

# Towards evidence based medicine for paediatricians

Edited by Bob Phillips

*Arch Dis Child* 2004;**89**:489–494. doi: 10.1136/adc.2004.050898

In order to give the best care to patients and families, paediatricians need to integrate the highest quality scientific evidence with clinical expertise and the opinions of the family.<sup>1</sup> *Archimedes* seeks to assist practising clinicians by providing “evidence based” answers to common questions which are not at the forefront of research but are at the core of practice. In doing this, we are adapting a format which has been successfully developed by Kevin Macaway-Jones and the group at the *Emergency Medicine Journal*—“BestBets”.

A word of warning. The topic summaries are not systematic reviews, through they are as exhaustive as a practising clinician can produce. They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature. What *Archimedes* offers are practical, best evidence based answers to practical, clinical questions.

The format of *Archimedes* may be familiar. A description of the clinical setting is followed by a structured clinical question. (These aid in focusing the mind, assisting searching,<sup>2</sup> and gaining answers.<sup>3</sup>) A brief report of the search used follows—this has been performed in a hierarchical way, to search for the best quality evidence to answer the question.<sup>4</sup> A table provides a summary of the evidence and key points of the critical appraisal. For further information on critical appraisal, and the measures of effect (such as number needed to treat, NNT) books by Sackett<sup>5</sup> and Moyer<sup>6</sup> may help. To pull the information together, a commentary is provided. But to make it all much more accessible, a box provides the clinical bottom lines.

The electronic edition of this journal contains extra information to each of the published *Archimedes* topics. The papers summarised in tables are linked, by an interactive table, to more detailed appraisals of the studies. Updates to previously published topics will be linked to the original article when they are available.

Electronic-only topics that have been published on the BestBets site ([www.bestbets.org](http://www.bestbets.org)) and may be of interest to paediatricians include:

- Is flexion/extension radiography useful in paediatric neck injuries?
- What is the sensitivity and specificity of proximal humeral fractures in diagnosing non-accidental injury?

Readers wishing to submit their own questions—with best evidence answers—are encouraged to review those already proposed at [www.bestbets.org](http://www.bestbets.org). If your question still hasn't been answered, feel free to submit your summary according to the Instructions for Authors at [www.archdischild.com](http://www.archdischild.com). Three topics are covered in this issue of the journal.

- In children undergoing chest radiography what is the specificity of rib fractures for non-accidental injury?
- Is ultrasonography required to rule out renal malformations in babies with isolated preauricular tags?
- Do non-steroidal anti-inflammatory drugs increase the risk of bleeding after tonsillectomy?

## GRADE: levels of evidence and grades of recommendation

With the explosion of evidence based guidelines there have been a large number of ways of describing the quality of evidence behind the recommendations offered. Faced with the current multiplication, a guideline user may be faced with the same recommendation which is classified “II-2, B”, “C+, 1”, or “strong evidence, strongly recommended”, depending on which system is used. Is there an easy way of understanding them? What do they mean anyway?

Most systems have the same basic methods at their heart. The guideline developers are first asked to assess the methodological quality of the studies which support a recommendation: this produces the “level of evidence”. With this information about the breadth of evidence supporting a decision or point of action, the developers are then asked to evaluate the whole of the evidence and how it applies to the recommendation at hand: this gives the “grade (or strength) of recommendation”. Where the systems vary is in how the study quality is assigned, which factors are included in assessing a grade or strength of recommendation, and if different axes are used for different types of question (for example, therapeutic, diagnostic, and prognostic). These differences can produce different “meanings” to the final judgements. A statement such as “All breast milk donors should be tested for HIV and HTLV” may receive a “D” recommendation because of the paucity of evidence, but this does not mean that such testing is not to be undertaken. In another system, this may receive a “1c+” recommendation that implies a low quality of evidence but overwhelming support for the action suggested.

An international collaborative group (GRADE) is developing a single consensus system to overcome some of these difficulties. The GRADE system is explained in greater detail on their website ([www.GradeWorkingGroup.org](http://www.GradeWorkingGroup.org)). In essence, the system asks guideline developers to think about the quality of the evidence by evaluating study design (for example, randomised controlled trial), execution (for example, allocation concealed), consistency and directness of the evidence (for example, using proteinuria rather than end stage renal failure). These factors should be looked at for each critically important outcome (for example, mortality rates, serious adverse events, and quality of life measures). To make a final judgement about the strength of a recommendation requires explicitly balancing the benefits and harms including the quality of evidence, the ability of the users to implement the recommendation, and the likely magnitude of impact. Including cost implications is the last step in the process. Each step can be recorded on an appropriate proforma to ensure the process is transparent.

