

Opinion

Therapeutic Appropriateness of Paracetamol and NSAIDs in Management of Fever and Pain in Pediatric Patients with Comorbidities: An Expert Opinion

Claudia Colomba ¹, Diego Maria Michele Fornasari ^{2,*}, Michele Miraglia del Giudice ³, Andrea Pasini ⁴
and Claudio Romano ⁵

- ¹ Department of Health Promotion, Maternal and Child Health, Internal Medicine and Excellence in Specialized Medicine “G. D’Alessandro”, University of Palermo Piazza delle Cliniche, 2, 90127 Palermo, Italy; claudia.colomba@unipa.it
 - ² Department of Medical Biotechnology and Translational Medicine, Università degli Studi di Milano, Via Vanvitelli 32, 20129 Milan, Italy
 - ³ Department of Woman, Child and of General and Specialized Surgery, University of Campania “Luigi Vanvitelli”, Via Luigi De Crecchio 2, 80138 Naples, Italy; michele.miragliadelgiudice@unicampania.it
 - ⁴ IRCCS University Hospital of Bologna, Via Giuseppe Massarenti, 9, 40138 Bologna, Italy; andrea.pasini@aosp.bo.it
 - ⁵ Unit of Pediatric Gastroenterology and Cystic Fibrosis, Department of Pediatrics, University of Messina, Via Consolare Valeria, 98124 Messina, Italy; romanoc@unime.it
- * Correspondence: diego.fornasari@unimi.it

Abstract

Background. Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are widely used treatments for mild to moderate pain and fever in pediatric patients. Notwithstanding, greater caution and awareness of their distinct safety profiles is warranted, especially in children with comorbidities. **Expert opinion.** Herein, expert opinion is presented on the use of these drugs in this setting. Paracetamol is suggested as first-line treatment for managing fever in pediatric patients. For pain, paracetamol is suggested for acute mild-to-moderate pain, whereas NSAIDs are preferred for pain associated with inflammatory conditions. A fixed-dose combination of paracetamol and ibuprofen may be considered for moderate pain, which allows effective analgesia while potentially reducing the risk of adverse events associated with monotherapy. Based on opinion and clinical experience, suggestions were made for pediatric patients considering a large variety of comorbidities. For example, in patients with infection/influenza, the panel concluded that paracetamol should be preferred over NSAIDs. In pediatric patients with inflammatory bowel disease, it was suggested to avoid long-term or high-dose NSAID treatment, particularly in those with active disease. In the presence of skin and soft tissue infections, it was suggested to limit the use of NSAIDs and prioritize paracetamol as first-line therapy. It was also recommended to exercise caution when using NSAIDs in pediatric patients with diabetes. Lastly, shared therapeutic flowcharts were developed that facilitate the patient journey of pediatric patients with comorbidity and fever or pain, which may help promote therapeutic appropriateness and reduce the risk of adverse events, providing practical guidance for general practitioners and pediatricians.

Keywords: paracetamol; NSAIDs; fever; pain; pediatric; comorbidities



Academic Editor: Jean Jacques Vanden Eynde

Received: 17 April 2026

Revised: 20 July 2026

Accepted: 22 July 2026

Published: 4 August 2026

Copyright: © 2026 by the authors.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and

conditions of the [Creative Commons](https://creativecommons.org/licenses/by/4.0/)

[Attribution \(CC BY\)](https://creativecommons.org/licenses/by/4.0/) license.

1. Introduction

Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used treatments for mild to moderate pain and fever in pediatric patients due to their efficacy, ease of administration, and overall favorable safety profile [1,2]. In the pediatric setting, paracetamol is administered orally at a dose of 15 mg/kg per dose every 6 h for antipyretic purposes. Ibuprofen, the most commonly used NSAID in pediatrics, is typically prescribed orally at a dose of 10 mg/kg per dose every 8 h [1,2]. Paracetamol can be administered since birth, whereas ibuprofen is indicated starting from three months of age (Figure 1) [2].

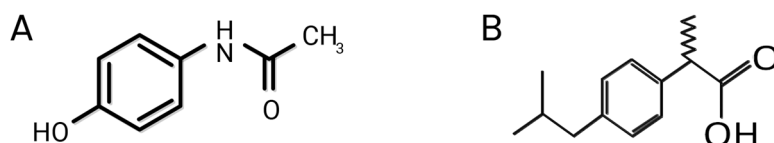


Figure 1. Chemical structures of paracetamol (A) and ibuprofen (B). Adapted from (A) [3] and (B) [4].

Nevertheless, despite national and international guideline recommendations for managing fever, inappropriate prescribing practices and drug combinations are still common, likely driven by “fever phobia”. At the same time, the management of mild to moderate acute pain in children is often suboptimal in most pediatric clinical settings due to fear of overdosing [5]. In one survey, 70% of physicians reported that neither ibuprofen nor paracetamol consistently caused adverse effects [6]. However, ibuprofen was associated with adverse effects in 25% of cases compared to 2% with paracetamol, including allergic reactions, gastrointestinal issues, and liver and renal problems [6]. Indeed, gastrointestinal adverse events are a well-known concern with NSAIDs in children, with risk factors including comorbid conditions, young age, and high-dose or multiple NSAID exposure [7]. Paracetamol, while generally safe, has been linked to hepatotoxicity in cases of dosing errors, such as overdosing or excessively frequent/prolonged administration [8]. The increasing use of drugs such as paracetamol and NSAIDs to treat pain and fever highlights that greater caution and awareness of their distinct safety profiles [9] is warranted, especially in children with comorbidities such as asthma [10].

Based on these premises, a meeting among experts was held with the aim of defining the therapeutic rationale for paracetamol and NSAIDs in pediatric patients with comorbidities and to raise awareness of the different safety profiles of the two drugs among physicians.

The experts were convened by invitation from the main Italian scientific societies relevant to pediatric care, with the aim of ensuring a multidisciplinary perspective. The experts were chosen based on their clinical experience and interest in the treatment of pain and fever in pediatric patients. The participants included a pharmacologist (DF, AISD President), pediatric nephrologist (AP, SInePe Past President), pediatric gastroenterologist (CR, SIGENP President), pediatric immunoallergist (MMG, SIAIP President), and a pediatric infectious disease specialist (CC). Prior to the meeting, the experts reviewed national and international guidelines, systematic reviews, and key studies addressing the safety and efficacy of paracetamol and NSAIDs in children, with a particular focus on populations with comorbidities. In order to facilitate this, a narrative literature search was performed on PubMed using the keywords “paracetamol”, “NSAIDs”, “fever”, “pain”, “pediatric”, and “comorbidities” alone and in various combinations. No time limitations were used, and the last search was done on 30 April 2025. Expert opinion was obtained by informal discussion, and no formal methodology was used. The safety and efficacy profiles of paracetamol and NSAIDs in pediatric patients were reviewed, with particular focus on potential concomitant

conditions and ongoing treatments that could increase the risk of complications when these drugs are used to manage fever or pain. The comorbidities chosen for the present expert review were selected based on those most commonly reported in the literature.

