Towards evidence based medicine for paediatricians

Edited by Bob Phillips

Arch Dis Child 2006;91:789-794

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.¹ *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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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,² and gaining answers.³) 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.⁴ 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 Sackett⁵ and Moyer⁶ 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.

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 www.archdischild.com. Three topics are covered in this issue of the journal:

- Does neonatal BCG vaccination protect against tuberculous meningitis?
- Does dexamethasone reduce the risk of extubation failure in ventilated children?
- Should metformin be prescribed to overweight adolescents in whom dietary/behavioural modifications have not helped?

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How to read your journals

Most people have their journals land, monthly, weekly, or quarterly, on their desk, courtesy of their professional associations. Then they sit, gathering dust and guilt, for a period of time. When the layer of either is too great for comfort (or the desk space is needed for some proper work), the wrapper is removed and the journal scanned. But does how people read reflect their information needs or their entertainment requirements?

It is not uncommon to find people straying from the editorial introduction to the value added sections (like obituaries, Lucina-like summary pages, and end-of-article fillers) rather than face the impenetrable science that sits between them. I think that this is probably unhelpful, and would urge readers to do one more thing before placing the journal in the recycling. Scan the table of contents; if it mentions a systematic review or a randomised trial, then read at least the title and the abstract's conclusions. If you agree, pat yourself warmly on the back for being evidence based and up-to-date. If you disagree, ask if it will make any impact on your clinical (or personal) life. If it might, run through the methods and quickly appraise them. Does it supply higher quality evidence than that you already possess? If it does, it's worth reading. If it doesn't, don't bother too much.

There are new innovations which might aid the tedious task of consuming research effort. The on-line Précis section of the *Archives* provides a highly readable version of the contents page to whet one's appetite. Finally, it's worth mentioning that evidence based summary materials (like *Archimedes*, or *Journal Watch*) are always worth reading—and if you didn't think that you wouldn't be here, would you?

Does neonatal BCG vaccination protect against tuberculous meningitis?

Report by

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doi: 10.1136/adc.2006.098459

An 8 month old baby girl, of Eastern European parents, presents with a week long history of coryzal symptoms for which she has been taking oral antibiotics. She is pyrexial, irritable, and unwell on examination. She is admitted with a clinical diagnosis of meningitis and commenced on intravenous cefotaxime. A lumbar puncture is performed and microscopy reveals an elevated number of white cells (majority lymphocytes), low glucose, and protein of 0.9 g/l. She does not respond to conventional therapy and

Table 1 Neonatal BCG vaccination and tuberculous meningitis (TBM)