How a single system will affect the way we read and write guidelines is yet to be seen. In time to come it may be that all guidelines have an open and disputable record to how their recommendations were arrived at. Until then, it's best to double check the system before you mistake your E for your A.

**Bob Phillips**, Evidence-based On Call, Centre for Evidence-based Medicine, University Dept of Psychiatry, Warneford Hospital, Headington OX3 7JX, UK; bob.phillips@doctors.org.uk

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Additional information on each of the topics is available on the ADC website ([www.archdischild.com/supplemental](http://www.archdischild.com/supplemental))

## In children undergoing chest radiography what is the specificity of rib fractures for non-accidental injury?

#### Report by

**R L Williams**, Department of General Practice, Manchester, UK; [docbob@medix-uk.com](mailto:docbob@medix-uk.com)

**P T Connolly**, Department of Intensive Care, Whiston Hospital, Merseyside, UK

doi: 10.1136/adc.2004.051615

While reading an orthopaedic text you find a table that states rib fractures are highly specific for non-accidental injury in children. No papers are referenced and you wonder what evidence exists to support this statement.

#### Structured clinical question

In children undergoing chest radiography [patients] are rib fractures on plain radiographs [test] specific for non-accidental injury [outcome]?

#### Search strategy and outcome

##### Secondary sources

Cochrane: rib fractures and non-accidental injury; no relevant reviews found.

##### Primary sources

Medline (including Medline corrections) 1966-01/02/2004. [(Validated paediatric search filter (March 2003) for Ovid<sup>1</sup>) AND (exp Child Abuse or non-accidental injury.mp or child abuse\$.mp or deliberate injury.mp or exp. domestic violence or child abuse, sexual or exp. Munchausen syndrome by proxy or exp torture or domestic violence.mp or Munchausen syndrome by proxy.mp. or torture.mp or non-accidental injuries.mp) and (exp.rib fractures or rib fracture\$.mp or posterior rib fracture\$.mp or multiple rib fracture\$.mp or bilateral rib fracture\$.mp or exp. thoracic injuries or thoracic injury.mp or chostochondral junction injuries.mp)] limited to human and English Language.

A total of 113 papers were identified; 105 were of insufficient quality for inclusion or irrelevant. One paper

was subsequently excluded on critical appraisal due to flaws in case selection.

#### Hand search of references

Three further papers of sufficient quality for inclusion.

#### Summary of papers

See table 1.

#### Commentary

A number of studies have sufficient data to derive a 2×2 table from which likelihood ratios could be calculated, if the data were alternatively presented. The paper (not appraised in this article) by Worlock and colleagues,<sup>1,2</sup> comparing patterns of injury in children with non-accidental and accidental injury is such an example. The rib fracture data are presented as total number of rib fractures, rather than absolute numbers of children in each sub-group. The presentation of data in this manner does not allow for the calculation of sensitivity, specificity, or likelihood ratios.

The small studies by Barsness and colleagues,<sup>2</sup> Bulloch and colleagues,<sup>4</sup> and Cadzow and Armstrong<sup>5</sup> support the premise that rib fractures in a child less than 3 years are predictive of non-accidental injury, while the data from Garcia and colleagues<sup>7</sup> show rib fractures in unselected age groups are poor predictors of non-accidental injury. Further analysis of the data by Garcia and colleagues<sup>7</sup> by age group may confirm the positive predictive value of rib fractures in non-accidental injury in young children. Thomas<sup>11</sup> also showed a lower predictive value for rib fractures in children who diagnoses at the time were felt not to be either pathological or accidental; however, on re-reading the paper these may well have been non-accidental in nature by current criteria. King and colleagues<sup>8</sup> and Merten and colleagues<sup>10</sup> reported data in a way that allows the calculation of test sensitivity. Their papers show rib fractures have low sensitivities in this setting, and as such the absence of a rib fracture does not rule out non-accidental injury.

