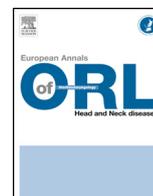




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SFORL Guidelines

Guidelines of the French Society of Otorhinolaryngology (SFORL): Nonsteroidal anti-inflammatory drugs (NSAIDs) and pediatric ENT infections. Short version



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ABSTRACT

Objectives: To present the guidelines of the French Society of Otolaryngology-Head and Neck Surgery concerning the use of non-steroidal anti-inflammatory drugs (NSAIDs) in pediatric ENT infections.
Methods: Based on a critical analysis of the medical literature up to November 2016, a multidisciplinary workgroup of 11 practitioners wrote clinical practice guidelines. Levels of evidence were classified according to the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system: GRADE A, B, C or “expert opinion”. The first version of the text was reworked by the workgroup following comments by the 22 members of the reading group.
Results: The main recommendations are: NSAIDs are indicated at analgesic doses (e.g. 20–30 mg/kg/day for ibuprofen) in combination with paracetamol (acetaminophen) in uncomplicated pediatric ENT infections (acute otitis media, tonsillitis, upper respiratory infections, and maxillary sinusitis) if: 0 pain is of medium intensity (visual analogue scale (VAS) score 3–5 or “Evaluation Enfant Douleur” (EVENDOL) child pain score 4–7) and insufficiently relieved by first-line paracetamol (residual VAS ≥ 3 or EVENDOL ≥ 4); 0 pain is moderate to intense (VAS 5–7 or EVENDOL 7–10). When combined, paracetamol and ibuprofen are ideally taken simultaneously every 6 h. It is recommended: (1) 0 not to prescribe NSAIDs in severe or complicated pediatric ENT infections; (2) 0 to suspend NSAIDs treatment in case of unusual clinical presentation of the infection (duration or symptoms); (3) 0 not to prescribe NSAIDs for more than 72 h.
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1. Introduction

The present guidelines are intended to update indications, contraindications and administration modalities for non-steroidal

anti-inflammatory drugs (NSAIDs), associated to antibiotics or not, in pediatric ENT infections, based on a critical analysis of the literature or else expert opinion. The rationale behind this work concerned changes to analgesia protocols in children due to the recently highlighted risks associated with codeine [1] and persistent controversy in France concerning risks of complications associated with NSAIDs.

The present guidelines do not focus on overall management of ENT infections in children, for which guidelines

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exist elsewhere [2–7], but seek only to clarify the role of NSAIDs.

The pathologies concerned comprise: acute otitis media, acute otitis externa, acute laterocervical and retropharyngeal adenitis, acute pharyngitis, tonsillitis, and acute rhinosinusitis. Dental and stomatologic infections are excluded.

2. Methods

2.1. Literature search

Relevant articles were selected on the PUBMED search engine developed by the American National Center for Biotechnology Information (NCBI) and hosted by the National Library of Medicine (NLM) of the National Health Institute (NHI). The search was conducted up to November 2016.

Search-terms comprised:

- non-steroidal anti-inflammatory drugs AND pharyngitis;
- non-steroidal anti-inflammatory drugs AND adenitis;
- non-steroidal anti-inflammatory drugs AND retropharyngeal abscess;
- non-steroidal anti-inflammatory drugs AND tonsillitis;
- non-steroidal anti-inflammatory drugs AND peritonsillar abscess;
- non-steroidal anti-inflammatory drugs AND deep neck infection;
- non-steroidal anti-inflammatory drugs AND otitis;
- non-steroidal anti-inflammatory drugs AND mastoiditis;
- non-steroidal anti-inflammatory drugs AND pediatric sinusitis;
- non-steroidal anti-inflammatory drugs AND ethmoiditis;
- non-steroidal anti-inflammatory drugs AND orbital infection;
- non-steroidal anti-inflammatory drugs AND meningitis;
- non-steroidal anti-inflammatory drugs AND subdural empyema;
- non-steroidal anti-inflammatory drugs AND epidural empyema.

The search was repeated, replacing “non-steroidal anti-inflammatory drugs” by “ibuprofen” and by “ketoprofen”. Guidelines were graded A, B, C or “expert opinion” according to level of evidence, in line with the January 2000 literature analysis and guideline grading guide of the French National Agency for Accreditation and Evaluation in Health (ANAES) [8].

2.2. Guideline writing

A 2-person organizational committee defined the objectives and program, and consulted the main relevant scientific societies to nominate 11 work-group members. The work-group drew up an initial version of the guidelines, which was submitted to a 22-member reading group set up by the organizational committee. The final version was drawn up by the work group in the light of the reading group’s comments.

The work and reading groups were composed so as to ensure balance between the various specialties, geographical regions and public or private sector practice.