2. Mechanism of Action of Paracetamol

2.1. Analgesic Action

While paracetamol shares antipyretic and analgesic properties with NSAIDs, it has no anti-inflammatory properties. Paracetamol inhibits cyclooxygenase 1 (COX-1) and COX-2 *in vitro*. However, its inhibitory potency is much lower than that of NSAIDs. Regarding COX-1, the IC_{50} of paracetamol in studies on human microsomes is in the range of 200–500 mM, indicating a very weak inhibitory capacity, with negligible effects on the gastric mucosa and platelets [11]. Regarding COX-2, the inhibitory potency is greater, but still lower than that of all commonly used NSAIDs [12]. Furthermore, the action of paracetamol is inhibited in situations of high peroxide concentrations, as typically occurs in inflamed tissues. This would explain the lack of anti-inflammatory effects of paracetamol [13]. Since the effects of NSAIDs on inflammatory pain are primarily linked to their peripheral action on prostaglandin synthesis—which forms the basis of the phenomena of peripheral sensitization of nociceptors and lowering of the pain threshold—the analgesic mechanism of paracetamol has thus been hotly contested. Therefore, it has been hypothesized that the analgesic effect of paracetamol resides in molecular and cellular mechanisms distinct from those of NSAIDs.

Paracetamol easily crosses the blood–brain barrier, distributing evenly throughout the central nervous system (CNS), regardless of dose. Numerous clinical studies have confirmed the presence of paracetamol in cerebrospinal fluid in humans. After deacetylation to *p*-aminophenol in the liver, paracetamol enters the CNS, where it is conjugated with arachidonic acid by the enzyme fatty acid amide hydrolase (FAAH), forming N-arachidonylphenolamine, better known as AM404. The chemical structure of AM404 is very similar to that of anandamide, the most important known endocannabinoid, and this underlies its pharmacological mechanism of action. AM404 is a weak agonist of the CB1 and CB2 cannabinoid receptors, but above all it is an inhibitor of the transporter responsible for the reuptake of anandamide, causing its synaptic and extrasynaptic accumulation and prolonging its pharmacological effects. Therefore, paracetamol, through its metabolite AM404, enhances endocannabinoid tone in numerous areas of the nervous system, with particular reference to the dorsal root ganglia and the posterior horns of the spinal cord, where the metabolite exerts part of its analgesic activity [14]. This production of endocannabinoids induced by paracetamol can also be observed in humans, according to some clinical evidence [15]. The chemical structures of AM404 and anandamide are shown in Figure 2.

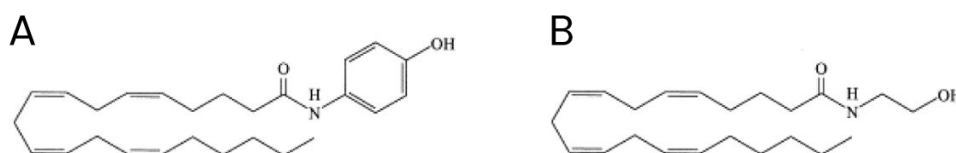


Figure 2. Chemical structures of AM404 (A) and anandamide (B). Adapted from [16].

Additional mechanisms are also responsible for the analgesic effects of AM404, such as the potentiation of the inhibitory descending pathways originating from the periaqueductal gray (PAG) [17], making paracetamol a multifunctional drug.

2.2. Antipyretic Action

The preoptic area of the anterior hypothalamus contains thermoregulatory mechanisms for maintaining normal body temperature and triggering the febrile response. Prostaglandins were among the first mediators studied for their involvement in the febrile response. The vessels and leptomeninges surrounding the preoptic area of the hypothalamus contain COX-2, whose expression is induced in conditions of infection. Prostaglandins, acting on the preoptic area and the ventromedial hypothalamus, would trigger the febrile response. All of this is the basis for the fact that selective or non-selective COX-2 inhibitors have antipyretic action. In hypothalamic endothelial cells that express COX-2, the peroxide content is significantly lower and this would allow paracetamol to inhibit the enzyme, contrary to what happens in inflamed peripheral tissues. Therefore, it is generally accepted that paracetamol exerts its antipyretic action in a manner similar to traditional NSAIDs and COXIBs, that is, through the inhibition of COX-2.

3. Expert Opinion

3.1. General Considerations

Firstly, it should be noted that three selective COX-2 inhibitors are available in Europe—etoricoxib, celecoxib and parecoxib—but none have indications for children. Overall, the panel suggested paracetamol as first-line treatment for managing fever in pediatric patients. For pain management, paracetamol has been recommended for acute mild-to-moderate pain, whereas NSAIDs may be preferred for pain associated with inflammatory conditions [18]. Additionally, a fixed-dose combination (FDC) of paracetamol and ibuprofen may be considered for moderate pain, as this approach allows effective analgesia while potentially reducing the risk of adverse events associated with monotherapy [19]. It is important to note that FDCs are indicated for pain management only and should not be used for fever. A specific formulation for children has been developed as an oral suspension, which offers the widest possible flexibility, since 1 mL contains 32 mg of paracetamol and 9.6 mg of ibuprofen, and can be administered starting from 4.5 mL to 12.5 mL according to the weight of patients, not their age. The ratio between paracetamol and ibuprofen has been optimized. The experts considered that since compliance is an issue, the fixed-dose allows to fully exploit the synergistic effects of the two drugs on pain and inflammation. The panel suggested that physicians should exercise caution when alternating or combining paracetamol and NSAIDs as separate monotherapies [1,20], which differs from using an FDC for moderate pain. However, the potential benefits of an FDC should be tempered with caution considering the evidence base, which is mostly expert opinion with limited clinical studies. Paracetamol is generally considered safe, but as mentioned, has been associated with hepatotoxicity in cases of erroneous dosing and frequent and/or prolonged administration [8]. Chemical structures of etoricoxib, celecoxib, and parecoxib are shown in Figure 3.

