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REVIEW

Ibuprofen in the treatment of children's inflammatory pain: a clinical and pharmacological overview

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ABSTRACT

Unlike fever, which is often over-treated especially in children, pain is underestimated and under-treated in pediatric age. The pharmacological agents approved for treating pain in these patients are few, also considering the recent limitation for codeine in children younger than 12 years. Paracetamol and the nonsteroidal anti-inflammatory drug (NSAID) ibuprofen are the most used at this purpose. The aim of this overview was to analyze the therapeutic appropriateness of ibuprofen in children based on its pharmacological properties. This work is a critical review of the pediatric literature over the last 20 years on efficacy and adverse events associated with the use of ibuprofen as analgesic in the pediatric population. Ibuprofen resulted effective in several pain conditions in children such as musculoskeletal pain, ear pain and acute otitis media, toothache and the inflammatory disease of the oral cavity and pharynx. The drug is a reasonable and efficacious alternative in postoperative pain, including tonsillectomy and adenoidectomy. It remains the treatment of choice for pain in chronic inflammatory diseases such as arthritis. Side effects and adverse events associated with ibuprofen are mild. It has the lowest gastrointestinal (GI) toxicity among NSAIDs, although some cases of GI toxicity may occur. Its renal effects are minimal, but dehydration plays an important role in triggering renal damage, so ibuprofen should not be given to patients with vomiting and diarrhea. Ibuprofen showed a good safety profile and provided evidence of effectiveness for mild-moderate pain of different origin in children. In case of fever or pain, the choice about the drug to be used should fall on ibuprofen in a clinical context where there is an inflammatory pathogenesis.

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KEY WORDS: Pain - Ibuprofen - Child.

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Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID). Together with paracetamol, ibuprofen is the recommended antipyretic and analgesic drug used from young age. Its effectiveness to relieve pain and reduce fever discomfort is widely demonstrated by numerous clinical trials. Moreover, because of its favorable clinical safety data, ibuprofen can be already taken by three-months-old newborns.

Pain can be often underestimated and under-treated during young age. Even though a variety of guidelines on pain management are available for pediatricians, their application in daily practice is not yet sufficient. Paracetamol is often preferred over ibuprofen, even though numerous clinical studies recommend both equally, often displaying a better efficacy of the NSAID in the management of pain, characterized with inflammation in children, and with no difference safety-wise.

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The aim of this review is to describe the pharmacological properties of ibuprofen in terms of its efficacy and safety, as well as to underline some pathophysiological aspects in clinical conditions such as fever, pain and inflammation.

Considering the ibuprofen fields of application, its use as an antipyretic in pediatrics will be mentioned, but an in-depth study will be dedicated to clinical conditions characterized by pain and inflammation.

Pharmacodynamic characteristics

Ibuprofen is the first member of the propionic acid derivatives NSAIDs, synthesized in 1969 as a safer alternative to aspirin.[1] Over the years, it became the most used NSAIDs both as prescription drug and as OTC and, regardless the new molecular discoveries, it still remains the most frequently used and most prescribed NSAIDs in both the adult and pediatric population.

Ibuprofen is a stereoisomeric mixture. Half of its composition is made of S(+) enantiomer, that is the pharmacologically active prostaglandin inhibitor, and the other half mass of R(-) ibuprofen, less active as prostaglandin synthesis inhibitor (Figure 1). When taken orally, about 40/50% of R(-) enantiomer is metabolically transformed into the active S(+) form in the intestine and the liver.[2] However the R(-) isomer may have some pharmacological properties that participate especially in its anti-inflammatory properties, and its presence may partially explain the favorable safety profile of the drug.

It is known that the efficacy of NSAIDs results from their ability to inhibit cyclo-oxygenase-1 and cyclo-oxygenase-2 (COX-1 and COX-2) enzymes, which catalyze the conversion of arachidonic acid to prostaglandins. The prostaglandins

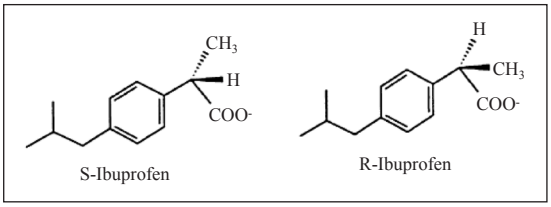

Figure 1.—Molecular structure of ibuprofen enantiomers. S(+) ibuprofen is the enatiomer pharmacologically active as COX inhibitor.

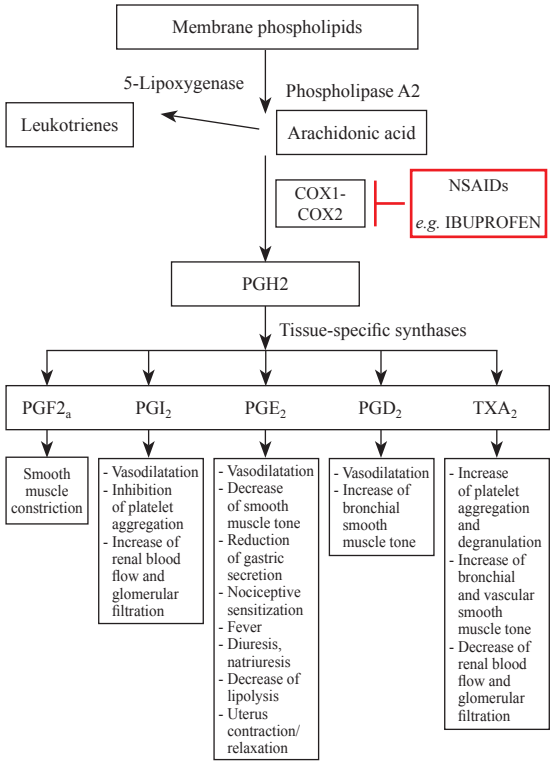

Figure 2.—Schematic description of arachidonic acid metabolism, and site of action of ibuprofen. Only the main activities of the different Prostanoids are reported.
COX: cyclooxygenase; NSAIDs: non steroidal anti-inflammatory drugs; PG: prostaglandin; TXA: thromboxane A.

are then involved in the generation of pain, fever, and inflammation.[1, 3]

Both COX-1 and COX-2 use arachidonic acid that generate prostaglandin H. A number of enzymes further modifies this product to generate bioactive prostanoids such as prostacyclin, thromboxane A_2, and prostaglandins D_2, E_2, and F_2. These prostanoids influence immune, cardiovascular, gastrointestinal, renovascular, central nervous system and reproductive function (Figure 2).[4]

Ibuprofen is a non-selective balanced inhibitor of both the constitutive COX-1 and the inducible COX-2 enzymes.[1, 5] It is generally believed that COX- 1, located in most cells, is responsible for the production of prostanoids (PGs, tromboxaneA2). Prostanoids control many physiological functions, including hemostasis, blood flow, gastric and renal function. COX-2, induced by cytokines, shear stress and cancer promoters, is

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the most important source of prostanoids in inflammation and pain. However, both enzymes contribute to the generation of prostanoids with important functions in normal physiology. *In vitro* and *in vivo* assays have shown that the dose range of ibuprofen currently used creates the inhibition of both COX-1 and COX-2 >80%. This indicates a direct relationship between inhibition of the synthesis of prostanoids and the drug effect.[1, 6]

However, the inhibitory action of ibuprofen towards both cyclooxygenase (COX) isoforms is competitive and reversible. This is relevant also for side effects. Reversibility of inhibition allows recovery of enzymatic activity when ibuprofen is metabolized and eliminated, allowing a fast return to constitutive synthesis of prostaglandins. This will restore their functions in organs such as the stomach and kidneys, thus, it will reduce the potential side effects of ibuprofen.

Pharmacokinetic profile of oral ibuprofen

The pharmacokinetic of ibuprofen has been widely evaluated in adults and it has been relatively well characterized also in the pediatric patients.[1, 7] Table I[1] reports the main PK parameters after oral administration in children. Although the physiological development of infants and children may have a considerable impact on the ADME of drugs, there are no major differences in the pharmacokinetics and antipyretic effects of ibuprofen between children >3 years and adults.[8, 9] Changes in half-life, volume of distribution and clearance of ibuprofen occur progressively (increasing values) from the neonatal stage to children aged 1-3 years, whereupon they assume adult values.

Kauffman *et al.*[10] studied the effect of age on the pharmacokinetics and antipyretic effect of ibuprofen in infants and children and concluded that the pharmacokinetics of ibuprofen was not significantly influenced by the patient's age. Apparently, there are no major differences in the pharmacokinetics and antipyretic effects of ibuprofen between children and adults.