The full version of the guidelines with rationales is available on-line at the French ENT Society website: <https://www.ENTfrance.org/wp-content/uploads/2017/06/NSAIDs-et-infections-ENT-pediatriques.pdf>.

3. Guidelines

3.1. Objectives of NSAID treatment

NSAIDs with market authorization for use in children under 15 years of age, along with the dosages and presentations of the main

Guideline No. 1

The sole objective of NSAID treatment in childhood ENT infection is to manage pain (GRADE A).

Among common non-complicated ENT infections, the most painful, and therefore those in which NSAIDs could be most useful for analgesic purposes when pain persists despite paracetamol treatment, are acute otitis media and pharyngitis (GRADE B). Rhinopharyngitis and maxillary sinusitis tend to be less painful and NSAIDs are thus less indicated as analgesics [9–11].

Treatment of fever is not a therapeutic priority (GRADE A).

Table 1

NSAIDs with market authorization for use in children, according to age (<15 years).

Drug	Formulation	Age/Weight
Ibuprofen	Oral route solution	3 months
	Tab 100/200 mg	6 years
Ketoprofen	Tab 400 mg	10–12 years or 40 kg
	Syrup	6 months
Tiaprofenic acid	Tab 25 mg, 50 mg	15 years
	IV	15 years
Niflumic acid	Tab 100 mg	4 years or 15 kg
	Tab 200 mg	
Diclofenac	Suppositories 400 mg	6 months
	Cap 250 mg	12 years
Naproxen	Tab 25 mg	6 years
	Tab 50 mg	12 years or 35 kg
Naproxen	Tab 250 mg, 275 mg	6–8 years or 25 kg

Table 2

Dosage and presentation of main analgesics available for oral administration.

Molecule	Dosage	Presentation
Paracetamol	60 mg/kg/day in 4 doses (max. 80 mg/kg/day)	Tablet, soluble tablet, capsule, syrup, sachet, IV vial, suppositories
Ibuprofen	20 to 30 mg/kg/day in 3 or 4 doses 2 presentations as syrup: according to concentration, the pipette delivers 7.5 mg/kg (every 6 h) or 10 mg/kg (every 8 h) (max. 400 mg per dose)	Tablet, soluble tablet, syrup
Tramadol	1 to 2 mg/kg every 6 to 8 h ^a (max. 100 mg per dose)	Drops and tablet
Morphine	Initial dose: 0.2 mg/kg 6 times daily (max. 20 mg) ^b or 0.1 mg/kg per dose for under-1 year-olds Possible loading dose ^c 0.4 to 0.5 mg/kg (max. 20 mg)	IR tablets and capsules drops and single-dose pipette

IR: immediate release.

^a Dose may be increased according to pain, up to 400 mg/day.

^b Dose adapted to pain by 50%/24 h steps, with no ceiling; target dose according to pain relief without troublesome side-effects.

^c Loading dose reserved to very intense pain and according to clinical situation.

oral analgesics used in pediatrics, are shown in Tables 1 and 2. Ibuprofen is the most widely studied and prescribed NSAID. Recommended analgesic dose is 20–30 mg/kg/day (Table 2), above which anti-inflammatory effects set in [12]. A literature review, comparing efficacy between ibuprofen and paracetamol in case of intense pain, in adults or children, demonstrated superiority for ibuprofen [13]. This superiority over other analgesics has been especially well shown in pediatric traumatology, moreover with fewer side effects such as nausea and vomiting [14–19]. There is less evidence for the analgesic efficacy of NSAIDs in otitis and pharyngitis, which is mainly a matter of expert opinion. There are no studies of the analgesic effects of NSAIDs in other childhood ENT infections.

The fact that treatment of fever is not a therapeutic priority was highlighted in 2005 in a review of

“management of fever in children” by the French health products safety agency, AFSSAPS (now ANSM), available at http://ansm.sante.fr/var/ansm_site/storage/original/application/8a3e72e8fec9c0f68797a73832372321.pdf. It is specified that:

- fever is only a symptom, and should not be a cause of fear;
- it very rarely leads to complications;
- there is no evidence of any preventive effect of antipyretic treatment with respect to hyperthermic convulsions or major hyperthermia syndrome;
- only episodes exceeding 41 °C can induce multi-organ failure;
- treatment is nevertheless recommended for fever exceeding 38.5 °C to reduce associated discomfort (headache, muscle ache, etc.);
- drug treatment should only be secondary to first-line measures: undressing, drinking, airing the room;
- there is no proven difference in antipyretic action between paracetamol and ibuprofen.

