediatric acetylsalicylic acid use has led to a reduction in Reye syndrome cases [303, 304]. The etiology of Reye syndrome still needs to be elucidated, however there is no increased incidence of Reye syndrome in patients with Kawasaki disease who are taking high-dose acetylsalicylic acid (30–100 mg/kg/day) [304].

The antipyretic efficacy of acetylsalicylic acid was proven in studies in the 1980s but the drug is not preferably used in Western countries for this indication [305, 306].

Acetylsalicylic acid is one of the most frequently used agents for thromboprophylaxis in critically ill children (46% of cases) [152]; however, there was the limitation that only 12.4% of patients in that study received thromboprophylaxis, and only 34.7% of patients who were indicated to receive prophylaxis, based on consensus recommendations. Cyanotic congenital heart disease strongly predicted the administration of thromboprophylaxis (OR 7.35, $p < 0.001$). Thromboprophylaxis was most frequently administered to infants and adolescents.

Acetylsalicylic acid should be continued to be used for pediatric thromboprophylaxis at a dose of 3–5 mg/kg/day when used alone, or 1–3 mg/kg/day when used in combination with other antiplatelet agents, e.g. $P2Y_{12}$ inhibitors such as clopidogrel.

5.6 Sulfoanilides

Nimesulide was studied in children and infants with asthma and fever in relation to its safety and efficacy (see Table 10) [307–310], and was attributed to having at least an equal, or faster and longer-lasting, antipyretic effect compared with acetaminophen, as well as anti-inflammatory properties for pediatric asthma. Adverse effects include those that NSAIDs are known for, but most relevant were reports on nimesulide-induced liver injury, also involving pediatric patients [309, 311, 312]. Consequently, nimesulide was withdrawn from some European markets from the year 2002 onwards, and its use has been restricted in some countries, e.g. in India to patients older than 12 years of age after a controversial discussion [311, 313]. Nimesulide is still available in several countries within the EU and in Russia, as well as Southeast Asian and South American countries, since it is regarded as a particularly valuable and safe option for the treatment of

Table 7 Efficacy and safety of fenamate niflumic acid used in infants and children. Overview of studies published after 2000 [297, 298]

References	No. of patients exposed to drug; age	Design	Indication, clinical setting, and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Niflumic acid						
Menniti-Ippolito et al. [297]	$N = 22$ (15 cases and 7 controls) Cases: 10 months–10 years	Case–control study	Endoscopically confirmed gastroduodenal lesions; neurological disorders (convulsions are included only if not associated with fever); non-infectious mucocutaneous diseases and vasculitis; and thrombocytopenia (< 100,000 platelets) Emergency department	Not evaluated	Stevens–Johnson syndrome, $n = 1$; purpura Schönlein–Henoch, $n = 3$; vasculitis, $n = 7$; urticarial, $n = 3$; exanthematous eruption, $n = 1$. Adjusted OR of niflumic acid for mucocutaneous reactions: 4.9 (95% CI 1.9–12.8)	Niflumic acid bears an increased risk for mucocutaneous reactions and therefore its use should be restricted in children given the availability of safer alternatives (e.g. acetaminophen)
Sturkenboom et al. [298]	$N = 32{,}150$; 0–14 years; age 0–3 years: 57%; 4–6 years: 28.8%; 7–9 years: 9.6%; 10–14 years: 4.6%	Retrospective cohort study	Children receiving NSAIDs for several indications (mainly URTI)	Not evaluated	Adjusted RR of niflumic acid for severe mucocutaneous reactions 0.5 (95% CI 0.23–1.27) and for mild 0.9 (95% CI 0.79–1.11). Adjusted RR by age: children ≤ 3 years: 0.7 (95% CI 0.2–2.2); > 3 years: 0.2 (95% CI 0.0–1.6)	Prescription of niflumic acid was concentrated among children aged 1–6 years. No increased risk of mild or severe mucocutaneous reactions for niflumic acid when compared with other NSAIDs or acetaminophen

OR odds ratio, *CI* confidence interval, *NSAIDs* non-steroidal anti-inflammatory drugs, *URTI* upper respiratory tract infection, *RR* relative risk

Table 8 Efficacy and safety of oxicam meloxicam in infants and children. Overview of studies published after 2000 [63, 126]