When given orally, ibuprofen is well absorbed from the upper part of the gastrointestinal (GI) tract and peak plasma levels can be reached quickly, within an hour in children with an empty stomach (45 minutes). If ibuprofen is taken after meals, the absorption is slower and variable, and the peak of plasma concentration is achieved between 1 and 2 hours. Recent researches suggest that faster absorption with higher and earlier peak concentrations may produce better symptom relief. Therefore, it is important to rethink about taking ibuprofen with food, in order to reduce the risk of gastric irritation and erosion.[11]

Ibuprofen is extensively (>98%) bound to whole human plasma and purified albumin at therapeutic concentrations. The drug has a relative short plasma half-life (t1/2 of approximately 2 hours) that has been suggested as one of the reason for relative lower risk of GI events than with other NSAIDs.[1]

Elimination half-lives are longer in newborns than in children.[12] In infants younger than 6 months of age it has been reported an altered conversion of R- to S+, as demonstrated by the lower S+ levels measured in comparison to adults.[13] However, a recent review by Ziesenitz[14] assessed the safety and efficacy just in a pediatric population <6 months of age and concluded that, despite some differences in pharmacokinetic, the drug can be safely administered if dosed considering the body weight.[14]

The metabolism of ibuprofen is mostly accomplished through P450 cytochrome enzymatic complex (Cyp2C8, Cyp2C9 and Cyp2C19), as well as with a conjugation with glucuronic acid. The metabolites are then cleared through the kidney within 24 hours after the last dose[1, 15] None of the metabolites have any pharmacological effect, nor have been found being toxic. This indicates the absence of the risk of active metabolite accumulation.

A key pharmacokinetic feature about the anal-

TABLE I.—*Pharmacokinetic parameters of oral ibuprofen in children (>6 months of age).*[1]

T1/2 (hours)	0.9-2.3
C_{max} (mg/mL^{-1}) of (10 mg/kg)	44
T_{max} (hours)	1-2
V/F (L/kg)	0.16-0.22
Protein binding	99%
Metabolism	Cyp450 2C9, 2C8, 2C19

T1/2: half-life; C_{max}: maximum concentration; T_{max}: time to C_{max}; V/F: apparent volume of distribution; CYP450: cytochrome P450.

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gesic and antipyretic actions of ibuprofen is that the drug has the ability to penetrate the CNS and is present in free (*i.e.* non-protein bound) concentrations in the CSF.[16]

Safety

Gastrointestinal tolerability

In the stomach, PGE2 and PGI increase mucus secretion (cytoprotection), they reduce acid secretion and pepsin content, and they enhance mucosal blood flow. PGE2 also inhibit gastric damage caused by ulcerogenic agents and promote healing of gastric and duodenal ulcers. COX-1 is the dominant source of cytoprotective PGs under physiological condition, and NSAIDs that block this isoform may induce a dose-related gastrointestinal toxicity.[17] Selective COX-2 inhibitors are less at risk of GI adverse effects, although an important role of COX-2 in gastric healing has been demonstrated.[17]

Another aspect that is often considered when administering NSAIDs is also local irritation from contact of orally administered NSAIDs with the gastric mucosa. However, evidences suggest that the contribution of topical effects to the overall risk is minimal.[11]

This aspect is relevant since it shows that there is no indication of the assumption of ibuprofen with food. In fact, the absorption of the drug is significantly slowed in the presence of food delaying the onset of the effect.[18]

Epidemiological studies and controlled clinical trials in the adult population have demonstrated that ibuprofen is among the NSAIDs associated with the lowest risk of severe gastrointestinal adverse events.[19] The short plasma elimination half-life of ibuprofen together with the competitive-reversible COX inhibition may contribute to the low risk for GI injuries, since the ranking of GI complications of NSAIDS was directly related to the plasma elimination half time.[20-22] Moreover, one of the reasons for low gastro-ulcerogenicity may relate to the competition of the inactive R(-) isomer with the active S(+) enantiomer for the active site of COX-1 diminishing the inhibition of PG synthesis in the stomach and gut mucosa, before hepatic transformation into the active isomer. The risk of ibuprofen-induced gastrointestinal bleeding is higher in patients who take more than one type of NSAID simultaneously (because of a synergistic effect) and/or platelet antiaggregants/anticoagulants.[23, 24] Other predisposing factors are a positive history of peptic ulcer or gastrointestinal bleeding, *Helicobacter pylori* infection, diverticulosis or chronic inflammatory bowel disease.[21, 25] In patients with a history of chronic inflammatory bowel disease such as Crohn's disease or ulcerative colitis, the use of ibuprofen must be carefully evaluated.[21]

Renal effects

The NSAIDS have little effect on the renal function and blood pressure in healthy pediatrics and adults because of the redundancy of systems that regulate kidney physiology. COX-2 derived PGE2 and PGI increase medullary blood flow and inhibit tubular Na reabsorption. Cortical COX2-derived PGE2 and PGI 2 increase renal blood flow and glomerular filtration through local vasodilator effects as part of tubuloglomerular feedback mechanisms that control renin release. However, in situations that challenge the regulatory system, such as dehydration, hypovolemia, chronic kidney disease or other states of activation of the renin-angiotensin system regulation of renal functions by PG formation become crucial.[26, 27]

Asthma

Aspirin-induced asthma (AIA) is a well-recognized and distinct clinical syndrome of asthma and rhinitis affecting up to 5% of asthmatic children aged 10 years and older, peaking around the third decade of life. Symptoms of asthma and rhinitis occur about 30 min to 3 h after ingestion of aspirin or other NSAIDs.[28] Although the name would suggest a direct link solely to aspirin exposure, there is cross sensitivity to all classes of NSAIDs, which may be relevant to OTC users who suffer from asthma and those who prescribe it to them.[29]

The underlying pathophysiologic basis of AIA has been proposed to be the inhibitory effect of aspirin on the COX pathway of arachidonic acid metabolism. By inhibiting the COX pathway,

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aspirin alters the balance between lipoxygenase and COX activity in favor of lipoxygenase activity. This indirectly causes an increase in the production of leukotrienes and subsequent bronchoconstriction.[29]

Hepatotoxicity

One of the main concerns with regard to paracetamol use is hepatotoxicity due to overdose. On the other hand, large pediatric studies have not revealed significant adverse hepatic effects of ibuprofen.[1, 30]

Efficacy

Fever

The hypothalamus regulates the set point at which body temperature is maintained. This set point is elevated in fever, resulting from infection, tissue damage inflammation, graft rejection or cancer. All these conditions enhance formation of cytokines, such as IL-beta, IL-6, TNF and interferons which act as endogenous pyrogens. The initial phase of the thermoregulatory response to such pyrogens may be mediated by the release of ceramide compounds in the preoptic area of the hypothalamus. The second phase is mediated by induction of COX-2 and formation of PGE_2. PGE_2 can cross the blood bran barrier and act on specific receptors (EP_3 and EP_1) on thermosensitive neurons. This triggers the hypothalamus to elevate temperature both increasing heat generation (*i.e.* inducing shivering) and a decrease in heat loss.[31]

Inflammation and pain

Inflammation is a physiological response to tissue injury and infection. Within minutes of tissue injury and infection plasma proteins mediate vasodilation and vascular permeability. Vasodilation increases blood flow to the damaged area resulting in reddening and heating. Fluid leakage from the blood vessels into the tissue results in swelling. Within a few hours leucocytes arrive at the site of injury. They adhere to activated endothelial cells in the inflamed region and pass into the tissue. The leukocytes phagocyte the pathogens and release soluble mediators, cytokines, prostaglandins, leukotrienes that further contribute to the inflammatory response and recruitment of other effector cells. Prostanoids biosynthesis by COX-2 is significantly increased in inflamed tissue. PGE_2 and prostacyclin (PGI2) are the primary prostanoids that mediate inflammation. They enhance leucocyte chemotaxis and endothelial adhesion.[32]

Acute inflammation provides protection by restricting the damage to the localized tissue and initiating the process of wound repair. It displays a rapid onset and resolves relatively quickly. However, in some situations and diseases, (hypersensitivity, autoimmune diseases, chronic inflammation) it may become chronic, exaggerated and with no apparent benefit, leading to progressive tissue destruction.

Acute pain associated with tissue injury is detected by nociceptors on small myelinated A delta fibers, whereas diffuse dull pain is transmitted by a second set of neurons, very small unmyelinated C fibers. These fibers are nociceptors that respond to strong mechanical and chemical stimulation and are cold/heat sensitive. These nociceptors are activated by numerous chemicals released at the site of cell injury and inflammation. These include peptides (*e.g.*, cholecystokinin, bradykinin, substance P, CGRP, VIP, somatostatin), amines (*e.g.*, histamine or serotonin), and excitatory amino acids (*e.g.*, glutamate or aspartate). Inflammatory mediators such as prostaglandin enhance the sensitivity of receptors to tissue damage and ultimately can result in more intense pain sensation. Pain messages are transmitted along the sensory nerves, reaching the dorsal horn of the CNS. Excitation of nociceptive sensory neurons causes neurotransmitter release (glutamate and Substance P) from central terminals in the spinal cord. The activation is then relayed up the spinal cord and registered in the pain-sensing areas of the thalamus. It is then modified in the rostral ventromedial medulla (RVM) and translated in the cerebral cortex into a conscious feeling.

Pain messages are also suppressed by a descending system of neurons that originate in the gray matter of the midbrain. Noradrenaline, serotonin and opioid peptides are the main neu-

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rotransmitters of the inhibitory descending pathways. Aberrant expression of ion channels, receptors, and regulatory proteins can contribute to abnormal pain signaling.