3.2. Indications for NSAIDs according to pain intensity

Guideline No. 2

In common non-complicated pediatric ENT infection (acute otitis media, pharyngitis, rhinopharyngitis, maxillary sinusitis), indications for and choice of analgesics depend on pain intensity (Grade A):

- in mild pain (visual analogue scale (VAS) score < 3 or “Evaluation ENfants DOuLeurs” (EVENDOL) child pain score < 4), abstention or, if necessary, isolated paracetamol is recommended.
- in moderate pain (VAS 3–5 or EVENDOL 4–7), paracetamol is recommended in first line, plus ibuprofen if paracetamol is insufficient (adjusted prescription).
- in moderate to intense pain (VAS 5–7 or EVENDOL 7–10) or pain resistant to paracetamol, NSAIDs should be associated to paracetamol [1].
- when associated, paracetamol and ibuprofen should ideally be administered simultaneously every 6 h. They may also be alternated every 3 h (i.e., every 6 h each), although with a risk of forgetting.
- in intense to severe pain (VAS ≥ 7 or EVENDOL ≥ 10) or pain resistant to associated paracetamol + ibuprofen, one or two doses of an oral morphine derivative (oral morphine, or tramadol in over-3 year-olds) should be associated [1].
- the objective is always to achieve no more than mild pain: VAS < 3 or EVENDOL < 4.
- in the particular case of acute otitis media with intense to severe pain, the classic option of analgesic paracentesis (also known as myringotomy) is borne out by no evidence.

To assess pain, if the child can understand and respond, the faces scale, pediatric VAS or a numerical scale is recommended (Table 3). In younger children, a behavioral score such as EVENDOL may be used. One needs to be on the lookout for children who are “too calm”: immobility, withdrawal, taking apparent refuge in sleep, and prostration may mask possibly intense pain [20].

In associating morphine derivatives for uncontrolled pain, attention should be paid to possible upper airway obstruction, even with tramadol, due to the risk of respiratory depression [21]. The French health authority recommends one or two low doses of morphine (0.1 mg/kg each) in uncontrolled pain, notably in hyperalgetic otitis [1].

Table 3
Pain scales for children.

Age	Scale	Threshold for treatment
0–7 years	EVENDOL (for all pain, acute or prolonged, 0–7 years) PPMP (Postoperative Pain Measure for Parents)	4/15
Self-assessment	According to child’s understanding and preference	
As of 4 years	Faces (FPS-R)	4/10
As of 6 years	VAS	3/10
As of 8 years	NS (0–10 numerical scale)	3/10

NB: when presenting a self-assessment scale, stay neutral and avoid disturbing or exaggerated descriptions of the upper limit such as “It really hurts a lot” or “It’s a very bad pain”.

The classic option of analgesic paracentesis (also known as myringotomy) for acute otitis media with intense to severe pain is borne out by no evidence [22].

3.3. NSAIDs have no impact on the progression of infection

Guideline No. 3

In pediatric ENT infection, there is no evidence that analgesic-dose NSAIDs reduce infectious symptom duration (GRADE A) or prevent progression of acute otitis media toward otitis media with effusion (GRADE B).

3.4. Contraindications and prescription limitations

A detailed list of contraindications for NSAIDs and precautions for use, particularly regarding drug interaction, is provided in a 2013 French National Drug Safety Agency (ANSM) document [23].

3.4.1. Contraindicated infections

Guideline No. 4.

NSAIDs are contraindicated in pediatric ENT infection in the following cases:

- on-going varicella;
- severe bacterial ENT infection (particularly exteriorized acute mastoiditis, retropharyngeal, retrostyloid or prestyloid abscess, facial, cervical or cervicomedial cellulitis, and non-maxillary acute sinusitis) or infection with complication (particularly labyrinthitis, facial palsy, meningitis, orbital or intracranial infection, locoregional or remote abscess, septic thrombophlebitis, septic metastasis or septic shock) (Expert opinion);
- any associated severe bacterial infection (particularly pleuropulmonary, cutaneous or soft tissue) (GRADE D)

Ongoing varicella is a well-known contraindication to NSAIDs due to the increased risk of invasive group-A beta-hemolytic streptococcus infection (GRADE C) [24,25].

Non-maxillary (ethmoidal, frontal or sphenoidal) sinusitis is included in the list of severe ENT infections due to the high rate (0.7%) of orbital or intracranial complications [26].

There is no clear evidence that NSAIDs aggravate risk of progression in childhood ENT infection. Associations between NSAIDs and occurrence of severe infection (ENT abscess, empyema) were reported only in retrospective studies of dubious quality [27,28].

