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**MORTALITY RISK OF NSAID USE IN CHILDREN**

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This article discusses the mortality risk associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in children. While NSAIDs are commonly used for pain relief and fever reduction in children, their side effects can be severe, including gastrointestinal bleeding, renal impairment, and cardiovascular events. The risk of these adverse effects is even higher in children with underlying medical conditions or those taking other medications. The article provides an overview of the mechanisms of action of NSAIDs, their potential side effects, and measures that can be taken to minimize the risk of adverse effects.

**Key words:** NSAIDs, children, mortality, adverse effects, COX enzymes, medication interactions.

Mortality due to adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs) in children is a concerning issue. NSAIDs are commonly used for pain relief and fever reduction in children, but their side effects can be severe, including gastrointestinal bleeding, renal impairment, and cardiovascular events. The risk of these adverse effects is even higher in children with underlying medical conditions or those taking other medications. Therefore, it is crucial to weigh the benefits and risks of NSAID use in children and take appropriate measures to prevent severe adverse effects. In this article, we will discuss the current evidence on mortality due to NSAID use in children and the measures that can be taken to minimize the risk of adverse effects. The effects that occur when used together with other drugs have not been fully studied and require further study.

**Methods:** To conduct this study, a comprehensive literature search was performed using several electronic databases, including Google scholar, PubMed, Elicit. The search was limited to articles published in the English language from 2015 to 2022. The following keywords and their combinations were used for the search: "mortality", "nonsteroidal anti-inflammatory drugs", "NSAIDs", "children", "pediatrics", "adverse effects", "side effects", "gastrointestinal bleeding", "renal impairment", and "cardiovascular events". Researching the mortality risk of NSAID use in children is important for understanding the safety profile of these widely used medications, informing clinical decision-making, and guiding the development of evidence-based treatment guidelines for pediatric patients.

NSAIDs (nonsteroidal anti-inflammatory drugs) are commonly used among children for several purposes, including:

1. Pain relief: NSAIDs can help reduce pain caused by a variety of conditions, including headaches, toothaches, ear infections, muscle strains, and injuries.

2. Fever reduction: NSAIDs can also help lower fever, which is a common symptom of many illnesses, including viral infections.

3. Inflammation reduction: NSAIDs can help reduce inflammation, which is a common symptom of conditions such as arthritis and juvenile idiopathic arthritis.

In addition to the above treatment properties, anti-inflammatory drugs can be used for other purposes. For example, it has been found to increase their effectiveness when used together with antitumor drugs. While NSAIDs have shown promise in reducing the risk of certain types of cancer, such as colon cancer, their use as a primary treatment for cancer is still under investigation. NSAIDs work by inhibiting the COX enzymes, which are responsible for producing prostaglandins that promote inflammation and cell growth. By inhibiting COX enzymes, NSAIDs may help prevent the growth and spread of cancer cells. Several studies have suggested that NSAIDs may be effective in reducing the risk of certain types of cancer, including colon, breast, and lung cancer. However, the use of NSAIDs as a primary cancer treatment is still being studied and is not yet an established treatment option. Some clinical trials are currently investigating the use of NSAIDs in combination with other cancer treatments such as chemotherapy or radiation therapy. The hope is that NSAIDs may enhance the effectiveness of these treatments and improve outcomes for cancer patients[1].

Due to the above properties, nonsteroidal anti-inflammatory drugs are widely used in children. The main side effects of NSAIDs are due to blocking of COX-1, and long-term use can cause serious effects in children.

**Mechanism of action of NSAIDs.** The main mechanism of NSAID action is the cyclooxygenase (COX) enzyme inhibition, both centrally and peripherally, thus interfering with the conversion of arachidonic acid into E2 prostaglandins, prostacyclins and thromboxanes. Prostaglandins have

a vasodilatation effect, which is extremely important for preglomerular resistance maintenance, maintaining glomerular filtration rate and preserving renal blood flow[2].

Enzymes related to the action of NSAIDs can be divided into COX-1 and COX-2, acting in different regions. COX-1 is the one that occurs in most cells, even fetal and amniotic fluid, and participates in physiological effects, such as regulatory and protective effects. COX-2 is activated by inflammation and pro-inflammatory cytokines[3].