In any study, patient selection affects the applicability of the results, a point of particular relevance to diagnostic test studies. A study carried out in ventilated children in a tertiary referral central is not applicable to a general practitioner presented with a report confirming a rib fracture in a 2 year old child. The largest UK data set is from Carty and Pierce;<sup>3</sup> however, this personal case series, while large in number, is unreflective of the situation in the emergency department or paediatric assessment unit. This selection bias leads to an overestimation of the specificity of rib fractures in the paediatric population.

To the authors' knowledge there is no nationally or globally agreed gold standard diagnostic tool for the diagnosis of non-accidental injury. As a result, the various studies use a variety of criteria against which the performance of radiological rib fracture in the diagnosis of non-accidental injury is assessed. A further weakness of the selected gold standards is the inclusion of the test being validated (chest x ray) within the gold standard test.

In all the reviewed papers there is a lack of explicit blinding between radiologists and investigating parties. The clinical information that accompanies a radiograph is an important factor in the interpretation of subtle differences in rib morphology. To minimise bias, partial blinding could be achieved by independent reporting of the chest radiograph without the accompanying components of a skeletal survey and clinical details.

The studies reviewed have obvious radiological and ethical limitations, which are difficult to circumvent in clinical practice. The study to answer the question asked in the title would need to look at all children undergoing chest radiography, with each child being investigated for non-accidental

injury through a standardised protocol. This would allow the calculation of the sensitivity and specificity of rib fractures for non-accidental injury in the population undergoing chest radiography. Issues of consent for such a study may be difficult to resolve, as the consent form would explain the reason for the study (the diagnosis of non-accidental injury) and lead to an underestimation of the prevalence of non-accidental injury, as abusers may not give consent for their child's inclusion.

### CLINICAL BOTTOM LINE

- In children with rib fractures, the likelihood of non-accidental injury decreases with increasing age.
- Rib fractures in children less than 3 years of age are highly predictive of non-accidental injury.
- The absence of a rib fracture on a chest radiograph in a child does not rule out non-accidental injury.

**Table 1** Chest radiography in non-accidental injury

Citation	Study group	Study type (level of evidence)	Outcome (for non-accidental injury)	Key results	Comments
Barsness <i>et al</i> , USA (2003)	62 children with rib fractures (<3 years). Sub-analysis of 3 758 trauma evaluations presenting to a US Level 1 Trauma Centre	Case series with non-independent reference standard (3B)	PPV Paper	95%	Retrospective study Unclear how figure in paper is derived
			Raw data analysis	82.3 (70–91)%	Criteria for diagnosis of non-accidental injury not defined
Carty and Pierce, UK (2002)	467 (425 <2 years) children referred for second opinion as to cause of injuries	Case series with non-independent reference standard (3B)	Specificity PPV	100 (96–100)% 100 (96–100)%	Retrospective personal case series
Bulloch <i>et al</i> , USA (2000)	39 children (<12 months of age) identified as having rib fractures on basis of standard American radiology codes	Case series with non-independent reference standard (3B)	Positive predictive value	82 (66.5–82.5)%	Retrospective study Each film reported by a single radiologist, with causality determined by case review involving 2 paediatricians Small numbers
Cadzow and Armstrong, Australia (2000)	18 infants (<2 years) with documented rib fractures in a tertiary referral paediatric centre	Case series with non-independent reference standard (3B)	Positive predictive value	83 (58.6–96.4)%	Retrospective study Each child's case reviewed by multi-disciplinary team to determine whether child was abused or not Small numbers
Leventhal <i>et al</i> , USA (1993)	215 children (<3 years) with fractures. Data collection from Emergency Medicine Department logs and Child Abuse Register	Case series with non-independent reference standard (3B)	Specificity	100 (94–100)%	Retrospective study
Garcia <i>et al</i> , USA (1990)	Case review of 2 080 trauma evaluations at Level 1 trauma centre. 33 children (0–13 years) with a rib fracture	Case series with non-independent reference standard (3B)	Positive predictive value	21 (9–39)%	Retrospective review No gold standard for NAI defined Not specifically looking at rib fractures in non-accidental injury Set in trauma centre
King <i>et al</i> , USA (1988)	189 (<1 month to 13 years) children referred to an assessment team for investigation of abuse. 163 less than 2 years of age	Case series with non-independent reference standard (3B)	Sensitivity	18 (12.8–24.2)%	Retrospective study Not explicitly stated whether all children received a chest radiograph Wide age range
Schweich and Fleisher, USA (1985)	21 children (3 months to 15 years 4 months) admitted to paediatric emergency care facility with rib fractures	Case series with non-independent reference standard (3B)	Positive predictive value	23 (5–41)%	Retrospective study Small numbers Wide age range
Merten <i>et al</i> , USA (1983)	Initial recruitment of 904 infants and children (3 weeks to 16 years) with "strong clinical evidence of abuse". 494 complete radiological examinations included in the analysis	Case series with non-independent reference standard (3B)	Age (years) stratified sensitivity		Retrospective
			<1 (n = 190)	10 (6–15)%	
			1–2 (n = 101)	8 (4–15)%	
			2–5 (n = 128)	2.3 (0.5–6.7)%	
			>5 (n = 75)	1.3 (0.0–7.2)%	
			All ages	6.3 (4.3–8.8)%	
Thomas, UK (1977)	25 infants (<1 year) with rib fracture	Case series with non-independent reference standard (3B)	Positive predictive value	24 (8–40)%	Inpatients and outpatients analysed Data collected 1969–1979 Small numbers