Following persistent tissue injury or inflammation, the sensory nervous system undergoes various adaptive changes that result in pain hypersensitivity. In chronic pain such changes in sensitivity can become persistent, such that pain occurs spontaneously, or non-noxious sensory stimuli start to produce pain (called allodynia), or the pain response to a nociceptive stimulus is amplified (hyper-algesia). The sensitization occurring in chronic pain involves plasticity changes of neurons located in both the peripheral and central nervous systems (CNS).[33]

Efficacy and safety of ibuprofen in pediatrics

Ibuprofen in pediatric fever management

Fever is an adaptive physiological reaction. The increase in body temperature is a response to exogenous and endogenous pyrogens, and it is considered useful during infectious, inflammatory and neoplastic diseases as it improves its response. Although fever is a common clinical sign in pediatric age and its degree does not directly correlate with the clinical severity and/or the relevance of the causative etiology, this is relevant to caregivers, called as fever phobia (over 30% of requests for child medical examinations are attributable to fever). For this reason, in the first years of life, the use of drugs is constant in case of pyrexia even if guidelines state that antipyretics should be only used in order to alleviate the feeling of malaise (understood as distress/discomfort) in young patients.[34]

The only recommended pediatric antipyretics are paracetamol and ibuprofen. Acetylsalicylic acid is not indicated for the risk of Reye's Syndrome (serious, potentially fatal condition characterized by encephalopathy and liver disease) and corticosteroids should not be used as antipyretics for the high cost-benefit ratio, the possibility of side effects and the risk of masking underlying infectious, inflammatory or neoplastic diseases, delaying the diagnosis.

As antipyretic ibuprofen has shown rapidity of action (acts in just 15 minutes), duration of the result up to 8 hours and effectiveness in the relief of malaise derived from the body's temperature rise, especially in the first 24 hours.[35, 36]

Ibuprofen as analgesic

Acute pain is a frequent symptom during pediatric illnesses. Children are particularly susceptible to suboptimal pain management. Untreated pain in childhood has been reported to lead to short-term problems such as slower healing and to long-term issues such as anxiety, hyperesthesia and fear of medical care.[37-39] Pain in children is often under-diagnosticated and then undertreated in relation to challenges in its evaluation and fear of using relieving drugs. This is true also for ibuprofen in which, for example, as shown by various data, under-dosage is frequent.

The analgesic efficacy of NSAIDs depends both on their anti-inflammatory activity as well as their ability to prevent/reverse peripheral sensitization. Nociceptors are specialized peripheral terminals of primary afferent fibers that can be activated by various stimuli such as heat, pressure, acid. Prostanoids, such as PGe2 and PGI2, released by a variety of non-neuronal cells during tissue injury and inflammation, reduce the thresholds of stimulation of nociceptors, causing peripheral sensitization. Reversal of peripheral sensitization induced by inflammatory mediators represents the basis of peripheral component of the analgesic effects of NSAIDS. Therefore, ibuprofen can act immediately reducing peripheral nociceptor sensitization and starting to decrease the inflammatory reaction that would lead to further pain.[40]

Moreover, it has been suggested a central role for COX-1 and COX-2 in nociception transmission also in the spinal cord.

The medications used for the treatment of acute pain in children are divided into opioids, to be reserved for cases of moderate-severe pain, and not opioids (paracetamol and NSAIDs), for mild-moderate pain. The therapeutic decision must consider the duration of pain (acute or chronic, episodic or recurrent), its pathophysiology (nociceptive, neuropathic, psychogenic, mixed), the associated clinical conditions (de-

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ficiency of metabolization or elimination). The expected duration and adaptation properties of the child and the family to the prescribed therapy are different variables to be taken into consideration. The route of administration should be as simple and painless as possible (the oral route is always the first recommended choice in pediatric age). An important treatment principle is to limit as much as possible the occurrence of predictable pain, administering, in cases that require it, analgesics at fixed time. A pain-relieving plan should be arranged, including therapy at regular intervals, which will be established according to the intensity of the discomfort and the length of the pain relieving impact of the medication utilized, and one based on the use of reinforcement or rescue doses.[41]

The use of ibuprofen for the pain control in pediatric age is increasing, also considering the growing evidence of potential adverse events associated to the use of opioids in children (sedation, risk of respiratory depression, nausea and vomiting, constipation), especially if "rapid metabolizers." The European Medicine Agency (EMA), in fact, has limited the use of codeine to children older than 12 years, due to reported cases of obstructive sleep apnea in children after tonsillectomy. Moreover, a recent warning of FDA recommended that codeine should not be used in adolescents aged 12–18 who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems.

The most common clinical settings of acute pain in children are sore throat, ear pain, headache, toothache, post-traumatic musculoskeletal pain, postoperative pain and arthritis. Ibuprofen is the most studied NSAID in the management of acute pain in children; in general, it showed a good safety profile and provided evidence of effectiveness (Table II).[37, 38, 42-65] In most cases it has been reported to be at least as effective as paracetamol or even more efficacious, especially when a sustained inflammatory component is present. We must in fact remind that paracetamol does not exert any anti-inflammatory action.[38] Moreover, the systematic review by Hartling *et al.*,[66] that assessed the safety profiles of three groups of oral medications, paracetamol, nonsteroidal anti-inflammatory drugs, and opioids, to manage acute nonsurgical pain in children (<18 years) treated in ambulatory settings concluded that ibuprofen and paracetamol had similar reported mild adverse effects.

TABLE II.—*Effectiveness of ibuprofen as analgesic in pediatric age.*

Musculoskeletal pain	Poonai *et al.*,[37] 2014 Shepherd *et al.*,[42] 2009 Clark *et al.*,[43] 2007
Ear pain and acute otitis media (AOM)	Sjoukes *et al.*,[44] 2016 Bertin *et al.*,[45] 1996
Sore throat and pharyngotonsillitis	Schlachtel *et al.*,[46] 1993 Bertin *et al.*,[47] 1991
Headache	Richer *et al.*,[48] 2016 Hämäläinen *et al.*,[49] 1997
Toothache and dental procedures	Ashley *et al.*,[50] 2016 Bradley *et al.*,[51] 2007 Moore *et al.*,[52] 1985
Post-surgical pain	Poonai *et al.*,[53] 2017 Kelly *et al.*,[54] 2015 Moss *et al.*,[55] 2014 Merry *et al.*,[56] 2013 Stewart *et al.*,[57] 2012 Kokki,[58] 2003
Arthritis and other rheumatic diseases	Kermond *et al.*,[59] 2002 Hollingworth,[60] 1993 Giannini *et al.*,[61] 1990 Steans *et al.*,[62] 1990
Osteochondrosis	Weiser,[63] 2012
Growing pains	Lehman,[64] 2017

Although other NSAIDs are also indicated in children, ibuprofen is the only one that can be used in 3-month old infants because of its efficacy and safety profile (*e.g.* ketoprofen over 6-years old children).

The recommended dosage of ibuprofen administered orally for acute pain, is 10 mg/kg every 6 to 8 hours and cumulative daily dose should not exceed 30 mg/kg.

Musculoskeletal pain

Acute musculoskeletal traumatic injuries, including fractures, bruises, and sprains are among the most frequent causes of admission of children to Emergency Departments.

In children ibuprofen must be considered as very beneficial in the management of post-traumatic musculoskeletal pain.

Clark *et al.*[43] compared single oral doses of

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paracetamol (15 mg/kg), ibuprofen (10 mg/kg), and codeine (1 mg/kg) administered to 336 children 6 to 17 years old with pain from a musculoskeletal injury (to extremities, neck, and back) that occurred in the preceding 48 hours before presentation in an emergency department. Patients in the ibuprofen group had a significantly better improvement in pain score than those in the codeine and paracetamol groups at 60 minutes. At 30 minutes, however, there was no significant difference among the 3 groups.

In addition, a better pain relief was seen among children with fracture (54% of cases), perhaps to be ascribed to the anti-inflammatory effects of ibuprofen.

Poonai *et al.*[37] randomized in double blindness 134 children aged 5-17 years who presented to the pediatric emergency department (ED) with an uncomplicated (nonoperative) extremity fracture to receive orally either morphine (0.5 mg/kg) or ibuprofen (10 mg/kg) for 24 hours after discharge. Both drugs resulted in improved pain scores with no significant difference in analgesic efficacy. However, the opioid was associated with a greater frequency of adverse effects.

Shepherd *et al.*[42] conducted a prospective, randomized controlled study in a children's ED. Ninety-four children aged 5-14 years with an acute limb fracture were randomized to be prescribed paracetamol 15 mg/kg/dose every 4 h or ibuprofen 10 mg/kg/dose every 8 h. Among the 72 children who completed the study, the two drugs showed to be equally effective in child-reported pain and parent-reported sleep quality.

To determine if exposure to ibuprofen is associated with an increased risk of bone healing complications in children with fractures DePeter *et al.*[67] performed a retrospective study of children aged 6 months to 17 years who presented to the pediatric emergency department (PED) with a limb fracture. Of the 808 patients included in the final analysis, 338 (42%) were exposed to ibuprofen. There was no significant association between ibuprofen exposure and the development of a bone healing complication despite adjustment for potential confounders.

Ibuprofen should be the drug of choice for analgesia in children with uncomplicated extremity fractures.