Based on the classification of these enzymes, NSAIDs can be classified into non-target NSAIDs (ketoprofen, aspirin, naproxen, flunixin, meglumine and others), COX-2 preferential inhibitors

(meloxicam, etodolac, nimesulide) and highly selective COX2 inhibitors (coxib). Most of the side effects are related to COX-1 inhibition, due to its action in several systems associated with cell cleansing. In the kidneys, they are in greater quantities acting in glomerular filtration maintenance. Therefore, studies indicate that individuals with previously compromised renal function are the most affected by the time-dependent use of non-selective NSAIDs. The action of COX-2 is associated with water and electrolytic maintenance in the renal environment, which worsens its effects under dehydration, low renal perfusion or previously existing renal damage[2]

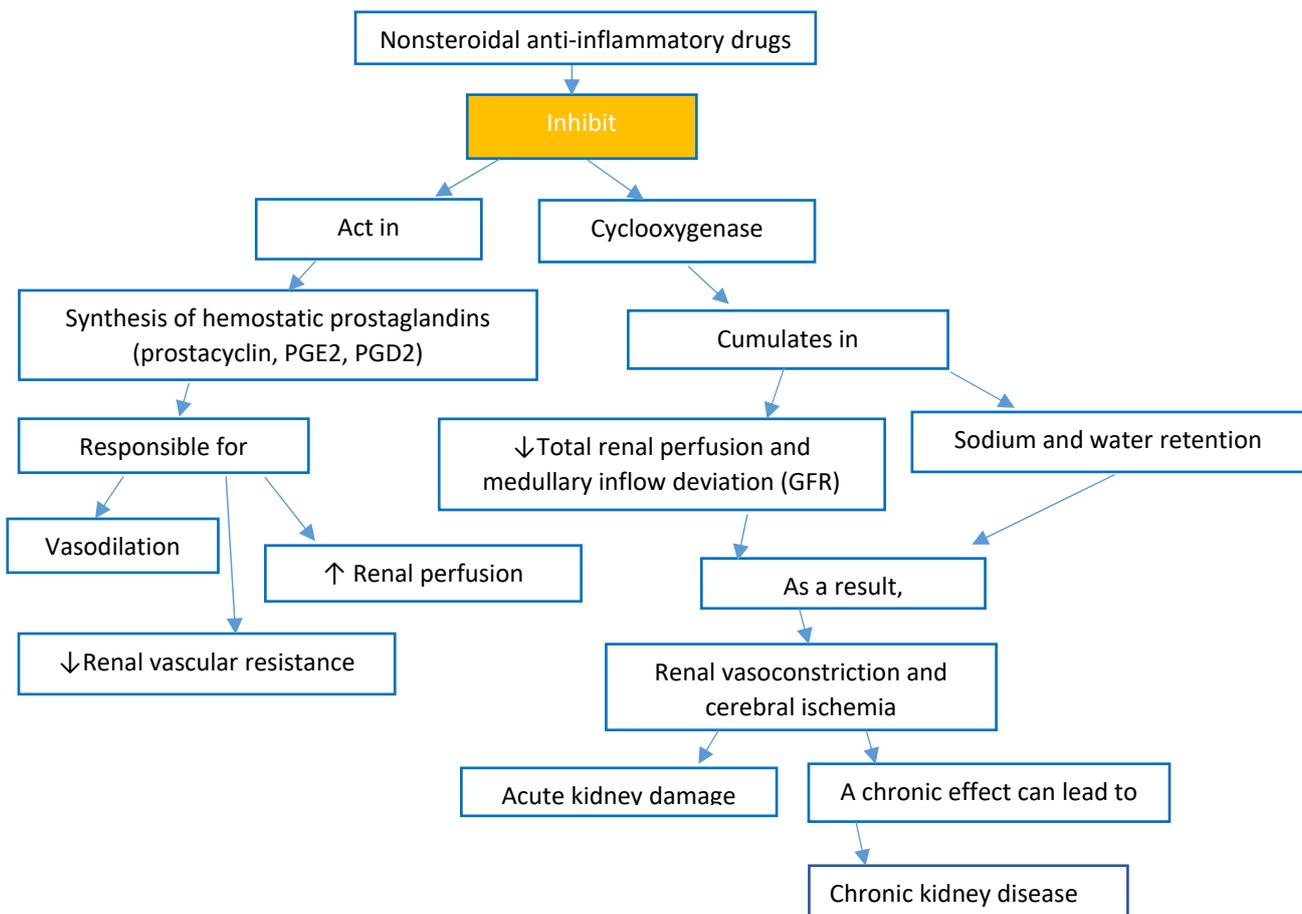


Fig. 1. NSAID-induced kidney injury pathophysiology [4]

- Stomach issues: Gastric ulcers, stomach irritation, nausea, vomiting, diarrhea, etc. Especially with prolonged use or high doses. Warn parents to follow dosage instructions carefully.

- Kidney problems: NSAIDs may reduce blood flow to the kidneys and raise blood pressure. Potential for kidney damage, especially in dehydrated children or those with underlying kidney disease. Recommend hydrating children and monitoring kidney function if on long term NSAIDs. NSAIDs can also affect platelet function and lead to bleeding disorders in children. This effect is usually mild and reversible but

can be significant in children with pre-existing bleeding disorders or those who are undergoing surgical procedures. In such cases, the use of NSAIDs should be carefully monitored, and alternative therapies should be considered [5].