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## Is ultrasonography required to rule out renal malformations in babies with isolated preauricular tags?

### Report by

**R S Arora**, Senior House Officer, SCBU, University Hospital of Wales, Cardiff, UK;  
reemaraman@doctors.org.uk

**R Pryce**, Specialist Registrar, Paediatrics, Royal Gwent Hospital, Newport, UK  
doi: 10.1136/adc.2004.050427

**Y**ou join a new neonatal unit. On your routine baby check you find a newborn with an isolated preauricular tag/pit. The baby has no other malformation or dysmorphic feature on detailed examination. You know that this baby needs to have their hearing tested but you are not sure whether it needs an ultrasonogram as part of routine evaluation to rule out urinary tract anomalies. The unit where you worked previously had a policy of performing routine scans, but your registrar tells you that this is not the policy here. You decide to search for the evidence behind this.

### Structured clinical question

In newborns with isolated preauricular tags/pits [patients] is an ultrasonogram of the renal tract [test] required to rule out urinary tract malformations [outcome]?

### Search strategy and outcome

#### Secondary sources

Cochrane—None.

#### Primary sources

Pubmed—((((“Kidney/abnormalities”[MeSH] OR “Kidney/ultrasonography”[MeSH]) OR (“Urinary Tract/abnormalities”[MeSH] OR “Urinary Tract/ultrasonography”[MeSH])) AND “Ear/abnormalities”[MeSH])). Field: title/abstract. Limits: all infant: birth–23 months.

Sixty five results found and then each abstract read for relevant articles.

Embase—same search strategy. No additional papers.

### Search outcome

Six relevant papers found. See table 2.

### Commentary

The association between external ear abnormalities and renal malformation has been reported previously. There is a general consensus on the need to rule out a urinary tract malformation in a child with a gross ear malformation or when the isolated preauricular tag/pit is accompanied with other dysmorphic features.<sup>7</sup> Some experts have recommended that there is no need for renal ultrasound if isolated tags/pits are not associated with other malformation or dysmorphic feature.<sup>8</sup> However, the studies above give mixed results. The three older studies did not find any increase in number of renal malformations in those with isolated preauricular tags/pits, but they are all limited by small sample size and absence of controls. The other three studies have controls but are underpowered. The fact that the two largest studies which are from the same country with comparable sociodemographic population give opposite results, underlines the need for a larger sample size. This is not easy when you consider the fact that the incidence of preauricular tags and sinuses is around 5–10/1000 live births, and the prevalence of mild renal pelvis dilatation in general population by postnatal screening is 4.6% compared to a reported prevalence of renal malformations ranging from 2.2% to 8.6% in those with tags/pits. So to achieve a significant sample size, the study would have to be done over multiple centres for a considerable period of time.

At this stage what seems a sensible practice is that the presence of a preauricular tag or pit should lead to a careful search for other malformations or dysmorphic features, the presence of which will tilt the balance in favour of doing a renal ultrasonogram.