Ear pain and acute otitis media

Ibuprofen is commonly used to control pediatric ear pain. According to the national and international guidelines[68, 69] during an episode of acute otitis media (AOM) is possible postpone antimicrobial therapy of 48-72 hours, starting instead immediately an analgesic treatment, also considering that antibiotic treatment does not provide symptomatic relief in the first 24 h. Children older than 2 years with mono- or bilateral AOM and without severe symptomatology, or those between the ages of 6 months and 2 years with a monolateral and non-serious form, in fact, can be managed with watchful waiting, if approved by the parents and in the case in which the possibility of follow-up is guaranteed. This approach contributes to decrease costs and side effects of antimicrobial treatment and to reduce bacterial resistance from antibiotics.[70, 71]

Bertin *et al.*[45] enrolled 219 children (age 1-6.75 years) with otoscopically proven AOM, either unilateral or bilateral, in a DB-RCT. They were randomized into three parallel oral treatment groups. Children received for 48 h ibuprofen, acetaminophen and placebo, respectively. The authors demonstrated that ibuprofen and acetaminophen determined the same relief of ear pain.

These data were confirmed by a recent Cochrane systematic review of literature that included randomized controlled trials (RCTs) comparing the effectiveness of paracetamol or NSAIDs, alone or combined, for pain relief in children with AOM.[44] Using the GRADE approach to rate the overall quality of evidence, the review showed the equivalence between paracetamol and ibuprofen, for short term use, in the control of ear pain at 24 and 48 hours with no differences regarding the adverse events.

Some data on experimental animals would suggest a better outcome of the AOM caused by *Streptococcus pyogenes* when ibuprofen is associated to antimicrobial treatment. This observation seems to be reasonable, considering that damage related to this bacterium is mostly caused by elicitation in the production by human peripheral blood mononuclear cells of substantial amounts of Th1-derived proinflammatory cytokines. However, this conclusion must to be demonstrated by clinical trials.

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Sore throat and pharyngotonsillitis

Appropriate analgesic and antipyretic treatment (with ibuprofen or paracetamol) is recommended by guidelines for the relief of pain or fever associated with discomfort in children with acute pharyngotonsillitis.[72] Two double-blind, randomized clinical trials (DB-RCTs)[46, 47] found that paracetamol and ibuprofen were to be equally effective in treatment of symptoms of tonsillitis and pharyngitis in children. This data were confirmed by a recent meta-analysis assessing safety and efficacy of ibuprofen and paracetamol in pediatric patients with acute pharyngotonsillitis.

In cases of greater inflammatory component, as in exudative pharyngotonsillitis or when lymphadenitis is associated, ibuprofen should be preferred due to its anti-inflammatory properties.

Headache

In childhood, paracetamol and ibuprofen are the most used drugs for the treatment of headache during the acute phase. Several studies have shown the efficacy of ibuprofen in providing pain relief within 2 hours from administration to children and adolescents that complain headache.

Eighty-eight children with migraine, aged 4.0 to 15.8 years, were enrolled in a double-blind crossover study by Hämäläinen *et al.*[49] Three attacks per child were randomly treated with single oral doses of 15 mg/kg paracetamol, 10 mg/kg ibuprofen and placebo. Ibuprofen alleviated pain in 2 hours and most of the patients became pain-free. Almost as many benefitted from paracetamol. Paracetamol, which reaches peak plasma levels within 0.5 to 1 hour, tended to be more effective at 1 hour than ibuprofen, which peaks at approximately 1 to 2 hours. Overall, through an intention-to-treat analysis, the study indicated ibuprofen as more effective. However, a recent systematic review of the literature has not confirmed superiority of ibuprofen over paracetamol in this clinical context.[48]

Toothache and dental procedures

In pediatric age ibuprofen must to be considered very useful for the treatment of toothache due to caries or after dental procedures. For example, in the application of orthodontic spacers performed without general anesthesia, the preprocedural use of ibuprofen leads to a reduction in postprocedural pain of -13.44 (95% CI -23.01 and -3.889 in two trials, P=0.006) on a visual analogue scale (VAS) with a score from 0 to 100.[50]

A pediatric study (age range 5-12 years) including children suffering from toothache showed that pain control with ibuprofen was equivalent to that determined by the paracetamol/codeine association.[52] A randomized study compared the efficacy of ibuprofen and paracetamol for control of pain in pediatric patients aged 12 to 16 years undergoing dental procedures: a preprocedural dose followed by a second postprocedural of ibuprofen provided greater pain.[51]

Post-surgical pain

Publications have shown that untreated surgical pain can lead to increase in clinical complications, prolonged hospitalization and increase in mortality. Underestimation of pediatric post-surgical pain may also be counterproductive from a psychological point of view. Unfortunately, pediatric postoperative pain is treated suboptimally in many hospitals, so too many children receive less medication following the same type of procedure compared with adults. Sagerdahl *et al.*[73] found that postoperative pain was the major criticism of pediatric patients that underwent ambulatory surgery. Many factors contribute to inadequate pain relief in children: incomplete knowledge of pain pathophysiology, difficulties in quantifying pain (especially in newborns and infants), lack of training and experience with the fear of potential adverse effects, availability of a reduced number of approved analgesic drugs for pediatric age (compared to adults). However, ibuprofen, among NSAIDs approved in pediatric age, is the most studied and showed to have the best safety and efficacy profiles. Ibuprofen is expected to be more effective in preventing pain than in the relief of established pain so the proactive approach is to be preferred. When ibuprofen is administered as early as possible and continued on a regular basis for as long as the pain is expected to last, the pain management is best achieved. This concept is well applicable for post-surgical pain.

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A review evaluated the effectiveness of ibuprofen in the pain prevention following minor surgical corrective procedures on the gastrointestinal and urogenital system (hernia, hypospadias, circumcision, hydrocele, orchidopexy) and from lumbar puncture.[58] Ibuprofen reduced postprocedural pain experience and, in some cases, spared the use of morphine.

Stewart *et al.*[57] recruiting 107 children (50, tonsillectomy; 24, orchidopexy; 31, inguinal hernia repair) have recently confirmed these data, with ibuprofen that provide adequate analgesia after the first postoperative day already.

Following the limitations regarding codeine in children and searching for an adequate substitute, two recent studies have compared the efficacy and safety of oral morphine with ibuprofen in moderate pain following fractures[37] and for home treatment of postoperative orthopedic pain.[53] In both studies morphine and ibuprofen decreased pain with no apparent difference in efficacy, but morphine was consistently associated with significantly more adverse effects.

Ibuprofen has been considered in the treatment of pain after pediatric tonsillectomy and/or adenoidectomy in last few years, related to the recent limitations on the use of codeine, especially in this clinical context. Codeine is a pro-drug metabolized to morphine in the liver by the cytochrome P450. Its easy-to-use oral and rectal formulations making it a formerly much prescribed opioid in pediatric age. Some recent publications questioned about the safety of codeine. Postoperative respiratory depression and death (most post-tonsillectomy) is reported by literature and so the European Medicines Agency (EMA) restricted the use of codeine to children over 12 years of age, because of the risk, in ultra-rapid codeine metabolizers, of producing more morphine than the general population, potentially leading to overdose.

Furthermore, slow metabolizers transform less codeine into morphine with an insufficient analgesic effect. So, despite opioids are effective in relieving postoperative pain, the use of other analgesic drugs such as ibuprofen has become most frequent. Merry *et al.*[56] published a multicenter DB-RCT that enrolled 154 children (6-14 years) undergoing a tonsillectomy and randomized to receive ibuprofen (24 mg/kg/day), paracetamol (48 mg/kg/day) or the combination of both for 48 hours after surgery. A substantial equivalence among all three therapeutic regimens was showed. Moss *et al.*[55] performed a DB-RCT of 161 pediatric patients aged 6-17 years undergoing tonsillectomy. In this study a single dose of intravenous ibuprofen (10mg/kg) was compared with placebo, showing lower use of fentanyl without any increase in post-surgical complications. Kelly and al[54] have published a DB-RCT on 91 pediatric patients (1-10 years) undergoing adenoidectomy and/or tonsillectomy and randomized to receive ibuprofen or the combination of paracetamol and morphine. Both regimens resulted to be equally effective but while the treatment with ibuprofen proved to be safe, the other therapeutic intervention was associated with statistically significant oxygen desaturations.

Adenotonsillectomy is one of the most common procedures performed on children and may have another significant postoperative morbidity other than pain, such as bleeding (on average between 3% and 5% of pediatric tonsillectomy patients suffers hemorrhage after tonsillectomy). As previously reported nonsteroidal anti-inflammatory drugs are useful in postoperative pain control but some surgeons remain doubtful about the risk of postoperative bleeding. The typical NSAID mechanism of action results in the inhibition of formation of thromboxane A2, and thus, there is potential for qualitative effects on platelet function. Four meta-analyses of the current literature regarding post-tonsillectomy bleeding and risk with NSAIDs are contradictory in their results. However, a Cochrane meta-analysis of 2011[74] limited to pediatric patients and inclusive of quality studies, showed NSAIDS did not significantly alter bleeding events requiring surgery (OR 1.32, 95% CI: 0.47-3.7) or not requiring surgery (OR 1, 95% CI: 0.39-2.53). A recent large case series found no increased bleeding associated with ibuprofen.[75]

Therefore, from the current evidence the use of ibuprofen can be to be considered effective; however, further studies are needed to validate its safety and so its use in his clinical context.

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Arthritis and other rheumatic diseases

Given its anti-inflammatory activity, ibuprofen can to be considered the treatment of choice for pediatric pain with an inflammatory component.