References	No. of patients exposed to drug; age	Design	Indication, clinical setting, and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Meloxicam						
Foeldvari et al. [63]	$N = 36$; 8.4 ± 7.3 (mean ± SD); including 9 patients aged 2–6 years ($n = 31$ completed)	Open label, phase I/II	Active JIA (oligo- or polyarticular), follow-up over 4, 12, 52 weeks	0.25 mg/kg once daily PO (suspension)	A response according to *Pediatric Rheumatology International Trials Organisation* outcome criteria was seen at week 4 in 44% of patients, at week 12 in 62%, and at week 52 in 74%. Drug-related adverse events were observed in five patients	Meloxicam suspension 0.25 mg/kg once daily is effective and well tolerated for treating active JIA over 52 weeks
Ruperto et al. [126]	$N = 225$ (all children, including the naproxen group with $n = 78$: 7.5 ± 3.7 years); ($n = 181$ completed)	Randomized, double-blind, multicenter, controlled (naproxen)	Active JIA (oligo- or polyarticular) Follow-up over 2 weeks until week 8, week 12, then every 3 months until 12 months	Naproxen 5 mg/kg twice daily PO (control group)	No statistically significant differences in response rates between groups. No differences in the frequency of adverse events or abnormal laboratory values between groups Response rates according to the American College of Rheumatology Pediatric-30 criteria improved from month 3 to month 12: from 64 to 74% in the naproxen group	In conclusion, the short- and long-term safety and efficacy of meloxicam oral suspension appear to be comparable with the safety and efficacy of naproxen in the treatment of oligo-course and poly-course JIA
	$n = 73$: 8.9 ± 3.8 years (mean ± SD), including 23 children aged ≤6 years			0.125 mg/kg once daily PO	from 63 to 77% in the meloxicam 0.125 mg/kg group	
	$n = 74$: 9.0 ± 3.9 years (mean ± SD), including 20 children aged ≤6 years			0.25 mg/kg PO	from 58 to 76% in the meloxicam 0.25 mg/kg group	

SD standard deviation, *JIA* juvenile idiopathic arthritis, *PO* oral

Table 9 Efficacy and safety of the coxibs celecoxib, parecoxib, and rofecoxib used in infants and children. Overview of studies published after 2000 [72, 124, 333]

References	No. of patients exposed to drug; age	Design	Indication, clinical setting, and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Celecoxib						
Foeldvari et al. [124]	$n = 77$; 10.44 ± 4.09 $n = 82$; 10.16 ± 4.24 years (mean ± SD)	Multicenter, randomized, double-blind, controlled (naproxen), parallel-group, non-inferiority study	JIA; 12 weeks + optional 12 weeks open-label phase	3 mg/kg bid 6 mg/kg bid PO	Both dosages were least as effective as naproxen 7.5 mg/kg bid, with the American College of Rheumatology Pediatric-30 criterion reached by 68.8% (celecoxib 3 mg/kg), 8.5% (celecoxib 6 mg/kg) vs. 67.5% (naproxen) of patients Adverse events related to the study medication: 3 mg/kg: Adverse events in 14.3% of patients; three serious adverse events (3.9%): abdominal pain, acute cytomegalovirus infection, viral infection 6 mg/kg: adverse events in 12.2% of patients; two serious adverse events (2.4%): exacerbations of JRA, asthma; no clinically significant differences in vital signs and laboratory values during the study	Celecoxib is at least as effective as naproxen and well tolerated in patients with JIA
Parecoxib						
Tan et al. [72]	$n = 18$; 9.2 (4.8–15.1) $n = 18$; 9.76 (4.5–14.1) $n = 23$; 9.06 (4.1–14.8) (total $n = 59$); age in years [mean (range)]	Double-blind, randomized	Postoperative pain after tonsillectomy ± adenectomy; day-stay surgery (≥4 h post-surgery)	0.25 mg/kg 1 mg/kg 2 mg/kg IV	Rescue opioid needed by 41/59 children (69.5%). Mean morphine equivalents for the dose groups were 0.13 mg/g, 0.11 mg/kg, and 0.09 mg/kg Adverse events: postoperative vomiting, $n = 2$; late tonsillectomy bleeds, $n = 2$ (in the 0.25 mg/kg group)	Parecoxib reduces morphine requirements after tonsillectomy ± adenectomy, but doses above 1 mg/kg have no additional analgetic effect

Table 9 (continued)

References	No. of patients exposed to drug; age	Design	Indication, clinical setting, and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Rofecoxib						
Pickering et al. [333]	$N = 40$; 7.5 (5–11) years [median (interquartile range)]	Double-blind, randomized, controlled (placebo, ibuprofen)	Postoperative pain after tonsillectomy ± adenectomy; inpatient surgery; 24 h	0.625 mg/kg (max. 25 mg) PO	Supplementary analgesic needed in 68% of patients receiving rofecoxib vs. 43% (ibuprofen) vs. placebo (72%); time to supplementary analgesia 62 (35–278) min, 156 (55–300) min, and 62 (35–250) min for rofecoxib, ibuprofen and placebo, respectively No difference in total analgesic consumption in the first 24 h, incidence of vomiting, need for antiemetic, postoperative hemorrhage. No episodes of bronchospasm, pruritus, or dizziness. One child with mild erythematous, non-itchy rash in the ibuprofen group	Analgesic benefit of adding ibuprofen to standard acetaminophen treatment, but no additional beneficial effect of rofecoxib

SD standard deviation, *JIA* juvenile idiopathic arthritis, *bid* twice daily, *PO* oral, *IV* intravenous

Table 10 Efficacy and safety of nimesulide in infants and children. Overview of studies published after 2000 [307–310]

