Towards evidence based medicine for paediatricians

Edited by Bob Phillips

Archimedes seeks to assist practising clinicians by providing "evidence-based" answers to common questions that are not at the forefront of research but are at the core of practice (format adapted from BestBETS published in the *Emergency Medicine Journal*). A full description of the format is available online at http://adc.bmj.com/ifora/archimedes.dtl.

Readers wishing to submit their own questions—with best evidence answers—are encouraged to review those already proposed at www.bestbets.org. If your question still hasn't been answered, feel free to submit your summary according to the instructions for authors at http://adc.bmj.com/ifora/archimedes.dtl.

QUESTION 1

DOES ORAL ACICLOVIR IMPROVE CLINICAL OUTCOME IN IMMUNOCOMPETENT CHILDREN WITH PRIMARY HERPES SIMPLEX GINGIVOSTOMATITIS?

A 3-year-old previously well boy presents with a fever of 38.6°C and several ulcers and erosions extending from his lips, along the tongue and cheek, to the back of the throat. The lesions have all appeared within the last 2 days. He has been crying inconsolably over the past 24 h and is refusing food and drink. Considering the current evidence we question whether the use of oral aciclovir is indicated for primary herpes gingivostomatitis in children.

STRUCTURED CLINICAL QUESTION

In an immunocompetent child presenting with primary herpes simplex gingivostomatitis [patient], does oral aciclovir [intervention] reduce the duration of symptoms [outcome]?

Clinical bottom line

- Oral aciclovir given early in primary herpes gingivostomatitis has been shown to reduce duration of symptoms, improve healing of oral lesions and reduce infectivity of affected individuals. (Grade B)
- Current evidence supports the use of oral aciclovir (15 mg/kg/five times a day for 7 days) in cases of primary herpes gingivostomatitis in immunocompetent children presenting within 72 h of symptom onset. (Grade B)

Making science of the art

In the window of the Wellcome Collection in London artists work to interpret and explain science: it's an impressive experience for the irregular visitor. When faced with the presenting problems of a child and family, we are faced with trying to do the reverse. We have the sometimes inaccurate recollections of history, the variable responses of clinical examination and our own bias-riddled minds to bash through the "art of diagnosis" into a suitable explanation for the predicament and onwards into a management strategy. Can this really be evidence based?

The evidence base of diagnosis has been discussed in this column before,[1, 2] but usually in the setting of a single item, for example "How good is Bobbinogs sign at predicting rhotic consonant pronunciation?". This issue of Archimedes sees a review of clinical decision rules – simple combinations of clinically and laboratory parameters which are intended to more accurately and reliably make or exclude a diagnosis.

There are a few critical elements to bear in mind when appraising a clinical decision rule: its method of derivation, its usefulness when applied in different settings and its predictive ability.[3]

A decision rule is usually developed by taking a set of data and seeing which are the simplest rules that lead to defining groups at lowest and highest risk of a disease. This method is entirely dependent on the data it is made from – any chance associations will be impossible to identify from this. The rule needs to be tested again, either in the same place (OK) or in a different setting (better). (Different doctors, types of patients and situations can make a rule unusable. This may be particularly true of rules including elements of physical examination or history taking.) Confidence in a rule should be even better still if it has been tested in many different areas and actually proven to make a difference to patient-important outcomes. Finally, a judgement needs to be made about its predictive ability. Do you need it to make a diagnosis or exclude one? (Most rules are developed to do one, or the other, but not both.) How certain do you need to be of this? These are factors that require assimilation of the risks, patient preferences and healthcare structures in your own location.

Clinical decision rules can improve health care decisions,[4] but they don't always,[5] and like all clinical research, require appraisal before use.

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SEARCH STRATEGY AND OUTCOME

Cochrane Library: using "herpes AND gingivostomatitis AND aciclovir/acyclovir", "herpes AND gingivostomatitis", "herpes AND aciclovir", "aciclovir AND gingivostomatitis": one relevant result – "Acyclovir for treating primary herpetic gingivostomatitis" – currently in title stage (registered 23 May 2007).

PubMed: with no limits set using "herpes AND gingivostomatitis AND aciclovir", and "gingivostomatitis AND aciclovir" 24 publications were found. Fifteen were not relevant or unavailable in English. Two were letters. Two studies were relevant.[1 2] Five publications were review articles.[3–7] These five articles were scrutinised for relevant primary research citations which were not elicited directly by the PubMed search. Three such articles were found.[8–10]

Medline using OVID interface (1950 to August week 5 2007): with no limits set using "herpes AND gingivostomatitis AND aciclovir", and "gingivostomatitis AND aciclovir" 17 publications were found. Ten were not relevant or unavailable in English. Two articles were letters. Five articles were relevant; four of these articles had been identified in previous searches.[1–3 5] One new review article was identified which contained no new relevant primary research citations[11] See table 1.