- Cardiovascular side effects: While cardiovascular side effects are more frequently observed in adults, some studies have reported an increased risk of hypertension and heart failure in children treated with NSAIDs. In one study conducted by Southworth, S.R. et al. in

2016, there was a small but statistically significant increased risk of hypertension in children taking NSAIDs compared to non-users[4]. Sachdeva, A. also reported an increased risk of cardiovascular side effects in children treated with NSAIDs[6]. In addition to this NSAIDs can also have cardiovascular (CV) effects, including increased risk of heart attack and stroke. The risk of CV events associated with NSAID use is also dose-dependent. A study by Trelle et al. (2011) found that the risk of CV events increased with higher doses of NSAIDs. The authors suggest that the CV risk associated with NSAIDs should be taken into consideration when prescribing these drugs, especially at higher doses[7].

- Hepatic side effects:

Although hepatic side effects are uncommon in children, they can still occur and may include elevated liver enzymes, acute liver injury, and even liver failure in rare cases. A study conducted by Al-Sallami, H.S. et al. in 2014 found that children who were treated with NSAIDs had a 2.5-fold increased risk of developing liver injury compared to those who did not receive NSAIDs[8].

- Medication interactions: NSAIDs can interact with other drugs like corticosteroids, blood thinners, blood pressure medications, etc. Caution parents to tell their doctor about all medications, and follow directions for spacing out doses to avoid interactions.

- Hypersensitivity reactions:

NSAID use in children has been associated with hypersensitivity reactions such as rash, urticaria, angioedema, and anaphylaxis. The risk of these reactions can vary depending on the individual NSAID and the patient's history of allergy or atopy[9].

- Other side effects: Less commonly, headaches, dizziness, rashes, etc. Best to monitor child and discontinue NSAID if any unexplained symptoms appear.

NSAIDs can interact with a wide range of drugs, including blood thinners, ACE inhibitors, diuretics, and steroids. These interactions can increase the risk of bleeding, lower blood pressure, decrease kidney function, and affect the effectiveness of other medications. For example, taking NSAIDs with blood thinners can increase the risk of bleeding, while taking NSAIDs with ACE inhibitors can lower blood pressure too much.

One of the large retrospective study evaluated the association between ibuprofen use and acute kidney injury (AKI) in hospitalized children in China. The study found that ibuprofen use was common and

was associated with a significantly increased risk of hospital-acquired AKI, even after adjusting for confounders. The risk appeared to be dose-dependent. The incidence of hospital-acquired AKI in this study was 6.9%, which is lower than reported in previous studies. This may be due to differences in study populations, length of stay, disease severity, frequency of serum creatinine testing, and AKI detection method. Ibuprofen use was associated with a 23% increased risk of pediatric hospital-acquired AKI after adjusting for confounders. This association was also seen in propensity score-matched analysis and when using an alternative AKI definition. Previous studies have also found an association between ibuprofen use and increased risk of AKI in children, especially in the context of dehydration or with other nephrotoxins. However, some studies did not find this association. In this study, the association between ibuprofen and AKI was greater in children with chronic kidney disease, those requiring intensive care, and older children. The reasons for these interactions are not fully understood. Close monitoring of kidney function is needed for children receiving ibuprofen, especially those at higher risk of AKI. Judicious use of ibuprofen may help reduce the risk of AKI[10]. This study adds to the evidence that ibuprofen use is associated with an increased risk of AKI in hospitalized children. Careful monitoring and limited use when possible may help reduce this risk.

During the investigation, 18 out of 21 children with acute respiratory diseases in our country died as a result of drinking Dok-1 Max syrup. The deceased children took this drug together with other drugs at home for 2-7 days, up to 2.5-5 milliliters 3-4 times a day. Naturally, this amount is much more than the norm for a child. All children were given the drug without a doctor's prescription. Since the main substance in the drug is paracetamol, Dok-1 Max syrup was incorrectly used by parents as an anti-cold remedy independently or on the recommendation of pharmacists. This caused the condition of patients to worsen. In addition, preliminary laboratory studies have shown the presence of ethylene glycol in this series of Dok-1 Max syrup. This substance is toxic, and about 1-2 ml/kg of a 95% concentrated solution can cause serious changes in the patient's health, such as vomiting, lethargy, seizures, cardiovascular problems and acute kidney failure[11].

Table 1 below lists some of the nonsteroidal anti-inflammatory drugs and their possible side effects.

Table 1.