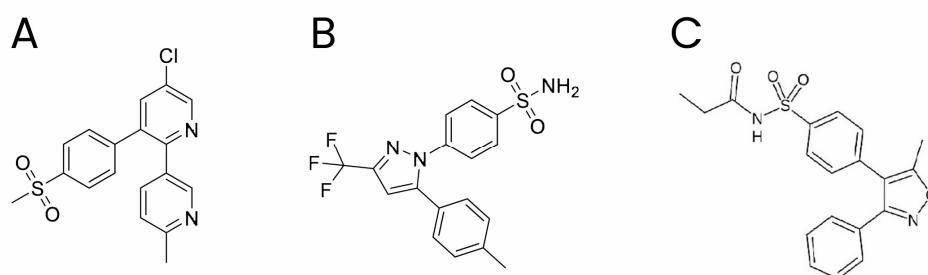


Figure 3. Chemical structures of etoricoxib (A), celecoxib (B), and parecoxib (C). Adapted from (A,B) [21] and (C) [22].

3.2. Additional Considerations from the Panel Discussion

First, children with fevers run the risk of becoming dehydrated, particularly young children who may not be getting enough fluids. In such cases, nephrotoxic damage can be exacerbated by the administration of NSAIDs [23]. This risk may be further increased when NSAIDs are given concomitantly with other nephrotoxic drugs, such as certain antibiotics [24]. Moreover, it is also important for prescribers to know that NSAIDs, together with proton pump inhibitors (PPIs) and some antibiotics (β -lactams, fluoroquinolones, glycopeptides), are among the drugs with the strongest associations with tubulointerstitial nephritis [25]. Regarding fever, the panel discussed its importance both as a pivotal clinical sign to orient diagnosis and as a cardinal protective mechanism that has been preserved throughout evolution [26]. Among the general considerations, it was highlighted that steroids should not be used for management of fever.

3.3. Considerations for Pediatric Patients with Comorbidities

It should firstly be highlighted that the below considerations are based on expert opinion and clinical experience.

3.3.1. Preterm Children, Small for Gestational Age (SGA), Solitary Kidneys, and Congenital Anomalies of the Kidney and Urinary Tract (CAKUT)

Preterm and SGA children often escape the pediatrician's attention, particularly with regard to their renal status. In these patients, the process of glomerulogenesis is not fully completed and may be further impaired by prenatal events (e.g., intrauterine growth restriction) as well as postnatal factors (e.g., extrauterine growth restriction, neonatal acute kidney injury (AKI), or exposure to nephrotoxic drugs in the neonatal intensive care unit) [27]. Children with solitary kidneys or CAKUT may present with normal renal function but have a reduced glomerular endowment (with a single kidney effectively halving the nephron pool) and limited functional reserve [28]. This condition may be overlooked from birth through childhood but can become clinically evident during adolescence, with the onset of hypertension, proteinuria, or declining renal function [29]. For these reasons, the panel agreed to suggest avoiding the use of NSAIDs in ex-preterms, SGA children, and patients with a solitary kidney or CAKUT.

3.3.2. Infection/Influenza

In cases of fever or pain of suspected infectious origin, the panel first emphasized the importance of educating parents to carefully observe and report the characteristics of the fever, particularly its onset and progression. Such information should guide the clinician in the proper prescription of an antipyretic and, when appropriate, antibiotic therapy. In light of the observed greater risk of such complications in cases where NSAIDs are used without concomitant antibiotic coverage, aligning antipyretic and antimicrobial treatment strategies emerges as a necessary objective. An integrated model of stewardship, which recognizes fever as an evolutionarily conserved biological signal and incorporates both microbiological and immune-physiological dimensions, would reduce the risk of diagnostic delays [30]. In this context, the panel therefore suggested that paracetamol should be preferred over NSAIDs, which should be used with caution. In patients with chickenpox the use of NSAIDs should be discouraged due to evidence suggesting a potential increased risk of severe bacterial skin infections, including necrotizing soft tissue infections and invasive group A β -hemolytic streptococcal infections. This risk is documented in multiple reviews and case-control studies [31].

3.3.3. Asthma

Regarding possible interactions between corticosteroids and NSAIDs, these two drug classes have different but partially overlapping mechanisms in modulating inflammation. Corticosteroids act on multiple mechanisms of the inflammatory response. In particular, they induce anti-inflammatory proteins (such as lipocortin/annexin-1), which inhibit phospholipase A₂, the enzyme that releases arachidonic acid from phospholipid membranes [32]. This reduces the availability of substrate for the synthesis of prostaglandins and leukotrienes. Corticosteroids also inhibit the expression of COX-2 (and other pro-inflammatory enzymes) by reducing the transcription of the COX-2 gene and other mediators (e.g., iNOS, TNF- α , interleukins) [33]. They reduce the production of cytokines, chemokines, and adhesion molecules, thereby blocking leukocyte recruitment into inflamed tissues, and decrease the activity of dendritic cells, macrophages, eosinophils, etc. Finally, they induce vasoconstriction (via adrenergic effects) and antagonize vasodilation induced by prostaglandins and bradykinin. In summary, corticosteroids suppress inflammation at various levels: they act “upstream” in the inflammatory cascade, whereas NSAIDs act “downstream”. Both can reduce prostaglandin production, though through distinct mechanisms. For this reason, the main clinical concern with their combined use is the increased risk of serious gastrointestinal lesions (ulcers, bleeding) according to the experts. Caution is also warranted when treating asthmatic children with non-steroidal anti-inflammatory drugs-exacerbated respiratory disease (NERD), which may be present in up to 19% of those with severe asthma [34].

3.3.4. Children Already Treated with NSAIDs and Taking PPIs

Proton pump inhibitors (PPIs) are often co-administered with NSAIDs due to their proven efficacy in preventing NSAID-related gastric complications. However, this common prescribing practice may have potentially adverse effects on the gastrointestinal mucosa, possibly through mechanisms involving gut dysbiosis and increased intestinal permeability [35]. Therefore, the panel does not suggest the routine use of PPIs during short-term NSAID therapy.

3.3.5. Inflammatory Bowel Disease

In children with inflammatory bowel disease, NSAIDs are sometimes prescribed despite the lack of consensus among gastroenterologists. It is well established that NSAIDs can induce colitis, exacerbate pre-existing inflammatory bowel disease, or complicate diverticular disease (e.g., causing perforation or bleeding) [36]. Regarding this clinical condition, the panel suggested avoiding long-term or high-dose NSAID treatment, particularly in patients with active disease, as established by the above-cited observational data.

3.3.6. Skin and Soft Tissue Infections

As highlighted by a French pharmacovigilance study, NSAID prescription, particularly ibuprofen, can worsen bacterial skin or lung infections caused by *Streptococcus pyogenes* [37] or *Pneumococcus*. In general, as mentioned above, the use of NSAIDs may promote or exacerbate skin infections caused by pyogenic bacteria [38]. For this reason, the panel suggested limiting the use of NSAIDs in these cases and prioritizing paracetamol as first-line therapy.