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Colditz <i>et al</i> (1995) ⁸	Meta-analysis of 5 RCT and 11 case-control studies; 5 case-control studies report on TBM specifically	Meta-analysis (1a)	Overall risk of developing TB reduced with BCG vaccination Increased protective effect against TBM particularly	TBM specific studies: overall OR 0.356 (95% CI 0.18 to 0.7) and combined protective effect 0.644 (95% CI 0.3 to 0.82)	Articles included from as early as 1946; vaccine efficacy was extracted or computed
Rodrigues <i>et al</i> (1993) ¹	Meta-analysis of 10 RCTs (published since 1950) and 8 case control studies ("evidence of control confounding and bias")	Meta-analysis (1a)	Variation in effect of BCG against pulmonary TB Higher protective effect for TBM and miliary TB than pulmonary TB	Statistically significant heterogeneity, therefore could not calculate summary protective effect Summary protective effect for RCTs 81% (95% CI 62% to 91%) Case control studies 75% (95% CI 61% to 84%)	Inclusion criteria not as robust as current meta-analyses, e.g. inclusion of a paper described as a trial which itself only included 2 cases Regression analysis was used to give a summary protective effect of BCG against TBM and miliary TB
Thilothammal <i>et al</i> (1996) ²	107 cases with confirmed AAFB in CSF. 321 controls, block matched for age and sex with diagnosis of febrile seizures	Case control study (3b)	BCG protects against TBM	Odds ratio 0.23 (95% CI 0.14–0.37); vaccine efficacy 77% (95% CI 71%–83%)	Data not statistically significant for >8 y old group
Zodpey <i>et al</i> (1996) ³	92 cases confirmed AAFB in CSF. 92 controls randomly selected with conditions other than TB, matched age, gender, socioeconomic status	Case control study (3b)	BCG vaccine effective against TBM	Odds ratio 0.1346 (95% CI 0.06–0.29); vaccine effectiveness 86.54% (95% CI 70.38–93.88%)	Does not divide group by age or weight/nutrition which has been reported to influence efficacy of vaccine in other studies
Mittal <i>et al</i> (1996) ⁴	128 records of cases of TBM; 182 controls from inpatients, matched for age (no other criteria given)	Case control study (3b)	BCG vaccine effective against TBM for <5 years old (same statistical analysis used for initial and subgroups)	Odds ratio 0.36 (95% CI 0.19–0.7), under 5 years old group	Data collected from case notes, assumes accurate documentation in notes recovered and also 20 records missing. Does not give criteria for diagnosis
Awasthi <i>et al</i> (1999) ⁵	192 cases of clinically or LP diagnosed TBM. 70 controls admitted with no disorder of CNS	Case control study (3b)	BCG vaccination offers protection against TBM	Odds ratio for TBM in children with BCG scar 0.44 (95% CI 0.24–0.81) and prevented proportion of cases 56% (95% CI 19–76%)	Excluded, as controls, cases with abnormal neurology. Observer bias if clinicians knew of TBM trial
Zhang <i>et al</i> (2000) ⁶	Shun-yi county population, 498 549 discontinued BCG vaccination	Cohort study (4)	Prevalence of TB fell in children aged 6–7 y despite not vaccinating with BCG	1950 TB in 46% of 5–9 y olds; 1995 TB in 1.4% of 6–7 y olds (without BCG scars)	TB prevalence and herd immunity was significantly altered between 1950 and 1995 therefore poor comparison

nothing is growing on CSF or blood culture. There is no history of contact with tuberculosis and she was vaccinated with a single dose of BCG at birth. She was an intrauterine growth retarded baby but had no subsequent problems. The possibility of tuberculous meningitis is discussed and a colleague tells you that there is contradictory evidence about the efficacy of neonatal BCG vaccination against pulmonary tuberculosis. You question the efficacy of neonatal BCG vaccination against tuberculous meningitis.

Structured clinical questions

How protective is BCG vaccination with regard to tuberculous meningitis?

In children suspected of having mycobacterial meningitis [patient] does a history of BCG vaccination (or presence of BCG scar) [risk factor] influence the likelihood of tuberculous meningitis [outcome]?

Search strategy

Secondary resources

Cochrane Library

Search term: TB meningitis; 3 reviews, none relevant.

Search term: BCG vaccine; 9 results, including Spruyt 2002. No other reviews relevant

Best BETS

Search term: tuberculosis; no results.

Search term: meningitis; no results linking TB and meningitis.

Clinical Evidence

Search term: tuberculosis; 56 results, none relevant.

Primary resources

Search performed January 2005.

PubMed

Search term: TB meningitis; 2986 hits.

Search term: TB meningitis AND BCG; 188 hits.

Limits of English language + human + all child (0–18 years).

A brief review of the articles at this point revealed one described as a meta-analysis, published in 1993. We therefore took an arbitrary decision to review this meta-analysis and subsequent papers.

This yielded 38 hits, of which 8 articles were relevant. Articles were excluded if: they were letters/comments only; they were studies where the majority of patients were adults; the effect of BCG vaccine or TB meningitis was not directly examined, i.e. results not site specific.

See table 1.