Juvenile idiopathic arthritis (JIA) is an example of a chronic inflammation disease that benefits from the use of NSAIDs. In these diseases, inflammation is not the initial cause of disease, but it's the mechanism that maintains the tissue damage. Pain, the most common and distressing symptom of JIA, has a dramatic impact in physical, social and emotional functions. Children with arthritis continue to experience clinically significant pain despite adequate doses of disease-modifying antirheumatic drugs. Ibuprofen has been used for many years in pediatric age in this clinical context, in order to manage pain and inflammation. Ninety-two children with juvenile rheumatoid arthritis were randomly assigned to treatment in a multicenter, double-blind, 12-week trial designed to compare the efficacy and safety of a liquid formulation of ibuprofen at a dosage of 30 to 40 mg/kg/day *versus* those of aspirin at a dosage of 60 to 80 mg/kg/day.[61] No significant intergroup differences in response rates or in the amount of improvement in articular indexes of disease activity were observed. More children treated with aspirin discontinued treatment early because of adverse reactions. After this trial, 84 additional patients with juvenile rheumatoid arthritis entered a 24-week, multidose (30, 40, and 50 mg/kg/day), open trial of ibuprofen suspension. Favorable response rates for the three groups were similar, and continued improvement was observed throughout the 24-week period. A dose-response relationship was observed with respect to adverse reactions of the upper gastrointestinal tract. The safety, efficacy and acceptability of ibuprofen syrup were assessed in a multicenter controlled open study in children with juvenile chronic arthritis. Forty-six children aged 18 months to 13 years (mean 6.8 years) were studied.[71] Dosage started at 10 mg/kg/day and increased to a maximum of 40 mg/kg/day depending on condition and individual disease control. Follow-up assessments of disease severity, active joint count and any side effects were made at each clinic visit, usually monthly or as often as deemed necessary by the physician. The study demonstrates that ibuprofen is a well-tolerated anti-inflammatory agent for children with juvenile chronic arthritis, and that the syrup form is particularly useful for small children who may not be able to swallow tablets.

The use of ibuprofen and other NSAIDs in children with arthritis, which are generally assessed differently from adults as they complain less of pain, was critically reviewed.[60]

Salicylates, indomethacin and ibuprofen are generally used for the fever of systemic juvenile chronic arthritis. For control of joint symptoms, diclofenac, ibuprofen, tolmetin and naproxen resulted equal in their efficacy and tolerance: salicylates and indomethacin were no more effective but more toxic. Children tolerate NSAIDs well. Renal toxicity was rare and gastrointestinal symptoms appeared to be less common than in adults. The pharmacokinetic and pharmacodynamic characteristics of ibuprofen allow a fast onset of action and a very good efficacy profile in these clinical contexts. The 20-30 mg/kg daily dosage of ibuprofen has proved to be clearly effective in the treatment of pain and in reducing fever in children while the dosage of 30 mg/kg/die can be safely used in the symptomatic treatment of JIA.

The number of positive clinical trials showing at least a comparable efficacy of ibuprofen with other NSAIDs in the above indications and its worldwide marketing experience in adults and children, allow to consider ibuprofen a very effective product.

Treatment with ibuprofen showed efficacy in transient synovitis of the hip, a very common cause of hip pain in preschool and younger school-age children, in which symptoms of limping, hip pain, refusal to walk, but no fever are present.[59] Thirty-six children, aged 1–12 years, were treated with ibuprofen (N.=17) or placebo (N.=19). It was demonstrated that the treatment with ibuprofen reduced the duration of symptoms of 2.5 days, without serious adverse events.

Osteochondrosis

The term osteochondrosis is used to describe a group of disorders that affect patients with an immature skeleton. Osteochondrosis results from

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abnormal development, injury, or overuse of the growth plate and surrounding ossification centers. Symptoms generally appear between 10 and 14 years of age and boys are more commonly affected because of their greater susceptibility to childhood trauma and overuse injuries. Pain and disability are common and hip, knee, foot, elbow, and back are the areas of the body most often affected.

Legg-Calvé-Perthes is the most frequent of these conditions and results from a partial interruption of the blood supply to the immature femoral head of unknown cause.

Another osteochondrosis is the Osgood-Schlatter disease, a frequent cause of pediatric anterior knee pain. It's caused by repetitive traction of the patellar tendon on the tibial tubercle ossification center or apophysis, which cause secondary inflammation and pain.

Other osteochondrosis are the Sever disease (or calcaneal apophysitis), the Sinding-Larsen–Johansson disease (affecting the inferior pole of the patella), the Freiberg disease (disordered ossification of the second metatarsal head), the Köhler bone disease (osteochondrosis of the navicular bone in the foot), the medial epicondyle apophysitis affecting throwing athletes, the Panner disease (distal humeral ossification center/capitellum) and the Scheuermann disease (common cause of back pain with a rigid kyphosis or humpback deformity).

Osteoarticular unloading and absolute rest are the cornerstone of the treatment. However, the use of ibuprofen to exploit its anti-inflammatory and analgesic actions is common.[63]

Growing pains

Growing pains are a mysterious but common complaint in young children, usually affecting boys and girls aged 3-11 years. These achy pains occur in the limbs muscles, not the joints. Growing pains should not make it hard to walk, run or play normally, and no pathological data are detected for the objective examination. The pains do not get worse when moving or exercising, though some children will find the pain worse after they have been doing a lot of activity. Growing pains occur in the afternoon and evening, and might be severe enough to wake a child up during the night. While their name suggests the pain is caused by growing, the cause of growing pains is not yet clear. Gently massaging the area and using heat treatments like a warm bath or warm heat pack, might ease growing pains. Analgesic and anti-inflammatory drugs, such us ibuprofen, can be used to help reducing pain.[64]

Safety and tolerability in childhood

Ibuprofen is the most widely used NSAID for the treatment of inflammation, mild-to-moderate pain and fever in children and, thanks to its good tolerability profile, the only NSAID approved for use in children over 3 months old. Since its marketing as an oral suspension for pediatric use, ibuprofen has replaced acetylsalicylic acid for the treatment of inflammation, avoiding the risk of Reye's Syndrome in children, when they have a viral illness. According to Italian post-marketing data, the proportion of packs of ibuprofen for pediatric use bought without a medical prescription increased from 28% in 2008 to 70% in 2015. This medically unsupervised use of ibuprofen raises issues concerning the correct use of the drug by parents/caregivers and the risks of its misuse. As already described above, ibuprofen is not a selective COX inhibitor, and therefore, it is not free of potential unwanted effects, above all involving gastrointestinal systems and kidneys. In last years, several reviews and meta-analyses showed that ibuprofen can to be considered effective and the least toxic NSAID in adults; this finding has been confirmed in children.[21, 65, 76-79] Dozens of relevant publications, including reviews, randomized clinical trials, observational clinical studies and case reports, demonstrate the efficacy and favorable tolerability profile of ibuprofen as a non-prescription analgesic/antipyretic drug for use in children. Compared to ketoprofen, indicated for children over 6 years of age, ibuprofen has fewer side effects. Nimesulide is contraindicated in patients aged under 12 years and ketorolac and acetylsalicylic acid in patients younger than 16.

Epidemiological studies and controlled clinical trials have demonstrated that ibuprofen is among the NSAIDs associated with the lowest risk of severe gastrointestinal adverse events.

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In one of the largest surveillance study on the safety of drugs, Lesko *et al.*[80] conducted a double-blind randomized clinical trial with the aim of evaluating the risk of hospitalization because of major side events related to the use of ibuprofen as antipyretic, compared to paracetamol. Among 84,192 children (aged 6 months to 12 years) included in this study, only 1% (N.=795) was hospitalized, with no statistically significant difference between the two groups. Regarding the only 4 cases of gastrointestinal bleeding in the ibuprofen group the estimated risk resulted to be 7.2 per 100,000 (95% CI: 2-18 per 100,000), that not statistically differs from the paracetamol group. Moreover, this study showed that the risk of hospitalization for renal failure or anaphylaxis was not increased following short-term use of ibuprofen.

Over the years a lot has been reflected on the risks of renal adverse effects related to the use of NSAIDs in children because of the capacity of these drugs to reduce the renal synthesis of prostaglandins. In euvolemic states, the effect of prostaglandins on renal hemodynamics is not significant but in cases of hypovolemia, up-regulation of the renin-angiotensin system, as well as of the catecholaminergic system, causes systemic and renal vasoconstriction, which leads to production of renal prostaglandins with the aim of maintaining renal perfusion and glomerular filtration. This protective effect can be inhibited by NSAIDs: blocked prostaglandin synthesis leads to unchecked vasoconstriction of the afferent arteriole, resulting in reduced GFR and eventually renal ischemia and acute tubular necrosis.

Based on the medical literature, in children with normal kidney function and effective circulating volume, it is very unlikely that ibuprofen by itself leads to acute kidney injuries. There were no incidences of acute renal failure in a large practitioner-based population study which included 55,785 children treated with ibuprofen[80] or in the Boston Collaborative Fever study which included 27,065 febrile children randomized to assume ibuprofen.[81] A further study found that, with short-term use of ibuprofen, the risk of less severe renal impairment is small and not significantly greater than with paracetamol.[82] Similarly, a large-scale pediatric study by Ashraf and colleagues found no incidences of renal conditions in over 31,000 children treated with either ibuprofen or paracetamol.[83]

There have, however, been rare case reports of reversible renal insufficiency in children with febrile illnesses treated with ibuprofen or other NSAIDs, largely associated with volume depletion.[84-86] So caution is recommended with the use of ibuprofen in the presence of dehydration due for conditions such as vomiting and diarrhea, in particular if fever is associated. In these cases, in fact, insensible fluid loss (for example, sweating) and the commonly present difficulty in consuming liquids, must to be taken into consideration. However, the milder forms of dehydration can be difficult to detect in children and may go unnoticed.