## NSAID Side Effects and Organ Damage

№	NSAID	Common Side Effects	Potential Organ Damage
1.	Aspirin (acetylsalicylic acid)	Gastrointestinal issues, bleeding, allergic reactions	Stomach, kidneys, liver
2.	Ibuprofen (Advil, Motrin)	Gastrointestinal issues, skin rash, dizziness, headache	Stomach, kidneys, liver, heart
3.	Naproxen (Aleve, Naprosyn)	Gastrointestinal issues, headache, dizziness, skin rash	Stomach, kidneys, liver, heart
4.	Diclofenac (Voltaren, Cataflam)	Gastrointestinal issues, skin rash, dizziness, headache	Stomach, kidneys, liver, heart
5.	Indomethacin (Indocin)	Gastrointestinal issues, headache, dizziness, skin rash	Stomach, kidneys, liver, heart
6.	Celecoxib (Celebrex)	Gastrointestinal issues, skin rash, headache, dizziness	Stomach, kidneys, liver, heart
7.	Meloxicam (Mobic)	Gastrointestinal issues, skin rash, headache, dizziness	Stomach, kidneys, liver, heart
8.	Ketoprofen (Orudis)	Gastrointestinal issues, skin rash, headache, dizziness	Stomach, kidneys, liver, heart
9.	Piroxicam (Feldene)	Gastrointestinal issues, skin rash, headache, dizziness	Stomach, kidneys, liver, heart
10.	Nabumetone (Relafen)	Gastrointestinal issues, skin rash, headache, dizziness	Stomach, kidneys, liver, heart

**Conclusion:** NSAID use in children poses potential risks, including severe side effects and increased mortality. It is crucial to avoid using NSAIDs without a doctor's prescription, consider alternative therapies for pain relief and fever reduction, use the lowest effective dose for the shortest duration, and closely monitor children for potential side effects. Further research on NSAIDs' effects on organ systems and the development of selective drugs is needed to enhance safety in pediatric patients.

We can give the following recommendations in order to prevent and avoid acute processes observed during the use of non-steroidal anti-inflammatory drugs:

- Avoid using NSAIDs in children without a doctor's prescription or recommendation.
- Consider alternative therapies for pain relief and fever reduction in children, such as acetaminophen or ibuprofen.
- Use the lowest effective dose of NSAIDs in children, and for the shortest duration possible.
- Monitor children closely for potential side effects of NSAIDs, especially those with underlying medical conditions or those taking other medications.

And again, it should be noted that it would be appropriate to conduct long-term studies on their stimulating effects on organ systems and to increase the number of groups of drugs with selective action.

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### **BOLALARDA YaQDVDAN FOYDALANISHDAGI O'LIM HAVFI**

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Ushbu maqolada bolalarda steroid bo'lmagan yallig'lanishga qarshi dorilarni (NSAID) qo'llash bilan bog'liq o'lim xavfi muhokama qilinadi. NSAIDlar odatda bolalarda og'riqni yo'qotish va isitmani pasaytirish uchun qo'llanilsada, ularning nojo'ya ta'siri og'ir bo'lishi mumkin, jumladan, oshqozon-ichakdan qon ketish, buyrak etishmovchiligi va yurak-qon tomir kasalliklari. Ushbu nojo'ya ta'sirlarning xavfi asosiy kasalliklarga chalingan yoki boshqa dori-darmonlarni qabul qiladigan bolalarda yanada yuqori. Maqolada NSAIDlarning ta'sir qilish mexanizmlari, ularning yuzaga kelishi mumkin bo'lgan nojo'ya ta'sirlari va nojo'ya ta'sirlar xavfini minimallashtirish uchun ko'rilishi mumkin bo'lgan choralar haqida umumiy ma'lumot berilgan.

**Tayanch iboralar:** YaQNDVlar, bolalar, o'lim, salbiy ta'sirlar, SOG fermentlari, dorilarning o'zaro ta'siri.

### **РИСК СМЕРТНОСТИ ПРИ ПРИМЕНЕНИИ НПВС У ДЕТЕЙ**

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В данной статье обсуждается риск смертности, связанный с применением нестероидных противовоспалительных препаратов (НПВП) у детей. Хотя НПВП обычно используются для облегчения боли и снижения температуры у детей, их побочные эффекты могут быть серьезными, включая желудочно-кишечные кровотечения, почечную недостаточность и сердечно-сосудистые события. Риск этих побочных эффектов еще выше у детей с сопутствующими заболеваниями или у тех, кто принимает другие лекарства. В статье представлен обзор механизмов действия НПВП, их потенциальных побочных эффектов и мер, которые можно предпринять для минимизации риска побочных эффектов.

**Ключевые слова:** НПВП, дети, смертность, побочные эффекты, ферменты ЦОГ, лекарственные взаимодействия.