3.3.7. Tonsillitis and Respiratory Tract Infections

As mentioned above, *Streptococcus* and *Staphylococcus* are two particularly insidious pathogens associated with an increased risk of complications when NSAIDs are used [39].

For this reason, the panel suggested limiting the use of NSAIDs also in these cases and prioritizing paracetamol as first-line therapy.

3.3.8. Children Taking Low-Dose Aspirin (ASA)

The interaction between NSAIDs and low-dose ASA varies among the different NSAIDs, but is highly dependent on many factors, including time of administration, dose of aspirin, and both pharmacodynamics and dose of the NSAID [40]. Moreover, real-world evidence of concomitant administration of NSAIDs with low-dose ASA has documented an increased incidence of venous thromboembolism following total joint arthroplasty in adults [40]. Unlike aspirin, NSAIDs are reversible COX1 inhibitors, causing partial inhibition of platelet thromboxane A₂. Paracetamol, however, has not shown this interaction with aspirin and therefore remains a safer option to co-administer in patients taking low-dose aspirin. For example, in children with Kawasaki's disease with coronary artery aneurysms requiring ongoing antiplatelet therapy, NSAIDs should be avoided due to their antagonistic effect on aspirin's platelet inhibition [41]. Therefore, the panel suggested avoiding the use of NSAIDs in patients taking low-dose ASA and instead preferring paracetamol for the treatment of fever and pain.

3.3.9. Preterm Infants Using NSAIDs to Close a Patent Ductus Arteriosus (PDA)

In neonatal intensive care units, ibuprofen still represents the first-line therapy for premature neonates with PDA, being considered more effective than paracetamol [42]. Despite this, the panel suggested preferring paracetamol instead of NSAIDs in patients at higher risk of renal injury.

3.3.10. Recurrent Abdominal Pain

Abdominal pain in children can be associated with reduced intake of food and fluids, exposing the patient to a significant risk of dehydration. Therefore, the panel considered that in cases of acute abdominal pain, the use of paracetamol rather than NSAIDs is more appropriate. In patients with diverticular disease, NSAIDs are particularly risky. In diverticulosis, regular NSAID use increases the risk of diverticular bleeding by damaging the mucosal lining and impairing platelet aggregation. In acute diverticulitis, NSAIDs can worsen inflammation, increase the risk of bowel perforation, and mask symptoms of peritonitis, delaying diagnosis and treatment. Because of these risks, NSAIDs should generally be avoided in anyone with known or suspected diverticular disease, gastrointestinal bleeding, or peptic ulcer disease. In cases of abdominal pain of unclear origin, NSAIDs should also be avoided until a diagnosis is made, since they can mask important symptoms and signs.

3.3.11. Children with Post-Traumatic Pain and Post-Operative Pain

These types of pain often respond poorly to paracetamol, frequently requiring stronger analgesic therapies, including opioids. Therefore, the panel held that in such cases, NSAIDs are more appropriate for managing mild-to-moderate pain secondary to trauma or surgical procedures. As mentioned, NSAIDs may be preferred in situations in which anti-inflammatory properties are needed, such as musculoskeletal pain [43]. Moreover, an NSAID may be more effective than paracetamol in certain conditions and is comparable to acetaminophen-codeine combinations for acute pain management [43]. Indeed, a systematic review found that ibuprofen provided better relief of pain with fewer adverse effects in children with musculoskeletal injuries vs. other analgesics [44]. An NSAID may provide pain relief for up to 24 h compared to around 2 for paracetamol, based on a recent Cochrane review [45]. However, the panel also considered that an FDC could be ideal, as it allows for limiting the adverse effects of NSAIDs while taking advantage of the synergistic action

of the two drugs. Indeed, the combination of the central analgesic effects of paracetamol and the peripheral anti-inflammatory effect of ibuprofen produces a synergistic therapeutic response, rather than an additive one [46]. Clinical evidence shows that the combination provides superior pain relief and a faster onset of action, compared to monotherapy (ibuprofen alone) or combinations containing opioids [47]. Clinical evidence demonstrates that the combination achieves superior pain relief and faster onset compared to monotherapy with either agent [47]. Importantly, a fixed dose formulation can contain a reduced dose (900 mg per day) of the ibuprofen component, with a lower risk of ibuprofen-related adverse events, while conserving full analgesic efficacy, due to synergy. Moreover, an FDC can contain a reduced dose of the ibuprofen component, with a lower risk of ibuprofen-related adverse events, while conserving full analgesic efficacy, due to synergy [48].

3.3.12. Cystitis and Other UTI

In this case, the panel did not suggest treating with NSAIDs since they may increase the risk of serious infections [49].

3.3.13. Fever of Unknown Origin

This is not an acute or urgent situation, and thus NSAIDs are not indicated for this condition.

3.3.14. Diabetes

NSAIDs have been shown to influence glucose metabolism, potentially causing drug-induced hyperinsulinemic hypoglycemia. Therefore, the panel suggested exercising caution when using NSAIDs in pediatric patients with diabetes [50].

3.3.15. Neuromuscular Disorders

Patients with neuromuscular disorders (such as Duchenne muscular dystrophy, spinal muscular atrophy, or other myopathies) may be at increased risk for paracetamol-induced hepatotoxicity even at recommended doses [51]. This risk is attributed to altered pharmacokinetics, reduced muscle mass (and thus reduced glutathione stores), and atypical drug-metabolizing enzyme profiles, which can increase the formation of toxic metabolites like N-acetyl-p-benzoquinone imine and decrease their detoxification. In this context, the panel suggested that paracetamol should be preferred over NSAIDs, but it should be used with caution at lower dosages. The chemical structure of N-acetyl-p-benzoquinone imine is shown in Figure 4.

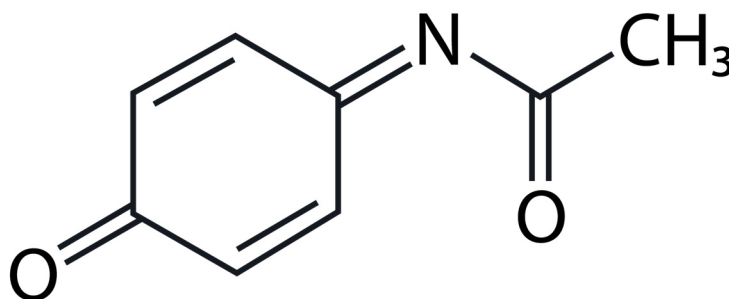


Figure 4. Chemical structure of N-acetyl-p-benzoquinone imine. Adapted from [16].