### CLINICAL BOTTOM LINE

- There is not enough evidence to derive a firm conclusion on the need for renal ultrasonogram in newborns with isolated preauricular tags/pits.
- The presence of a preauricular tag or pit should lead to a careful search for other malformations or dysmorphic features, the presence of which will tilt the balance in favour of doing a renal ultrasonogram.

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**Table 2** Ultrasonography in babies with isolated preauricular tags

Citation	Study group	Study type (level of evidence)	Outcome	Key result	Comments
Kugelman <i>et al</i> (2002)	Study group: 92 infants born with isolated preauricular tags or pits underwent renal ultra sonogram at 1–3 mth of age Control group: 95 consecutive healthy infants who underwent renal ultrasonography on 2nd day of life	Case control study (level 3b)	Urinary tract anomalies detected on ultra sonogram	2/92 (2.2%: 95% CI 0.2% to 7%) of study group had renal abnormalities 4/95 (4.2%: 95% CI 1.1% to 10%) of control group had renal abnormalities. (p=1.0)	The age disparity at time of examination between cases and controls might be a source of bias
Kohelet <i>et al</i> (2000)	Study group: 70 infants with isolated preauricular tags underwent renal ultrasonography on day 3–4 of life Control group: 69 infants without preauricular tags underwent urinary tract ultrasonography after day 5 as part of investigation for persistent regurgitation associated with cyanotic spells	Case control study (level 3b)	Urinary tract anomalies detected on ultra sonogram which were further investigated by voiding cystography and radionuclide scintigraphy (where necessary)	6/70 (8.6%: 95% CI 2.2% to 12.4%) of study group had abnormalities None (95% CI 0% to 3.6%) in control group had abnormalities. (p<0.02)	The study included only preauricular tags. There were no cases of renal malformation in the control group which is less than that of normal population. Also the study was not of sufficient power to make a firm conclusion
Mishra <i>et al</i> (2003)	Study group: 34 children with isolated preauricular tag  Control group: 34 children who underwent abdominal ultrasound for non-renal problems	Case control study (level 3b)	Urinary tract anomalies detected on ultra sonogram	3/34 (9%: 95% CI 0.6% to 8%) of study group had urinary tract abnormalities None in control group had urinary tract abnormalities (95% CI 0% to 3.5%). p<0.05	The study included only preauricular tags. There were no cases of renal malformation in the control group which is less than that of normal population. The sample size was small and the study was not of sufficient power to make a firm conclusion
Alexander <i>et al</i> (1992)	69 children preauricular sinus (2 with associated anomalies and 67 isolated) who were seen in ambulatory care paediatric clinic for problems unrelated to preauricular sinus or kidneys underwent renal ultrasonography	Case series (level 4)	Urinary tract anomalies detected on ultra sonogram who subsequently underwent voiding cystourethrogram	Overall 3/69 had significant abnormalities Only 1/67 (1.5%) of children with isolated sinus had an anomaly	The study only looked at preauricular sinuses and did not include tags. Also there were no controls
Kugelman <i>et al</i> (1997)	26 infants with preauricular tags (24) and pits (2). 24 had renal ultrasonography on day 3 of life	Case series (level 4)	Urinary tract anomalies detected on ultra sonogram)	No malformations found	Small sample size and no controls
Hudgins <i>et al</i> (1992)	Retrospective analysis of all paediatric ultrasounds over 2 year period and review of their medical records. 30 were for children with isolated ear abnormalities—microtia, pits, tags, and minor structural abnormalities	Case series (level 4)	Urinary tract anomalies detected on ultra sonogram	None of the 30 children with isolated ear abnormalities had abnormal renal ultrasounds	Small sample size and no controls

## Do non-steroidal anti-inflammatory drugs increase the risk of bleeding after tonsillectomy?

### Report by

**S R Desikan**, Registrar, St Richard's Hospital, Chichester, UK; meenadesikan@aol.com

**N G Meena**, SHO, East Surrey Hospital, Redhill, UK  
doi: 10.1136/adc.2004.050336

**Y**ou are a paediatric SHO covering the hospital wards. A 5 year old child has had tonsillectomy, and the nurse looking after this child says the child is in lots of pain.

She has given paracetamol but the child is still crying in pain. You consider giving a non-steroidal anti-inflammatory drug (NSAID) but you know that these agents interfere with platelet function and are worried about increased risk of bleeding. You also consider giving morphine but you know that it may cause nausea and vomiting.