Care must be taken with ibuprofen when treating children born prematurely or with a low birthweight because of their reduced nephron mass and therefore at higher risk of kidney damage throughout their life. Chronic use of NSAIDs in such individuals is a strong risk factor.[87]

Ibuprofen is not contraindicated in asthmatic children. In a randomized controlled, double-blind trial in 100 schoolchildren with mild-to-moderate asthma, only 2% of the cases had ibuprofen-induced bronchospasm leading the authors to conclude that the prevalence of ibuprofen-associated asthma is low.[21, 88] Two literature reviews[89, 90] showed that ibuprofen can be safely administered to febrile asthmatic children. Kauffman *et al.*[91] found little evidence that the use of ibuprofen increases morbidity in asthmatic children and concluded that the use of ibuprofen is substantially safe in asthmatic children.

Contraindications to the use of ibuprofen in children

The use of ibuprofen should be avoided during treatment of Kawasaki Syndrome with acetylsalicylic acid (ASA), as ibuprofen antagonizes the antiplatelet action of the ASA. Kawasaki disease is an acute, systemic inflammatory disease with associated vasculitis. Fever is invariably present and should not be treated with ibuprofen. Treatment of Kawasaki disease aims to reduce inflammation and prevent cardiac com-

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plications. Guidelines recommend administration of intravenous immunoglobulin in combination with high-dose ASA (80 to 100 mg/kg per day divided into 4 doses). After fever subsides for 48 to 72 hours, the guidelines recommend reducing the dose of ASA to 3 to 5 mg/kg once daily for 6 to 8 weeks. If coronary abnormalities such as stenosis or aneurysms develop and persist, low-dose ASA might be required for life. Aspirin owes its action, in this clinical context, to the acetylation of the platelet COX-1 that lead to its irreversible inhibition. Unlike aspirin, NSAIDs as ibuprofen behave like reversible COX-1 inhibitors, but competing with ASA for the platelet COX-1, may reduce its antiplatelet effect.[92]

Some reports evidenced that varicella seem to be associated with a higher rate of adverse events in people treated with a NSAID. One of the most common complication of varicella is the superinfection of the skin, caused by group A β-hemolytic streptococci (GAS), which is also responsible for necrotising fasciitis (a rapidly progressive inflammatory infection of the fascia, with secondary necrosis of the subcutaneous tissues). Lesko *et al.* conducted a prospective multicenter, case-control study to test the hypothesis that NSAID use increases the risk of invasive GAS infection, with a primary interest in necrotizing infections, in children with varicella.[93] Cases were defined as children, 19 years old who were hospitalized with necrotizing soft tissue infections (NSTI) or other invasive GAS infection within 2 weeks of onset of primary varicella. Among the 224 children, 123 had taken ibuprofen or paracetamol (alone or in combination). The authors observed no association between the use of ibuprofen, the only NSAID used in these children, and NSTI, while the probability of a GAS infection was higher in subjects who had taken ibuprofen alone. The authors did, however, caution against uncritical interpretation of these statistical findings because of the risk of potential confounding factors. Souyri *et al.* identified 38 cases of NSTI in the database of the Spontaneous Reporting System in France: 12 infants (0-23 months), 16 children (2-15 years) and 10 adults (>15 years).[94] They selected 228 matched controls. Of the 28 children, 26 had varicella and 2 had other viral infections, and of these 24 patients, 22 had taken NSAIDs (18 ibuprofen, 2 niflumic acid and 2 ibuprofen and niflumic acid concomitantly). This study indicates a strong association between the use of NSAIDs and severe NSTI, in particular in children with varicella. The pathogenetic mechanism remains unknown, although it is hypothesized that NSAIDs can inhibit the functions of neutrophils and/or alter the production of cytokines. Perhaps, the greater severity of NSTI in children treated with NSAIDs may be due to the masking effects of drugs and to the therapeutic delay rather than to the alteration of bacterial defenses. Despite the limitations related to a spontaneous reporting system and the very low number of cases, comprising only 1.9% of all serious skin reactions reported during the same period) more caution would be required when using ibuprofen in children with varicella and impetigo, due to the increased risk of complications.

Combination of ibuprofen and paracetamol

Recently, in the daily clinical practice, ibuprofen is associated or alternated with paracetamol for treating febrile children. There is some evidence that both alternating and combined antipyretic therapies may be more effective at reducing temperatures than monotherapy alone. In their Cochrane meta-analysis Wong *et al.* showed that, compared to administering a single antipyretic alone, administering combined paracetamol and ibuprofen to febrile children can result in a lower mean temperature at 1 and 4 hours after treatment.[95]

Approximately, 5-10% of paracetamol is oxidized by CYP450-dependent pathways (mostly CYP2E1 and CYP3A4) to a toxic, electrophilic metabolite, N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is detoxified by glutathione and eliminated in the urine or bile. The NAPQI that is not detoxified may bind to hepatocytes and produce cellular necrosis. Usually, because of the relatively small amount of NAPQI formed and the adequate supply of glutathione, paracetamol has an excellent safety profile. The inhibition of prostaglandin synthesis by ibuprofen could result

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in a reduction of glutathione production and in a reduction of renal perfusion during hypovolemic conditions (in febrile children dehydration signs can be more difficult to detect), which might lead to an impairment of the detoxification capacity of NAPQI. The association of all these pathophysiological aspects makes as biologically plausible a risk of renal and hepatic toxicity of combined use of paracetamol and ibuprofen. So, as far as the available studies provide evidence of good effects and relative safety of the combination of the two drugs for short periods, the guidelines did not recommend this practice in the management of the fever in pediatric age.[34, 96] Moreover, the combination of antipyretics can be confusing in caregivers, can increase the risk of errors in the drug administration and overdose and, finally, this alternate use of antipyretics encourages the fever phobia.

Conclusions

The guidelines produced over the years indicate unanimously ibuprofen as a drug of choice, like paracetamol, in the management of fever and mild-moderate pain in children, at a daily dose of 20-30 mg/kg bodyweight, divided 3 times a day at intervals of 6-8 hours.

For younger pediatric patients (*e.g.* birth to 8 years) who are unable to swallow capsules or tablets liquid formulations (including solutions, syrups, suspensions and emulsions), are most appropriate. Suspensions may be very useful for formulation of substances with poor taste characteristics; as by minimizing the amount of drug in solution, the palatability of the formulation can be improved.[97] The syrup formulation (100 mg/5 mL) can be used from 5.6 to 43 kg of bodyweight (age 3 months-12 years). A further advantage is the use of oral formulations with a single concentration of ibuprofen, lowering the risk of errors in dosage. A better compliance can be reached employing a taste making technology, that is coating ibuprofen particles in order to improve the flavor without considerable impact to the release ot the active ingredient. The use of pleasing flavors (for example banana and honey) increases children's agreement.

In case of fever or pain, the choice about the drug to be used, should fall on ibuprofen when you are in a clinical context where there is an inflammatory pathogenesis, such as acute pharyngotonsillitis and acute otitis media. The advantages of ibuprofen compared to other NSAIDs are the best demonstrated tolerability and safety in children. A large amount of data in the literature shows a low incidence of gastrointestinal, hepatic and renal side effects. Ibuprofen is not contraindicated in children with asthma, except for the established cases of paracetamol- or NSAID-induced asthma. Ibuprofen is safe even on an empty stomach, thus achieving high plasma concentrations in less time. This method of administration determines a greater effect, more precocious and more lasting, translating into a lower total recourse to the drug itself. Ibuprofen showed a rapid onset (15 minutes) and longer duration (8-12 hours) antipyretic activity, when compared with paracetamol, with the obvious advantage, therefore, of less frequent administration. Furthermore, some studies would seem to demonstrate greater efficacy in febrile illness, especially in the first 24 hours.

With regard to the analgesic effect, some trials show greater efficacy than paracetamol (and equal to the paracetamol/codeine association) in cases of post-traumatic musculoskeletal pain, toothache and headache, especially in the first two hours after starting the therapy. Post-surgical pain has also been extensively studied in pediatrics, and ibuprofen has been shown to be effective and safe (children undergoing adenotonsillectomy have not presented an increased risk of bleeding).

References

1. Rainsford KD. Pharmacology and toxicology of ibuprofen. In: Rainsford KD, editor. Ibuprofen. A critical bibliographic review. London: Taylor & Francis; 1999. p 145-27.

2. Lee EJ, Williams K, Day R, Graham G, Champion D. Stereoselective disposition of ibuprofen enantiomers in man. Br J Clin Pharmacol 1985;19:669–74.

3. Burian M, Geisslinger G. COX-dependent mechanisms involved in the antinociceptive action of NSAIDs at central and peripheral sites. Pharmacol Ther 2005;107:139–54.