3.4. Drug–Drug Interactions

Dosages should be carefully adjusted according to the underlying condition, and special consideration should be given to younger children, who generally metabolize drugs faster than adults [52]. Additionally, concomitant use of other drugs that modulate

CYP2C9 activity can alter the pharmacokinetics of NSAIDs, potentially affecting both their efficacy and safety profile [53]. Paracetamol, which is also metabolized in the liver via CYP2E1, may similarly be theoretically subject to these pharmacokinetic-related risks [54]. In addition to mechanisms related to metabolism, NSAIDs in children interact with other classes of drugs, such as anticoagulants, other NSAIDs, corticosteroids, nephrotoxic drugs, antihypertensives, methotrexate, and SSRIs, synergistically increasing side effects in terms of risk of bleeding, renal impairment, and other toxicities [55,56].

3.5. Safety Profiles of Paracetamol and NSAIDs

Most adverse events associated with NSAIDs are attributable to peripheral COX-2 inhibition and can therefore occur even at standard doses. Paracetamol primarily acts centrally by inhibiting hypothalamic COX enzymes, minimally affecting COX-2 pathways. This mechanism contributes to paracetamol's more favorable safety profile compared to NSAIDs, as its adverse effects typically occur only in cases of overdose. Additionally, paracetamol is often underdosed for analgesia and, conversely, overdosed when used to manage fever. An FDC, administered every 8 h, allows for a reduction in the NSAID component's dosage, thereby minimizing the risk of associated adverse effects [1,2].

4. Limitations

Among the limitations of the present expert review and proposal, the potential sponsorship influence and geographic focus on Italy should be mentioned, along with the nature of being an expert opinion. It is thus among the lowest levels in the hierarchy of scientific evidence, as it is not grounded in controlled clinical trials or systematic reviews and may be subject to biases and methodological limitations. Therefore, the conclusions should be interpreted with caution, since they may not reflect the broader scientific consensus or the best available evidence. It is recommended that future guidelines be based on studies of greater methodological rigor to ensure greater reliability.

5. Proposal of Algorithms for Management of Pain and Fever and Conclusions

Based on the premise that ibuprofen can be administered from 3 months of age, the experts proposed algorithms for management of pain and fever in pediatric patients with comorbidities. In children < 3 months of age, paracetamol should be preferred for both fever and pain (Figure 5). In patients > 3 months, paracetamol should be preferred for fever and pain if any of the risk factors shown in the figure are present (Figure 6).

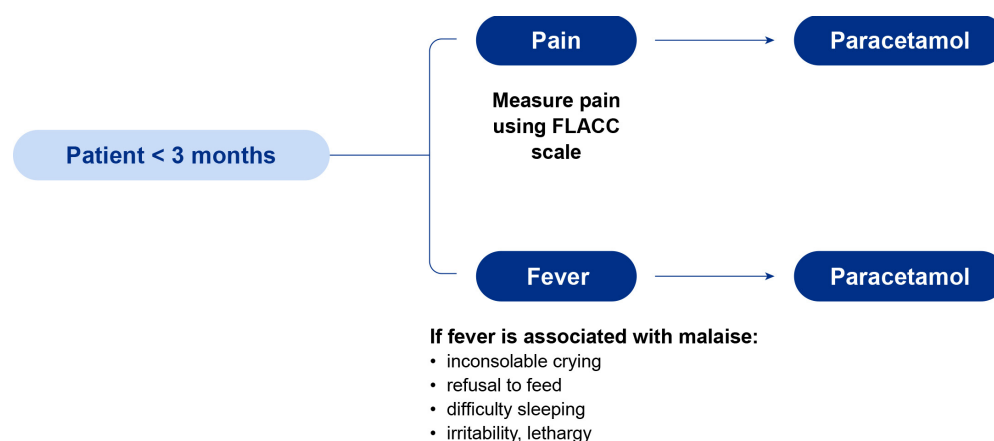


Figure 5. Proposed algorithm for management of pain and fever in pediatric patients < 3 months.

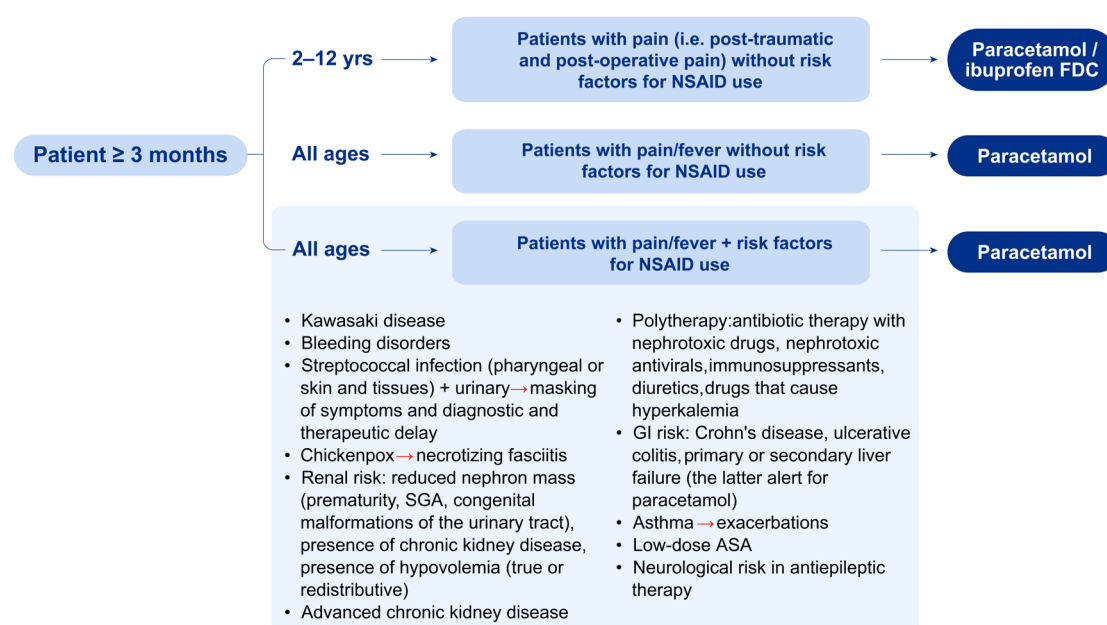


Figure 6. Proposed algorithm for management of pain and fever in pediatric patients ≥ 3 months. SGA, Small for Gestational Age; GI, gastrointestinal; ASA, acetylsalicylic acid; FDC, Fixed Dose Combination.