Thus, with the exception of varicella, large-scale prospective studies remain to be performed to test the hypothesis that NSAIDs may aggravate progression in certain infections, whether ENT or not. It is noteworthy that, in countries in which NSAIDs are widely prescribed in children, there have been no reports of increased rates of severe infection. The pharmacovigilance committee of the French drug safety agency (ANSM) published on its website a report of a meeting on May 17, 2016 concerning infection risk related to NSAIDs [29]; their review of the literature and of bacterial infection associated with NSAIDs reported on the national pharmacovigilance data-base concluded that epidemiological studies since 2002 tend to show that NSAIDs increase the risk of bacterial infection of the skin and soft tissues in adults with herpes zoster, of invasive group-A streptococcal infection in children, and of pleuropulmonary effusion in community-acquired pneumonia in both adults and children. It further confirmed the risk of bacterial infection of the skin and soft tissues in children with varicella. The authors therefore recommended (1) revising the summary of product characteristics (SPC) for NSAIDs prescribed for non-rheumatologic pain so as to mention the risk of severe bacterial complications, notably of the skin, soft tissues and lung, in adults and children; (2) informing practitioners and the general public of these risks; and (3) making ibuprofen a prescription drug not available over the counter. The following points, however, should be noted:

- three years after the publication of this report, the recommended changes have not been implemented in the SPCs available on the Public Drugs Data-Base website (<http://base-donnees-publique.medicaments.gouv.fr>), and ibuprofen is still available over the counter;
- no similar reports have been made by supranational drug agencies, including European Medicines Agency (<https://www.ema.europa.eu/en>), or foreign authorities such as the American Food and Drug Administration (<https://www.fda.gov>);
- the report by no means precludes prescribing NSAIDs as short-course analgesics in non-severe childhood ENT infection under the conditions specified by the present guidelines.

Contraindications other than infections are:

- progressive gastroduodenal ulcer or history of peptic ulcer;
- history of digestive tract bleeding or perforation under NSAIDs;
- any on-going progressive hemorrhage;
- history of asthma triggered by NSAIDs;
- severe hepatocellular failure;
- severe heart failure;
- severe kidney failure;
- pregnancy beyond 6 months.

3.4.2. Drug associations

Certain associations are at risk:

- digestive ulcer, with NSAID associations, and especially aspirin, or corticosteroids;
- bleeding, with aspirin at anticoagulant dose, oral anticoagulants, anti-platelets, or selective serotonin uptake inhibitors as antidepressant treatment;
- dehydration and kidney failure, with conversion enzyme inhibitors (CEIs), diuretics, or angiotensin-2 receptor blockers (ARBs);
- hyperkalemia, with CEIs, ARBs, heparin, cyclosporin, tacrolimus, trimethoprim, or hyperkalemia-inducing diuretics.

Association to proton pump inhibitors is not recommended by the ANSM for short-course NSAID therapy in children [29].

3.5. NSAID side-effects and complications

Side effects in children are well known and need monitoring, but are very rare, as confirmed by a recent literature review of short-course NSAIDs for fever in children [30].

3.5.1. Complementary examinations

Guideline No. 5

No particular complementary examinations are necessary before initiating NSAID treatment for ENT infection in children (Expert opinion).

3.5.2. Information to patient and family

Guideline No. 6

The risk of severe complications related to NSAIDs is reduced by good information provided to patient or family regarding risks and action to be taken in case of onset of suggestive symptoms (Expert opinion).

3.5.3. Monitoring

Guideline No. 7

Monitoring of children under NSAIDs for ENT infection is clinical. Treatment should be suspended (GRADE A) in case of:

- unusual presentation of infection in terms of duration or symptomatology, suggesting a complication;
- epigastralgia or other digestive symptoms;
- skin rash, mucosal lesion or other sign of hypersensitivity; asthma attack;
- sign of aggravation or onset of cardiopathy
- dehydration.

3.6. Choice of drug, presentation and treatment duration

Guideline No. 8

Ibuprofen (authorized as of 3 months of age) and ketoprofen (as of 6 months) are available as syrups, well suited to children (GRADE B). The pediatric infectology literature mainly focuses on ibuprofen. Suppositories are not recommended unless the oral route is made difficult by refusal, major dysphagia or odynophagia, or vomiting (Expert opinion).

Aspirin, although a possible treatment as of 3 months of age, has no longer been used in pediatrics for several years, as it is suspected to induce Reye syndrome in case of varicella or influenza syndrome [31].

Guideline No. 9

To minimize NSAID side effects, treatment duration should be short. In childhood ENT infection, in which NSAIDs are prescribed for analgesic purposes, treatment should be discontinued on resolution of pain, and within a maximum 72 h, beyond which complications should be suspected in case of persistent pain and NSAIDs should be discontinued (Expert opinion).

4. Conclusion

The present guidelines recommend NSAIDs for analgesic purposes in non-complicated childhood ENT infection, respecting very precise indications and contraindications and not exceeding a treatment duration of 72 h, with discontinuation in case of signs suggestive of complications, and notably of unusual presentation in terms of infection duration or symptomatology.

Disclosure of interest

The authors declare that they have no competing interest.

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