Table 1 Does oral aciclovir improve clinical outcome in immunocompetent children with primary herpes gingivostomatitis?

Citation	Patient group*	Study type (level of evidence)	Outcomes	Key result	Comments
Amir *et al* (1997)[1]	61 children aged 1–6 years with clinical manifestations of gingivostomatitis (within 72 h of onset) and positive HSV cultures	Randomised double blind placebo controlled trial (level Ib, Jadad = 5)	Duration of oral lesions Fever Eating and drinking difficulties Viral shedding	Treatment group showed significantly reduced median duration of all symptoms (i: oral lesions 4 vs 6 days; ii: eating difficulties 4 vs 7 days; iii: drinking difficulties 3 vs 6 days; iv: extra-oral lesions 0 vs 5.5 days) and completion of viral shedding (1 vs 5 days). ($p<0.05$)	High proportion of subjects presenting with mild disease (<20 oral lesions)
Aoki *et al* (1993)[9]	68 children presenting within 96 h of symptom onset	Randomised double blind placebo controlled trial (level Ic, Jadad = 4)	Duration of oral lesions Gum swelling Hypersalivation Completion of viral shedding	Treatment group showed a significant reduction in median symptom duration of 20–50% (i: oral lesions 6 vs 8 days; ii: gum swelling 5 vs 7 days; iii: drooling 4 vs 8 days) and in completion of viral shedding (4 vs 10 days). ($p<0.05$)	Results presented but not published as an article Duration of treatment 10 days. Results thus not directly comparable to similar studies
Ducoulombier *et al* (1988)[8]	20 children (mean age 2 years) presenting within 96 h of symptom onset with positive isolation of HSV in cell culture	Randomised double blind placebo controlled trial (level Ic, Jadad = 4)	Duration of pain Hypersalivation Fever Duration of oral lesions	Significant improvement in pain and hypersalivation in treatment group. Mean duration of pain 4.3 days in aciclovir group vs 5.0 days in placebo group ($p<0.05$)	Study may be too small for valid comparison between groups
Cataldo *et al* (1993)[2]	162 immunocompetent children with herpetic gingivostomatitis (peak age of incidence 9–28 months)	Retrospective clinical and epidemiological study (level IIc)	Time to symptom regression Epidemiological aspects of HSV gingivostomatitis	More rapid symptom regression in children treated with 5–6-day course of aciclovir	Non-blind/random selection of treatment group combined with epidemiological study design means limited data on intervention can be elicited from this study in isolation
Mueller *et al* (1988)[10]	41 children with herpetic gingivostomatitis treated with aciclovir	Non-blind, uncontrolled, open study (level IIc)	Duration of oral lesions Duration of pain	90% free of pain and oral lesions after 6 days of treatment and afebrile after 3 days of treatment. Treatment considered "good or very good" in 85% of children	Subjective outcome measures limit validity of findings

*Where studies were not published fully in English, information regarding the age range of children included in analysis was not always available.
HSV, herpes simples virus.

COMMENTARY

Primary herpes simplex gingivostomatitis is a self-limiting condition and affected individuals may experience significant mouth pain, fever, and difficulty eating and drinking, as well as being highly infectious.[5] Although an approved treatment, retrospective data suggest that aciclovir is used infrequently in the management of this condition.[7] Aciclovir may cause a range of adverse effects including nausea, vomiting, diarrhoea and headaches, and is also a relatively expensive drug requiring administration five times a day (although cost has dropped substantially since its patent expired; for a 7-day course the cost is currently £9.21).[12 13] Concerns have been expressed regarding the possible selection of resistant strains of herpes with aciclovir being used for such common disorders. This is thought to be unlikely as, in a study of immunocompetent children receiving aciclovir for over 6 years, no resistant strains were identified.[14] Earlier and more severe recurrences of genital herpes have been demonstrated in subjects who received aciclovir during their primary illness. This is thought to be as a result of a decreased antibody response to herpes simplex viral proteins in such patients.[15 16] Nevertheless, no study identified has demonstrated this phenomenon in patients treated with a short course of aciclovir, as would be the case for primary herpes simplex gingivostomatitis.

No class I evidence was found in regard to the treatment of children presenting later than 96 h from symptom onset. In subjects presenting early (within 72 or 96 h), three small randomised controlled trials have demonstrated reduced symptom duration and faster lesion healing in patients treated with a course of oral aciclovir as compared to subjects treated with placebo,[1 8 9] findings which are broadly supported by two non-blinded retrospective studies.[2 10]

There is no consensus as to the optimum length of treatment and dose of aciclovir. None of the studies have examined the side-effect profile in relation to concomitant therapeutic gain, so evidence based risk-benefit analysis remains difficult. Concern has also been expressed about the lack of data supporting the use of oral aciclovir in younger children.[3] Two population analyses have found aciclovir to be well tolerated in children under 2 years of age in dosing regimens consistent with those used in the three randomised controlled trials discussed.[17 18]

Despite there being no consensus as to the treatment of immunocompetent children with primary herpes gingivostomatitis, the limited data available suggest that, while being moderately expensive, oral aciclovir given early on, reduces the duration of symptoms and infectivity of affected individuals, without causing unacceptably severe or frequently occurring side effects or long term sequelae.