The shared therapeutic flowchart can help facilitate the patient journey of pediatric patients with comorbidity and fever or pain, which is hoped to promote therapeutic appropriateness and reduce the risk of adverse events.

Author Contributions: All authors equally contributed to conceptualization, methodology, writing—review and editing, and supervision. The authors declare responsibility for making the final decisions on the manuscript's key messages, especially its conclusions. All authors have read and agreed to the published version of the manuscript.

Funding: This project was supported by an unrestricted grant from Angelini SpA, who had no role in the design, execution, interpretation, or writing of the manuscript. Angelini SpA also provided funding for the medical writing service.

Institutional Review Board Statement: Ethical review and approval were waived for this study since no human participant was included herein: the manuscript was drafted according to the clinical experience of each panel member.

Informed Consent Statement: Patient consent was waived because no data regarding a specific patient or clinical case was included in the manuscript. The manuscript itself was drafted according to the clinical experience of each panel member without any referral to a specific clinical case.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: The authors thank Silvia Berlingeri (IQVIA), for providing medical writing support in the preparation of the manuscript.

Conflicts of Interest: Profs Colomba and Miraglia del Giudice declare no conflicts of interest regarding the manuscript. Prof Fornasari declares fees for Advisory Boards participation, as speaker at congresses and as consultant for the following companies: Alfasigma, Angelini, Abiogen, Chiesi, Daiichi-Sankyo, Dompè, Grunentahl, Istituto Gentili, Molteni, Sandoz, SPA, Viatrix, Zambon. Prof Pasini declares no financial relationships or commitments to disclosure in the past 36 months and Prof Romano declares fees from Nestlé Health Science, Alfasigma, Aboca, Sanofi to publish the results. Dr Silvia Berlingeri declares no conflict of interest with the sponsor.

Abbreviations

The following abbreviations are used in this manuscript:

AKI	acute kidney injury
CAKUT	congenital anomalies of the kidney and urinary tract
CNS	central nervous system
COX	cyclooxygenase
FAAH	fatty acid amide hydrolase
FDC	fixed-dose combination
NSAIDs	non-steroidal anti-inflammatory drugs
PAG	periaqueductal gray
PDA	patent ductus arteriosus
PPI	proton pump inhibitors
SGA	Small for gestational age
TRPV1	transient receptor potential vanilloid 1

References

1. NICE. NG143 on Fever in Under 5s: Assessment and Initial Management. Available online: <https://www.nice.org.uk/guidance/ng143> (accessed on 14 January 2025).
2. Chiappini, E.; Venturini, E.; Remaschi, G.; Principi, N.; Longhi, R.; Tovo, P.A.; Becherucci, P.; Bonsignori, F.; Esposito, S.; Festini, F.; et al. 2016 Update of the Italian Pediatric Society Guidelines for Management of Fever in Children. *J. Pediatr.* **2017**, *180*, 177–183.e1. [CrossRef] [PubMed]
3. Scaglione, F. Razionale farmacologico per l'uso clinico del paracetamolo. *Clin. Pract.* **2022**, *1*, 1–8.
4. Bushra, R.; Aslam, N. An overview of clinical pharmacology of Ibuprofen. *Oman Med. J.* **2010**, *25*, 155–1661. [CrossRef] [PubMed]
5. Doria, M.; Careddu, D.; Ceschin, F.; Libranti, M.; Pierattelli, M.; Perelli, V.; Laterza, C.; Chieti, A.; Chiappini, E. Understanding Discomfort in Order to Appropriately Treat Fever. *Int. J. Env. Res. Public Health* **2019**, *16*, 4487. [CrossRef] [PubMed]
6. Chiaretti, A.; Grattagliano, I.; Carlomagno, F.; Magi, M.; Carbone, L.; Zecca, S.; Bondone, C.; Gatto, A.; Di Sarno, L.; Franceschi, F. Management of fever and associated symptoms in children and adults: An Italian national survey. *Emerg. Care J.* **2024**, *20*, 1.
7. Cardile, S.; Martinelli, M.; Barabino, A.; Gandullia, P.; Oliva, S.; Di Nardo, G.; Dall'Oglio, L.; Rea, F.; De'Angelis, G.L.; Bizzarri, B.; et al. Italian survey on non-steroidal anti-inflammatory drugs and gastrointestinal bleeding in children. *World J. Gastroenterol.* **2016**, *22*, 1877–1883. [CrossRef] [PubMed]
8. Rajanayagam, J.; Bishop, J.R.; Lewindon, P.J.; Evans, H.M. Paracetamol-associated acute liver failure in Australian and New Zealand children: High rate of medication errors. *Arch. Dis. Child* **2015**, *100*, 77–80. [CrossRef] [PubMed]
9. Baiardi, P.; Barbieri, I.; Principe, D.; Pietro, P.; Manzoni, P.; Marchetti, F.; Napoleone, E.; Rocchi, F.; Rossi, P.; Rossi, R.; et al. Caution on the use of NSAIDs in children: Recommendations by the Paediatric Working Group of AIFA (Italian Drug Agency). *Med. E Bamb.* **2010**, *29*, 654–656.
10. Hadley, A.; Slaven, J.E.; Krupp, N.L.; Klopfer, K.M. Nonsteroidal anti-inflammatory drug hypersensitivity in a pediatric severe asthmatic population. *Pediatr. Pulmonol.* **2023**, *58*, 2983–2986. [CrossRef] [PubMed]
11. Riendeau, D.; Charleson, S.; Cromlish, W.; Mancini, J.A.; Wong, E.; Guay, J. Comparison of the cyclooxygenase-1 inhibitory properties of nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors, using sensitive microsomal and platelet assays. *Can. J. Physiol. Pharmacol.* **1997**, *75*, 1088–1095. [CrossRef]
12. Simmons, D.L.; Botting, R.M.; Hla, T. Cyclooxygenase isozymes: The biology of prostaglandin synthesis and inhibition. *Pharmacol. Rev.* **2004**, *56*, 387–437. [CrossRef] [PubMed]
13. Bertolini, A.; Ferrari, A.; Ottani, A.; Guerzoni, S.; Tacchi, R.; Leone, S. Paracetamol: New vistas of an old drug. *CNS Drug Rev.* **2006**, *12*, 250–275. [CrossRef] [PubMed]
14. Hogestatt, E.D.; Jonsson, B.A.; Ermund, A.; Andersson, D.A.; Bjork, H.; Alexander, J.P.; Cravatt, B.F.; Basbaum, A.I.; Zygmunt, P.M. Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system. *J. Biol. Chem.* **2005**, *280*, 31405–31412. [CrossRef] [PubMed]
15. Stockler, M.; Vardy, J.; Pillai, A.; Warr, D. Acetaminophen (paracetamol) improves pain and well-being in people with advanced cancer already receiving a strong opioid regimen: A randomized, double-blind, placebo-controlled cross-over trial. *J. Clin. Oncol.* **2004**, *22*, 3389–3394. [CrossRef] [PubMed]
16. Ghanem, C.I.; Perez, M.J.; Manautou, J.E.; Mottino, A.D. Acetaminophen from liver to brain: New insights into drug pharmacological action and toxicity. *Pharmacol. Res.* **2016**, *109*, 119–131. [CrossRef] [PubMed]