References	No. of patients exposed to drug; age	Design	Indication, clinical setting, and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Nimesulide						
Lal et al. [309]	$N = 29$; 2.27 (1.20–3.34) years [mean (95% CI)]	Double-blind, randomized, controlled (acetaminophen, ibuprofen/acetaminophen)	Fever > 38.5 °C; inpatient; 5 days	1.5 mg/kg three times daily PO	All drugs caused a significant reduction of temperature but no significant difference in antipyretic effect between studied drugs. Supplemental cold sponges needed in 1.7, 1.0, and 2.7% of patients in the nimesulide, acetaminophen, and ibuprofen/acetaminophen groups, respectively. Increased serum levels of AST (38.23 [95% CI 28.48–47.98] IU/L vs. 57.27 [95% CI 34.02–80.52] IU/L; ns) and ALT (30.29 [95% CI 23.18–37.40] IU/L vs. 64.38 [95% CI 18.95–109.81] IU/L; ns) after nimesulide administration. Serum AST and ALT were twice the normal in 10.7 and 14.3% of patients taking nimesulide, respectively. No serious adverse events	No significant difference in antipyretic effect between drugs Potential hepatotoxicity of nimesulide in children, although serum AST and ALT changes were not significant

Table 10 (continued)

References	No. of patients exposed to drug; age	Design	Indication, clinical setting, and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Kapoor et al. [307]	$N = 47$; 4.9 ± 3.8 years (mean ± SD)	Double-blind, randomized, controlled (acetaminophen)	Fever; inpatient; ≥ 24 h	1.5 mg/kg three times daily PO	Time to reach normal temperature: (8.6 ± 9.2 vs. 13.4 ± 9.9 h for acetaminophen, $p = 0.02$); time to reach lowest temperature in a dosing interval (3.3 ± 1.8 vs. 4.5 ± 3.2 h for acetaminophen, $p = 0.03$) No adverse effects reported; 1 death (due to post measles bronchopneumonia) in the nimesulide group; children needing referral: $n = 4$ for nimesulide and $n = 5$ for acetaminophen	Nimesulide was more effective to reach normal temperature compared with acetaminophen
Harish et al. [308]	$N = 50$; 5.23 (3–12) years [mean (range)]	Double-blind, age-matched, controlled (acetaminophen)	Postoperative pain; day-case surgery; 2 months	5 mg/kg/day for mean 3 days	Mean difference in pain scores after drug administration: 17.42 for nimesulide and 8.75 for acetaminophen ($p = 0.033$). No rescue analgesics needed No complaints of jaundice or gastrointestinal problems at follow-up	Significant efficacy in pain relief compared with acetaminophen
Sethi et al. [310]	$N = 30$; 6.29 ± 0.47 years (mean ± SD)	Double-blind, randomized, placebo controlled	Acute moderate to severe asthma; emergency department; 6 h	1.5 mg/kg single dose PO	Significant difference in overall clinical response at 1, 2, and 6 h after nimesulide vs. placebo No adverse effects reported	Nimesulide may be used in patients with asthma to control inflammation

CI confidence interval, *PO* oral, *AST* aspartate aminotransaminase, *ALT* alanine aminotransaminase, *ns* non-significant

several conditions in adults, when used appropriately [314]. Since better-studied alternatives are available for children, we strongly discourage the use of nimesulide in children and infants.

5.7 Limitations

This review aimed to summarize the current knowledge on the safety and efficacy of NSAIDs in infants. The main limitation of our review is that the discussed studies are heterogeneous in terms of study design, clinical setting, and studied clinical conditions. In some of the mentioned retrospective cohort studies assessing safety, no doses of the administered drugs were reported. Other studies also included young children and school children, therefore the reported data could be skewed towards this population.

5.8 Conclusion

Caution should be exerted when NSAIDs are coadministered with corticosteroids (increased risk of gastrointestinal bleeding) or nephrotoxic drugs (increased risk of renal damage). The immunological effect of NSAIDs still remains unclear regarding their use during viral infections and varicella because of their as yet unknown role in the pathogenesis of complicated bacterial infections. There are conflicting data regarding the risk of postoperative bleeding but, in general, the use of NSAIDs appears to be well tolerated in the pediatric postoperative setting.

6 Conclusion

There has been an increase in knowledge regarding the efficacy and safety of NSAIDs in infants and children over the past 20 years; however, despite NSAIDs being among the most frequently administered drugs in children, they are not among the most studied. Safety and efficacy studies might be conducted within the clinical routine, as well as in infants. Available data sources, such as (electronic) medical records, should be used for safety and efficacy analyses. On a wider level, existing data sources, e.g. adverse drug reaction programs/networks, spontaneous national reporting systems, and electronic medical records, should be assessed with child-specific methods in order to detect safety signals pertinent to certain pediatric age groups or disease entities [6, 315, 316].

To improve NSAID safety in infants, therapy should be initiated with the lowest age-appropriate or weight-based dose. Duration of treatment and drug doses used should be regularly evaluated and maximum dose limits and other recommendations by the manufacturer or expert committees should be followed. Treatment for non-chronic conditions such as fever and acute (postoperative) pain should be kept as short as possible. Patients with chronic conditions should be regularly monitored for NSAID adverse effects.

Declarations

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