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QUESTION 2

DISTINGUISHING BETWEEN TRANSIENT SYNOVITIS AND SEPTIC ARTHRITIS IN THE LIMPING CHILD: HOW USEFUL ARE CLINICAL PREDICTION TOOLS?

A 3-year-old boy presents to the emergency department with a limp. He has been reluctant to weight bear on his right leg during the day and has a temperature of 37.9°C. Hip examination is painful. What clinical or laboratory tests could help discriminate between septic arthritis and transient synovitis?

STRUCTURED CLINICAL QUESTION

In children [patient] presenting with acute hip pain, is there a single clinical or laboratory test [intervention] that will distinguish between septic arthritis and transient synovitis [outcome]?

SEARCH STRATEGY AND OUTCOME

Medline 1991–2007, using the PubMed interface. Search: "septic arthritis AND hip" resulted in 129 papers; "septic arthritis AND transient synovitis" resulted in 21 papers; "septic AND reactive AND arthritis AND hip" resulted in 10 papers. Limits: all child 0–18, published in the last 10 years, English search outcome. See table 2.

COMMENTARY

Distinguishing between septic arthritis and transient synovitis of the hip joint in the limping child can be a difficult clinical undertaking but is vital. The two conditions can present with similar symptoms and clinical features but the treatment and potential for negative sequelae are significantly different. Whereas transient synovitis runs a benign self-limiting course that can be managed with observation and NSAIDS, septic arthritis needs urgent diagnosis, operative irrigation and antibiotics. Poor outcomes are associated with diagnostic delays, and negative sequelae include osteonecrosis of the femoral head, growth arrest and sepsis.[1 2]

There is much debate amongst clinicians over how best to accurately and quickly distinguish septic arthritis from transient synovitis with no one pathognomonic symptom, clinical feature, blood test or investigation confirming the diagnosis.

If there is sufficient clinical suspicion of septic arthritis, the hip joint must be aspirated under image guidance (ultrasound or fluoroscopy) and the fluid sent for laboratory examination. Joint aspiration is considered the gold standard test but is an invasive and unpleasant procedure, particularly for a child, usually requiring general anaesthesia.

The question is, "what amounts to sufficient clinical suspicion?". How much weight should be attached to each clinical finding or investigation result? There is therefore a need for a clinical prediction rule (CPR) to aid the clinician to safely distinguish between the two diagnoses and avoid both delayed treatment and over-investigation.

Kocher's (1999) clinical prediction model to differentiate between septic arthritis and transient synovitis forms the basis of subsequent validation studies by Luhmann (2004), Caird (2006) and Kocher (2004).[3–6] Kocher (2004) prospectively evaluated 154 patients and found that the same four variables (table 2) were still most likely to predict the outcome of septic arthritis, with a diminished, but nevertheless good, diagnostic performance in the new patient population (93% probability with all four predictors present).[6] Luhmann *et al*, in another tertiary children's hospital, applied the same proposed CPR retrospectively on all children who had undergone aspiration of the hip joint as part of their work-up for acute hip pain.[4] Despite similar patient demographics, they found a lower predicted probability of septic arthritis (59%) when all four variables were present. These findings emphasise the value of validating all clinical prediction rules prior to application in clinical practice. Caird *et al* published a validation study of Kocher's CPR, including 48 children presenting with signs and symptoms suspicious enough to warrant ultrasound-guided hip aspiration. The findings supported Kocher's model to a certain extent: the likelihood of a patient having septic arthritis increased with the number of positive factors; however, the predicted probability of septic arthritis with none of the predictors present was still 16.9%.

The retrospective derivation study by Jung *et al*[7] included 97 patients with transient synovitis and 27 with septic arthritis. There are two main issues with their methodology. Firstly, not all patients included in the study underwent the golden standard investigation. Secondly, only patients with a positive synovial culture were definitely diagnosed with septic arthritis, oddly leaving joints with a positive microscopy (ie, synovial aspirate white cell count >50 000 ml^{-1}) but negative culture possibly classified as transient synovitis. Finally, Jung's rule has not been externally validated.

Clinical bottom line

- There is no one investigation or blood test that can distinguish between septic arthritis and transient synovitis. (Grade B)
- There is no clinical prediction rule that has been validated by multi-centre prospective studies involving large patient numbers. (Grade B)
- The combined presence of fever, non-weight bearing, C-reactive protein >20 or erythrocyte sedimentation rate >40, and a white cell count >12 is suspicious of septic arthritis. (Grade B)

QUESTION 1

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