4. Katsung BG. Farmacologia generale e clinica. Paduaa: Piccin, 2014; p. 1810

5. Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. Am J Med 1998;104:413–21.

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6. Blain H, Boileau C, Lapicque F, Nédélec E, Loeuille D, Guillaume C, *et al.* Limitation of the in vitro whole blood assay for predicting the COX selectivity of NSAIDs in clinical use. Br J Clin Pharmacol 2002;53:255–65.

7. Bushra R, Aslam N. An overview of clinical pharmacology of Ibuprofen. Oman Med J 2010;25:155–1661.

8. Kelley MT, Walson PD, Edge JH, Cox S, Mortensen ME. Pharmacokinetics and pharmacodynamics of ibuprofen isomers and acetaminophen in febrile children. Clin Pharmacol Ther 1992;52:181–9.

9. Nahata MC, Durrell DE, Powell DA, Gupta N. Pharmacokinetics of ibuprofen in febrile children. Eur J Clin Pharmacol 1991;40:427–8.

10. Kauffman RE, Nelson MV. Effect of age on ibuprofen pharmacokinetics and antipyretic response. J Pediatr 1992;121:969–73.

11. Rainsford KD, Bjarnason I. NSAIDs: take with food or after fasting? J Pharm Pharmacol 2012;64:465–9.

12. Jacqz-Aigrain E, Anderson BJ. Pain control: non-steroidal anti-inflammatory agents. Semin Fetal Neonatal Med 2006;11:251–9.

13. Rey E, Pariente-Khayat A, Gouyet L, Vauzelle-Kervroëdan F, Pons G, D'Athis P, *et al.* Stereoselective disposition of ibuprofen enantiomers in infants. Br J Clin Pharmacol 1994;38:373–5.

14. Ziesenitz VC, Zutter A, Erb TO, van den Anker JN. Efficacy and safety of ibuprofen in infants aged between 3 and 6 months. Paediatr Drugs 2017;19:277–90.

15. García-Martín E, Martínez C, Tabarés B, Frías J, Agúndez JA. Interindividual variability in ibuprofen pharmacokinetics is related to interaction of cytochrome P450 2C8 and 2C9 amino acid polymorphisms. Clin Pharmacol Ther 2004;76:119–27.

16. Har-Even R, Stepensky D, Britzi M, Soback S, Chaim AB, Brandriss N, *et al.* Plasma and cerebrospinal fluid concentrations of ibuprofen in pediatric patients and antipyretic effect: pharmacokinetic-pharmacodynamic modeling analysis. J Clin Pharmacol 2014;54:1023–30.

17. Wallace JL. Prostaglandins, NSAIDs, and gastric mucosal protection: why doesn't the stomach digest itself? Physiol Rev 2008;88:1547–65.

18. Kanabar DJ. A clinical and safety review of paracetamol and ibuprofen in children. Inflammopharmacology 2017;25:1–9.

19. García Rodríguez LA, Hernández-Díaz S. Relative risk of upper gastrointestinal complications among users of acetaminophen and nonsteroidal anti-inflammatory drugs. Epidemiology 2001;12:570–6.

20. Henry D, Lim LL, Garcia Rodriguez LA, Perez Gutthann S, Carson JL, Griffin M, *et al.* Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. BMJ 1996;312:1563–6.

21. de Martino M, Chiarugi A, Boner A, Montini G, De' Angelis GL. Working towards an appropriate use of ibuprofen in children: an evidence-based appraisal. Drugs 2017;77:1295–311.

22. Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. Proc Natl Acad Sci USA 1999;96:7563–8.

23. Lanas A, Gargallo CJ. Management of low-dose aspirin and clopidogrel in clinical practice: a gastrointestinal perspective. J Gastroenterol 2015;50:626–37.

24. Grimaldi-Bensouda L, Abenhaim L, Michaud L, Mouterde O, Jonville-Béra AP, Giraudeau B, *et al.* Clinical features and risk factors for upper gastrointestinal bleeding in children: a case-crossover study. Eur J Clin Pharmacol 2010;66:831–7.

25. Usta M, Urganci N. Upper gastrointestinal bleeding in children: the role of Helicobacter pylori infection and nonsteroidal anti-inflammatory drug use. West Indian Med J 2015;64:113–6.

26. Lameire N, Van Biesen W, Vanholder R. Acute renal failure. Lancet 2005;365:417–30.

27. Taber SS, Mueller BA. Drug-associated renal dysfunction. Crit Care Clin 2006;22:357–74, viii.

28. Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. BMJ 2004;328:434.

29. Ledford DK, Wenzel SE, Lockey RF. Aspirin or other nonsteroidal inflammatory agent exacerbated asthma. J Allergy Clin Immunol Pract 2014;2:653–7.

30. Argentieri J, Morrone K, Pollack Y. Acetaminophen and Ibuprofen overdosage. Pediatr Rev 2012;33:188–9.

31. Morrison SF, Nakamura K. Central neural pathways for thermoregulation. Front Biosci 2011;16:74–104.

32. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol 2011;31:986–1000.

33. Woolf CJ. What is this thing called pain? J Clin Invest 2010;120:3742–4.

34. Chiappini E, Venturini E, Remaschi G, Principi N, Longhi R, Tovo PA, *et al.*; Italian Pediatric Society Panel for the Management of Fever in Children. 2016 Update of the Italian Pediatric Society Guidelines for Management of Fever in Children. J Pediatr 2017;180:177–183.e1.

35. Hay AD, Costelloe C, Redmond NM, Montgomery AA, Fletcher M, Hollinghurst S, *et al.* Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): randomised controlled trial. BMJ 2008;337:a1302.

36. Narayan K, Cooper S, Morphet J, Innes K. Effectiveness of paracetamol versus ibuprofen administration in febrile children: A systematic literature review. J Paediatr Child Health 2017;53:800–7.

37. Poonai N, Bhullar G, Lin K, Papini A, Mainprize D, Howard J, *et al.* Oral administration of morphine versus ibuprofen to manage postfracture pain in children: a randomized trial. CMAJ 2014;186:1358–63.

38. Poddighe D, Brambilla I, Licari A, Marseglia GL. Ibuprofen for pain control in children new value for an old molecule. Pediatr Emer Care 2018. [Epub ahead of print].

39. Milani GP, Benini F, Dell'Era L, Silvagni D, Podestà AF, Mancusi RL, *et al.*; PIERRE GROUP STUDY. Acute pain management: acetaminophen and ibuprofen are often underdosed. Eur J Pediatr 2017;176:979–82.

40. Yaksh TL, Dirig DM, Malmberg AB. Mechanism of action of nonsteroidal anti-inflammatory drugs. Cancer Invest 1998;16:509–27.

41. Benini F, Barbi E, Gangemi M, Manfredini L, Messeri A, Papacci P. Il dolore nel bambino: strumenti pratici di valutazione e terapia. Ministero della Salute; 2014 [Internet]. Available from: https://www.salute.gov.it/imgs/C_17_pubblicazioni_2077_allegato.pdf [cited 2018, Nov 15].

42. Shepherd M, Aickin R. Paracetamol versus ibuprofen: a randomized controlled trial of outpatient analgesia efficacy for paediatric acute limb fractures. Emerg Med Australas 2009;21:484–90.

43. Clark E, Plint AC, Correll R, Gaboury I, Passi B. A ran-

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domized, controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma. Pediatrics 2007;119:460–7.

44. Sjoukes A, Venekamp RP, van de Pol AC, Hay AD, Little P, Schilder AG, *et al.* Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. Cochrane Database Syst Rev 2016;12:CD011534.

45. Bertin L, Pons G, d'Athis P, Duhamel JF, Maudelonde C, Lasfargues G, *et al.* A randomized, double-blind, multicentre controlled trial of ibuprofen versus acetaminophen and placebo for symptoms of acute otitis media in children. Fundam Clin Pharmacol 1996;10:387–92.

46. Schachtel BP, Thoden WR. A placebo-controlled model for assaying systemic analgesics in children. Clin Pharmacol Ther 1993;53:593–601.

47. Bertin L, Pons G, d'Athis P, Lasfargues G, Maudelonde C, Duhamel JF, *et al.* Randomized, double-blind, multicenter, controlled trial of ibuprofen versus acetaminophen (paracetamol) and placebo for treatment of symptoms of tonsillitis and pharyngitis in children. J Pediatr 1991;119:811–4.

48. Richer L, Billinghurst L, Linsdell MA, Russell K, Vandermeer B, Crumley ET, *et al.* Drugs for the acute treatment of migraine in children and adolescents. Cochrane Database Syst Rev 2016;4:CD005220.

49. Hämäläinen ML, Hoppu K, Valkeila E, Santavuori P. Ibuprofen or acetaminophen for the acute treatment of migraine in children: a double-blind, randomized, placebo-controlled, crossover study. Neurology 1997;48:103–7.

50. Ashley PF, Parekh S, Moles DR, Anand P, MacDonald LC. Preoperative analgesics for additional pain relief in children and adolescents having dental treatment. Cochrane Database Syst Rev 2016;(8):CD008392.

51. Bradley RL, Ellis PE, Thomas P, Bellis H, Ireland AJ, Sandy JR. A randomized clinical trial comparing the efficacy of ibuprofen and paracetamol in the control of orthodontic pain. Am J Orthod Dentofacial Orthop 2007;132:511–7.