Commentary

Neonatal BCG vaccination is established in the UK for at-risk groups. The papers we reviewed made widely ranging suggestions, from the recommendation that in low risk areas routine BCG ought not to be used,⁶ to the comment that in some areas a second early childhood immunisation might be required to maintain immunity.⁴ New recommendations for BCG vaccination in the UK have been published recently.⁷

The meta-analysis published in 1993¹ sought to differentiate between different sites of disease and the protective effect of BCG. This study, however, included a range of papers from the previous three decades (earliest 1953), and the inclusion criteria used were not robust, for example a paper labelled a randomised controlled trial was included which only considered two cases. Some of their evidence, we suspect, might not be included if a formal meta-analysis were performed using current standards. The meta-analysis conducted in 1995⁸ was more substantial and aimed to quantify the efficacy of BCG and the duration of protective immunity.

Since this time there have been a number of case control studies concurring that neonatal BCG vaccination offers significant protection against TB.^{2 3 5} Papers that draw the conclusion that there is poor protection from BCG immunisation against TBM are weak in design and method; this is upheld by Colditz meta-analysis.⁷

A number of queries were raised considering other factors which may influence BCG effectiveness. Children who were malnourished or underweight or of low socioeconomic status were deemed to have less protective effect from BCG.^{2 5} It was also suggested that BCG loses its efficacy after a number of years. The 1995 meta-analysis concluded that BCG efficacy may persist 10 years after infant vaccination.

BCG vaccination does have a significant protective effect against tuberculous meningitis (75–87%). Therefore a history of vaccination and a BCG scar can afford a certain degree of reassurance when considering TBM in infants and young children. However, there have been questions raised about the duration of vaccine efficacy and therefore the effectiveness of BCG vaccination in older children. There will always be a proportion of children not protected by the vaccine they are given, including BCG. There is limited evidence to help determine whether a history of BCG vaccination and/or presence of a scar alters the likelihood of TBM. Indeed, it might be true that the BCG scar is a proxy marker for a higher risk of TB exposure. As always, each situation needs to be judged on clinical grounds. Although protective, it is clear that BCG vaccination is not 100% efficacious in preventing TBM.

CLINICAL BOTTOM LINE

- BCG vaccination is partially protective against tuberculous meningitis; therefore a history of BCG vaccination or the presence of a BCG scar affords some degree of reassurance when considering TBM. (Grade C)
- Where TB meningitis is clinically suspected, the diagnosis needs to be rigorously investigated and a history of BCG does not rule out the diagnosis. (Grade C)

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Does dexamethasone reduce the risk of extubation failure in ventilated children?

Report by

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doi: 10.1136/ad.2006.098798

John, a 4 year old boy, has been mechanically ventilated for three days during recovery from a blunt chest trauma. According to his level of ventilator support, he is considered to be ready to be extubated. The previous patient had to be reintubated as a result of postextubation laryngeal oedema. You wonder whether corticosteroids may reduce this risk of extubation failure.

Structured clinical question

In mechanically ventilated children [patient] does corticosteroid administration [intervention] reduce the chance of reintubation due to laryngeal oedema [outcome]?

Search strategy and outcome

Secondary sources

Cochrane Database of Systematic Reviews; 1 limited to newborn infants.¹

PubMed clinical queries

“Respiration, Artificial”[MESH] AND (Hydroxycorticosteroids) [MESH] AND systematic; 1 reference not related to the question.

(“Intubation, Intratracheal”[MeSH]) AND systematic[sb] AND (Hydroxycorticosteroids)[MESH]; no references.

PubMed

(Anti-Inflammatory Agents OR Anti-Inflammatory Agents/therapeutic use OR Anti-Inflammatory Agents/therapy OR hydroxycorticosteroids) AND systematic[sb]) AND (“Intubation, Intratracheal”[MeSH] OR “Respiration, Artificial”[MeSH]); 25 references, 2 relevant studies^{1 2} (table 2).

(“Intubation” or (“failure” and “extubation”)) AND (Anti-Inflammatory Agents OR Anti-Inflammatory Agents/therapeutic use OR Anti-Inflammatory Agents/therapy OR hydroxycorticosteroids); 30 references, with 4 relevant.^{3–6}