17. Barriere, D.A.; Boumezbeur, F.; Dalmann, R.; Cadeddu, R.; Richard, D.; Pinguet, J.; Daulhac, L.; Sarret, P.; Whittingstall, K.; Keller, M.; et al. Paracetamol is a centrally acting analgesic using mechanisms located in the periaqueductal grey. *Br. J. Pharmacol.* **2020**, *177*, 1773–1792. [CrossRef] [PubMed]
18. Doria, M.; Careddu, D.; Iorio, R.; Verrotti, A.; Chiappini, E.; Barbero, G.M.; Ceschin, F.; Dell’Era, L.; Fabiano, V.; Mencacci, M.; et al. Paracetamol and Ibuprofen in the Treatment of Fever and Acute Mild-Moderate Pain in Children: Italian Experts’ Consensus Statements. *Children* **2021**, *8*, 873. [CrossRef] [PubMed]
19. Parri, N.; Silvagni, D.; Chiarugi, A.; Cortis, E.; D’Avino, A.; Lanari, M.; Marchisio, P.G.; Vezzoli, C.; Zampogna, S.; Staiano, A. Paracetamol and ibuprofen combination for the management of acute mild-to-moderate pain in children: Expert consensus using the Nominal Group Technique (NGT). *Ital. J. Pediatr.* **2023**, *49*, 36. [CrossRef] [PubMed]
20. WHO. WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses. 2012. Available online: <https://iris.who.int/handle/10665/44540> (accessed on 22 January 2025).
21. Chahat; Gupta, S.; Joshi, G.; Wahajuddin, M.; Kumar, B. COX-2 inhibitors in inflammation and cancer: Recent developments in medicinal chemistry. *Eur. J. Med. Chem.* **2026**, *310*, 118781. [CrossRef] [PubMed]
22. Li, S.L.; Zhu, Y.L.; Zhu, C.Y.; Li, S.B.; Li, Z.H.; Qiu, X.J. Simultaneous Determination of Parecoxib and Its Metabolite Valdecoxib Concentrations in Beagle Plasma by UPLC-MS/MS and Application for Pharmacokinetics Study. *Drug Des. Dev. Ther.* **2020**, *14*, 1117–1125. [CrossRef] [PubMed]
23. Balestracci, A.; Ezquer, M.; Elmo, M.E.; Molini, A.; Thorel, C.; Torrents, M.; Toledo, I. Ibuprofen-associated acute kidney injury in dehydrated children with acute gastroenteritis. *Pediatr. Nephrol.* **2015**, *30*, 1873–1878. [CrossRef] [PubMed]
24. Patzer, L. Nephrotoxicity as a cause of acute kidney injury in children. *Pediatr. Nephrol.* **2008**, *23*, 2159–2173. [CrossRef] [PubMed]
25. Gerard, A.O.; Merino, D.; Laurain, A.; Cremoni, M.; Andreani, M.; Rocher, F.; Destere, A.; Esnault, V.L.M.; Sicard, A.; Drici, M.D. Drug-Induced Tubulointerstitial Nephritis: Insights from the World Health Organization Safety Database. *Kidney Int. Rep.* **2022**, *7*, 1699–1702. [CrossRef] [PubMed]
26. Evans, S.S.; Repasky, E.A.; Fisher, D.T. Fever and the thermal regulation of immunity: The immune system feels the heat. *Nat. Rev. Immunol.* **2015**, *15*, 335–349. [CrossRef] [PubMed]
27. Vidal, E.; Trevisanuto, D. Born too soon: Lifelong kidney risks and the importance of early intervention. *Nat. Rev. Nephrol.* **2025**, *21*, 151–152. [CrossRef] [PubMed]
28. Murugapopathy, V.; Gupta, I.R. A Primer on Congenital Anomalies of the Kidneys and Urinary Tracts (CAKUT). *Clin. J. Am. Soc. Nephrol.* **2020**, *15*, 723–731. [CrossRef] [PubMed]
29. Ardissino, G.; Testa, S.; Dacco, V.; Paglialonga, F.; Vigano, S.; Felice-Civittillo, C.; Battaglini, F.; Bettinelli, A.; Bordugo, A.; Cecchetti, V.; et al. Puberty is associated with increased deterioration of renal function in patients with CKD: Data from the ItalKid Project. *Arch. Dis. Child* **2012**, *97*, 885–888. [CrossRef] [PubMed]
30. Dik, J.H.; Poelman, R.; Friedrich, A.W.; Niesters, H.G.M.; Rossen, J.W.A.; Sinha, B. Integrated Stewardship Model Comprising Antimicrobial, Infection Prevention, and Diagnostic Stewardship (AID Stewardship). *J. Clin. Microbiol.* **2017**, *55*, 3306–3307. [CrossRef] [PubMed]
31. Stone, K.; Tackley, E.; Weir, S. BET 2: NSAIs and chickenpox. *Emerg. Med. J.* **2018**, *35*, 66–68. [CrossRef] [PubMed]
32. Fauci, A.S. Mechanisms of the immunosuppressive and anti-inflammatory effects of glucocorticosteroids. *J. Immunopharmacol.* **1978**, *1*, 1–25. [CrossRef] [PubMed]
33. Barnes, P.J. Corticosteroid effects on cell signalling. *Eur. Respir. J.* **2006**, *27*, 413–426. [CrossRef] [PubMed]
34. Hadley, A.; Kloepper, K. NSAID-Exacerbated Respiratory Disease in Pediatric Severe Asthmatic Population. *J. Allergy Clin. Immunol.* **2022**, *149*, AB171. [CrossRef]
35. Gwee, K.A.; Goh, V.; Lima, G.; Setia, S. Coprescribing proton-pump inhibitors with nonsteroidal anti-inflammatory drugs: Risks versus benefits. *J. Pain Res.* **2018**, *11*, 361–374. [CrossRef] [PubMed]
36. Hijos-Mallada, G.; Sostres, C.; Gomollon, F. NSAIDs, gastrointestinal toxicity and inflammatory bowel disease. *Gastroenterol. Hepatol.* **2022**, *45*, 215–222. [CrossRef] [PubMed]
37. Jonville-Bera, A.P.; Micallef, J. Deleterious impact of a non-steroidal anti-inflammatory taken for fever or acute pain in case of streptococcal infection. *Therapie* **2025**, *80*, 424–428. [CrossRef] [PubMed]
38. Hamilton, S.M.; Bayer, C.R.; Stevens, D.L.; Lieber, R.L.; Bryant, A.E. Muscle injury, vimentin expression, and nonsteroidal anti-inflammatory drugs predispose to cryptic group A streptococcal necrotizing infection. *J. Infect. Dis.* **2008**, *198*, 1692–1698. [CrossRef] [PubMed]
39. Schummer, W.; Schummer, C. Nonsteroidal anti-inflammatory drugs and streptococcal toxic shock syndrome. *Intensive Care Med.* **2002**, *28*, 1194. [CrossRef] [PubMed]
40. Krauss, E.; Cronin, M.; Dengler, N.; Segal, A. Interaction Between Low-Dose Aspirin and Nonsteroidal Anti-Inflammatory Drugs Can Compromise Aspirin’s Efficacy in Preventing Venous Thrombosis Following Total Joint Arthroplasty. *Clin. Appl. Thromb. Hemost.* **2020**, *26*, 1076029620920373. [CrossRef] [PubMed]