52. Moore PA, Acs G, Hargreaves JA. Postextraction pain relief in children: a clinical trial of liquid analgesics. Int J Clin Pharmacol Ther Toxicol 1985;23:573–7.

53. Poonai N, Datoo N, Ali S, Cashin M, Drendel AL, Zhu R, *et al.* Oral morphine versus ibuprofen administered at home for postoperative orthopedic pain in children: a randomized controlled trial. CMAJ 2017;189:E1252–8.

54. Kelly LE, Sommer DD, Ramakrishna J, Hoffbauer S, Arbab-Tafti S, Reid D, *et al.* Morphine or Ibuprofen for post-tonsillectomy analgesia: a randomized trial. Pediatrics 2015;135:307–13.

55. Moss JR, Watcha MF, Bendel LP, McCarthy DL, Witham SL, Glover CD. A multicenter, randomized, double-blind placebo-controlled, single dose trial of the safety and efficacy of intravenous ibuprofen for treatment of pain in pediatric patients undergoing tonsillectomy. Paediatr Anaesth 2014;24:483–9.

56. Merry AF, Edwards KE, Ahmad Z, Barber C, Mahadevan M, Frampton C. Randomized comparison between the combination of acetaminophen and ibuprofen and each constituent alone for analgesia following tonsillectomy in children. Can J Anaesth 2013;60:1180–9.

57. Stewart DW, Ragg PG, Sheppard S, Chalkiadis GA. The severity and duration of postoperative pain and analgesia requirements in children after tonsillectomy, orchidopexy, or inguinal hernia repair. Paediatr Anaesth 2012;22:136–43.

58. Kokki H. Nonsteroidal anti-inflammatory drugs for postoperative pain: a focus on children. Paediatr Drugs 2003;5:103–23.

59. Kermond S, Fink M, Graham K, Carlin JB, Barnett P. A randomized clinical trial: should the child with transient synovitis of the hip be treated with nonsteroidal anti-inflammatory drugs? Ann Emerg Med 2002;40:294–9.

60. Hollingworth P. The use of non-steroidal anti-inflammatory drugs in paediatric rheumatic diseases. Br J Rheumatol 1993;32:73–7.

61. Giannini EH, Brewer EJ, Miller ML, Gibbas D, Passo MH, Hoyeraal HM, *et al.*; Pediatric Rheumatology Collaborative Study Group. Ibuprofen suspension in the treatment of juvenile rheumatoid arthritis. J Pediatr 1990;117:645–52.

62. Steans A, Manners PJ, Robinson IG. A multicentre, long-term evaluation of the safety and efficacy of ibuprofen syrup in children with juvenile chronic arthritis. Br J Clin Pract 1990;44:172–5.

63. Weiser P. Approach to the patient with noninflammatory musculoskeletal pain. Pediatr Clin North Am 2012;59:471–92.

64. Lehman PJ, Carl RL. Growing Pains. Sports Health 2017;9:132–8.

65. Perrott DA, Piira T, Goodenough B, Champion GD. Efficacy and safety of acetaminophen vs ibuprofen for treating children's pain or fever: a meta-analysis. Arch Pediatr Adolesc Med 2004;158:521–6.

66. Hartling L, Ali S, Dryden DM, Chordiya P, Johnson DW, Plint AC, *et al.* How safe are common analgesics for the treatment of acute pain for children? A systematic review. Pain Res Manag 2016;2016:5346819.

67. DePeter KC, Blumberg SM, Dienstag Becker S, Meltzer JA. Does the use of ibuprofen in children with extremity fractures increase their risk for bone healing complications? J Emerg Med 2017;52:426–32.

68. Linee Guida della Società Italiana di Pediatria. Otite Media Acuta: dalla diagnosi alla prevenzione; 2010 [Internet]. Available from: http://sip.it/wp-content/uploads/2012/11/linee-guida-otite.pdf [cited 2018, Nov 15].

69. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, *et al.* The diagnosis and management of acute otitis media. Pediatrics 2013;131:e964–99.

70. Fischer T, Singer AJ, Chale S. Observation option for acute otitis media in the emergency department. Pediatr Emerg Care 2009;25:575–8.

71. Spiro DM, Tay KY, Arnold DH, Dziura JD, Baker MD, Shapiro ED. Wait-and-see prescription for the treatment of acute otitis media: a randomized controlled trial. JAMA 2006;296:1235–41.

72. Chiappini E, Principi N, Mansi N, Serra A, De Masi S, Camaioni A, *et al.*; Italian Panel on the Management of Pharyngitis in Children. Management of acute pharyngitis in children: summary of the Italian National Institute of Health guidelines. Clin Ther 2012;34:1442–1458.e2.

73. Segerdahl M, Warrén-Stomberg M, Rawal N, Brattwall M, Jakobsson J. Children in day surgery: clinical practice and routines. The results from a nation-wide survey. Acta Anaesthesiol Scand 2008;52:821–8.

74. Cardwell M, Siviter G, Smith A. Nonsteroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy. Evid Based Child Health 2011;7:244–87.

75. Pfaff JA, Hsu K, Chennupati SK. The use of ibuprofen in posttonsillectomy analgesia and its effect on posttonsillectomy hemorrhage rate. Otolaryngol Head Neck Surg 2016;155:508–13.

76. Rainsford KD. Ibuprofen: pharmacology, efficacy and safety. Inflammopharmacology 2009;17:275–342.

77. Southey ER, Soares-Weiser K, Kleijnen J. Systematic review and meta-analysis of the clinical safety and tolerability

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of ibuprofen compared with paracetamol in paediatric pain and fever. Curr Med Res Opin 2009;25:2207–22.

78. Pierce CA, Voss B. Efficacy and safety of ibuprofen and acetaminophen in children and adults: a meta-analysis and qualitative review. Ann Pharmacother 2010;44:489–506.

79. Leroy S, Mosca A, Landre-Peigne C, Cosson MA, Pons G. [Ibuprofen in childhood: evidence-based review of efficacy and safety]. Arch Pediatr 2007;14:477–84. French.

80. Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. JAMA 1995;273:929–33.

81. Lesko SM, Mitchell AA. The safety of acetaminophen and ibuprofen among children younger than two years old. Pediatrics 1999;104:e39.

82. Lesko SM, Mitchell AA. Renal function after short-term ibuprofen use in infants and children. Pediatrics 1997;100:954–7.

83. Ashraf E, Ford L, Geetha R, Cooper S. Safety profile of ibuprofen suspension in young children. Inflammopharmacology 1999;7:219–25.

84. Krause I, Cleper R, Eisenstein B, Davidovits M. Acute renal failure, associated with non-steroidal anti-inflammatory drugs in healthy children. Pediatr Nephrol 2005;20:1295–8.

85. Moghal NE, Hegde S, Eastham KM. Ibuprofen and acute renal failure in a toddler. Arch Dis Child 2004;89:276–7.

86. Ulinski T, Guigonis V, Dunan O, Bensman A. Acute renal failure after treatment with non-steroidal anti-inflammatory drugs. Eur J Pediatr 2004;163:148–50.

87. Carmody JB, Charlton JR. Short-term gestation, long-term risk: prematurity and chronic kidney disease. Pediatrics 2013;131:1168–79.

88. Debley JS, Carter ER, Gibson RL, Rosenfeld M, Redding GJ. The prevalence of ibuprofen-sensitive asthma in children: a randomized controlled bronchoprovocation challenge study. J Pediatr 2005;147:233–8.

89. Kader A, Hildebrandt T, Powell C. How safe is ibuprofen in febrile asthmatic children? Arch Dis Child 2004;89:885–6.

90. Body R, Potier K. Best evidence topic report. Non-steroidal anti-inflammatory drugs and exacerbations of asthma in children. Emerg Med J 2004;21:713–4.

91. Kauffman RE, Lieh-Lai M. Ibuprofen and increased morbidity in children with asthma: fact or fiction? Paediatr Drugs 2004;6:267–72.

92. Gengo FM, Rubin L, Robson M, Rainka M, Gengo MF, Mager DE, *et al.* Effects of ibuprofen on the magnitude and duration of aspirin's inhibition of platelet aggregation: clinical consequences in stroke prophylaxis. J Clin Pharmacol 2008;48:117–22.

93. Lesko SM, O'Brien KL, Schwartz B, Vezina R, Mitchell AA. Invasive group A streptococcal infection and nonsteroidal antiinflammatory drug use among children with primary varicella. Pediatrics 2001;107:1108–15.

94. Souyri C, Olivier P, Grolleau S, Lapeyre-Mestre M; French Network of Pharmacovigilance Centres. Severe necrotizing soft-tissue infections and nonsteroidal anti-inflammatory drugs. Clin Exp Dermatol 2008;33:249–55.

95. Wong T, Stang AS, Ganshorn H, Hartling L, Maconochie IK, Thomsen AM, *et al.* Combined and alternating paracetamol and ibuprofen therapy for febrile children. Cochrane Database Syst Rev 2013;(10):CD009572.

96. National Institute for Health and Care Excellence NICE. Fever in under 5s: assessment and initial management; 2013 [Internet]. Available from: https://www.nice.org.uk/guidance/cg160 [cited 2018, Nov 15].

97. Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency Reflection paper: formulations of choice for the paediatric population (EMEA/CHMP/PEG/194810/2005).

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