### Structured clinical question

In children after tonsillectomy [patient] does the use of NSAIDs [intervention] compared with opiates [comparison] increase the risk of bleeding and decrease the risk of nausea or vomiting [outcome]?

### Search strategies and outcome

Cochrane—none.

Pubmed: search words—NSAIDs and tonsillectomy and bleeding.

Limits—English.

**Table 3** NSAIDs and post-tonsillectomy bleeding

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Moiniche <i>et al</i> (2003)	25 RCT (14 in children) of NSAID use perioperatively. 970 received a NSAID (diclofenac, ketorolac, ibuprofen, tenoxicam, naproxen, indomethacin, nimosulide) and 883 received no NSAID	Quantitative systematic review (level 1a)	Risk of reoperation Risk of vomiting	Odds ratio 2.33 with NSAIDs (95% CI 1.12 to 4.83). NNH 60 (95% CI 34 to 277) Relative risk 0.73 with NSAIDs (95% CI 0.63 to 0.85). NNT 9 (95% CI 5 to 19)	NSAIDs and morphine equianalgesic. Data on children compared to adults, or on the individual NSAIDs were too sparse to allow subgroup analysis
Marret <i>et al</i> (2003)	7 RCT (5 in children) of postoperative NSAID use. 262 patients received NSAIDs and 243 patients received control treatment (1995–2001)	Systematic review of randomised double blind control trials (level 1a)	Risk of reoperation	Control rate of reoperation 0.8%. NSAID rate 4.2% Odds ratio 3.8 (95% CI 1.3 to 12). NNH 29 (95% CI 17 to 144)	Data on children not analysed separately. No patient required blood transfusion

Search outcome: 47 hits (40 were relevant), two systematic reviews including all 25 good quality RCTs. Though both the reviews included adult patients, the majority of the patients in both the reviews were children. See table 3.

### Commentary

Tonsillectomy is a commonly performed operation in children, and is done on an outpatient basis in many centres. It is associated with severe postoperative pain, nausea, and vomiting. Vomiting is among the most common reasons for unscheduled readmission after outpatient tonsillectomy. Two recent postal surveys conducted in the United Kingdom to evaluate pain treatment after tonsillectomy in children found that NSAIDs were used in 45–70% of patients. The incidence of post-tonsillectomy bleeding severe enough to require reoperation for haemostasis ranged from 1% to 5.5%.

A well performed systemic review<sup>1</sup> found perioperative NSAIDs increased the risk of reoperation (OR 2.33 and NNH of 60) but were equianalgesic to opiates, and the risk of emesis was significantly decreased (with NNT of 9). The balance is about two more reoperations against nine fewer cases of postoperative nausea and vomiting.

Another systematic review with meta-analysis of randomised, double blind controlled trials of postoperative NSAID treatment looking primarily at the need for surgical electrocautery to stop bleeding found that 1 in every 29 patients treated with NSAIDs will need a reoperation. The authors suggested the use of NSAID therapy should be abandoned both at the hospital and at home.

NSAIDs act by inhibiting cyclo-oxygenase (COX) and thereby reducing prostaglandin synthesis and inhibiting platelet aggregation. Two COX isoenzymes have recently

been identified, the constitutive COX-1 isoform expressed in gastric mucosa and platelets and COX-2 isoform, which is upregulated during inflammation. However, selective COX-2 inhibitors do not inhibit platelet aggregation *in vitro*. Available studies of NSAID therapy for relieving pain related to tonsillectomy evaluated non-selective COX inhibitors. The way forward could be to investigate the use of COX-2 inhibitors which may provide similar pain relief without the risk of increased bleeding associated with non-selective COX inhibitors, and the use of local anaesthetic infiltration or dissection with high frequency ultrasound.

### CLINICAL BOTTOM LINE

- For every 100 patients undergoing tonsillectomy and treated with NSAIDs rather than opioids, two may need reoperation because of bleeding, but nine fewer will have postoperative nausea and vomiting.
- Compared with opioids, NSAIDs seems to be equianalgesic following tonsillectomy.
- Research into the use of cyclo-oxygenase type 2 inhibitors, which have minimal effects on platelet aggregation, is needed in children undergoing tonsillectomy.

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