41. Gorelik, M.; Chung, S.A.; Ardalan, K.; Binstadt, B.A.; Friedman, K.; Hayward, K.; Imundo, L.F.; Lapidus, S.K.; Kim, S.; Son, M.B.; et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Kawasaki Disease. *Arthritis Rheumatol.* **2022**, *74*, 586–596. [[CrossRef](#)] [[PubMed](#)]
42. Mitra, S.; de Boode, W.P.; Weisz, D.E.; Shah, P.S. Interventions for patent ductus arteriosus (PDA) in preterm infants: An overview of Cochrane Systematic Reviews. *Cochrane Database Syst. Rev.* **2023**, *4*, CD013588. [[CrossRef](#)] [[PubMed](#)]
43. Poddighe, D.; Brambilla, I.; Licari, A.; Marsegia, G.L. Ibuprofen for Pain Control in Children: New Value for an Old Molecule. *Pediatr. Emerg. Care* **2019**, *35*, 448–453. [[CrossRef](#)] [[PubMed](#)]
44. Jin, J.; Wang, X.; Wang, J.; Wan, Z. Efficacy and safety of ibuprofen in children with musculoskeletal injuries: A systematic review and meta-analysis of randomized controlled trials. *Medicine* **2021**, *100*, e26516. [[CrossRef](#)] [[PubMed](#)]
45. Pessano, S.; Gloeck, N.R.; Tancredi, L.; Ringsten, M.; Hohlfeld, A.; Ebrahim, S.; Albertella, M.; Kredo, T.; Bruschetti, M. Ibuprofen for acute postoperative pain in children. *Cochrane Database Syst. Rev.* **2024**, *1*, CD015432. [[CrossRef](#)] [[PubMed](#)]
46. Derry, C.J.; Derry, S.; Moore, R.A. Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain. *Cochrane Database Syst. Rev.* **2013**, *2013*, CD010210. [[CrossRef](#)] [[PubMed](#)]
47. Coluzzi, F.; Tranquilli Leali, P.; Perugia, D.; Pellegrino, R.; Romualdi, P. The role of a fixed combination of ibuprofen/paracetamol in the management of acute pain: An Italian expert narrative review. *Eur. Rev. Med. Pharmacol. Sci.* **2025**, *29*, 609–619. [[CrossRef](#)] [[PubMed](#)]
48. Moore, R.A.; Derry, S.; Aldington, D.; Wiffen, P.J. Single dose oral analgesics for acute postoperative pain in adults—An overview of Cochrane reviews. *Cochrane Database Syst. Rev.* **2015**, *2015*, CD008659. [[CrossRef](#)] [[PubMed](#)]
49. Stuart, B.; Venekamp, R.; Hounkpatin, H.; Wilding, S.; Moore, M.; Little, P.; Gulliford, M.C. NSAID prescribing and adverse outcomes in common infections: A population-based cohort study. *BMJ Open* **2024**, *14*, e077365. [[CrossRef](#)] [[PubMed](#)]
50. Russom, M.; Yohannes, F.; Tekle, A.; Ghirmay, R. Ibuprofen and risk of hypoglycemia in diabetic and non-diabetic consumers: Analysis of international pharmacovigilance data. *J. Pharmacol. Clin. Toxicol.* **2021**, *9*, 5. [[CrossRef](#)]
51. Naume, M.M.; Zhao, Q.; Haslund-Krog, S.S.; Krag, T.; Winter, B.C.M.; Revsbech, K.L.; Vissing, J.; Holst, H.; Moller, M.H.; Hornsyld, T.M.; et al. Acetaminophen treatment in children and adults with spinal muscular atrophy: A lower tolerance and higher risk of hepatotoxicity. *Neuromuscul. Disord.* **2024**, *34*, 9–18. [[CrossRef](#)] [[PubMed](#)]
52. Batchelor, H.K.; Marriott, J.F. Paediatric pharmacokinetics: Key considerations. *Br. J. Clin. Pharmacol.* **2015**, *79*, 395–404. [[CrossRef](#)] [[PubMed](#)]
53. Kathuria, A.; Roosan, M.; Sharma, A. CYP2C9 Polymorphism and Use of Oral Nonsteroidal Anti-Inflammatory Drugs. U.S. Pharmacist. 2021. Available online: <https://www.uspharmacist.com/article/cyp2c9-polymorphism-and-use-of-oral-nonsteroidal-antiinflammatory-drugs> (accessed on 21 July 2026).
54. Tiwari, V.; Shandily, S.; Albert, J.; Mishra, V.; Dikkatwar, M.; Singh, R.; Sah, S.K.; Chand, S. Insights into medication-induced liver injury: Understanding and management strategies. *Toxicol. Rep.* **2025**, *14*, 101976. [[CrossRef](#)] [[PubMed](#)]
55. Barzaga Arencibia, Z.; Choonara, I. Balancing the risks and benefits of the use of over-the-counter pain medications in children. *Drug Saf.* **2012**, *35*, 1119–1125. [[CrossRef](#)] [[PubMed](#)]
56. Kokki, H. Nonsteroidal anti-inflammatory drugs for postoperative pain: A focus on children. *Paediatr. Drugs* **2003**, *5*, 103–123. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.