Management of febrile children in the age of the conjugate pneumococcal vaccine: a cost-effectiveness analysis


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Five strategies were studied for the management of febrile children:

Clinical judgement (CJ). Patients at low risk (i.e., with the best possible Yale Observation Score (YOS) which considers quality of cry, reaction to parent stimulation, state variation, colour, hydration and response to social overtures) would receive no testing or treatment; patients with any elevation in YOS would receive a blood culture (BC) and treatment at the initial visit, and those with positive blood cultures would receive appropriate follow-up management.

BC. Highly febrile patients who otherwise appeared well would receive a BC at the initial visit and would be sent home without antibiotic treatment. Those with positive BC would be asked to return and receive appropriate follow-up management.

BC plus treatment (BC+T). Highly febrile patients otherwise well appearing would receive BC and would be treated empirically with antibiotics. Those patients with positive BC would be asked to return for follow-up management. Those patients with false-positive BC would be evaluated and either hospitalised or sent home. Those patients with negative BC would not require further treatment although they may experience complications because of the antibiotic administration.

CBC plus BC plus selective BC plus treatment (CBC+BC+T). CBC would be performed in all highly febrile children, otherwise well appearing. If the white blood cell count (WBC) were greater than the specified cut-off, a BC would be performed. If the WBC were below the specified cut-off, no further testing or treatment would be given. For those patients with undiagnosed bacteremia, further complications of their condition would require additional evaluation, antibiotic therapy, and hospitalisation. If the WBC were above the cut-off, a BC would be performed and antibiotic treatment would be given. If the BC were positive, the patients would receive appropriate follow-up management.

BC plus BC plus selective treatment (CBC+BC+ST). Highly febrile patients who appeared non-toxic would receive a CBC and BC at the initial visit. If the WBC were less than the specified cut-off, the patient would be sent home without treatment. If the BC were positive, follow-up would be initiated. If the WBC were greater than the specified cut-off, an antibiotic would be administered at the initial visit. In that case, if the BC were positive, follow-up management would be initiated.

The authors stated that the follow-up management of children with positive BC depended on the clinical state at the follow-up visit: febrile children without an identifiable source of infection were given repeated BC, were administered antibiotics, and were discharged from the hospital; those with positive BC and persistent fever, entered one of the following states: resolved, persistent bacteremia, pneumonia, cellulitis, bone/joint infection, or meningitis. They would receive BC and antibiotics and would be admitted to the hospital. Those children with persistent bacteremia would enter one of the following states: resolved, pneumonia, cellulitis, bone/joint infection, or meningitis. Children with false-positive BC would be followed-up and could be either discharged home or admitted to the hospital and treated with antibiotics until the identification of the contaminant.

Type of intervention
Treatment.

**Economic study type**
Cost-effectiveness analysis.

**Study population**
The study population comprised febrile 3- to 36-month-old children, temperature 39 degrees or more, with no identified source of infection.

**Setting**
The setting appears to have been hospital. The economic study was carried out at the Children's Hospital, Boston, USA.

**Dates to which data relate**
The studies included in the effectiveness analysis were published between 1976 and 2001. The costing was derived from data corresponding to the period between 1991 and 1999, and from a study published in 2000. The price year was 1999.

**Source of effectiveness data**
Effectiveness data were derived from a review of the literature.

**Modelling**
A decision analytic model was used to model health outcomes and costs of the proposed strategies.

**Outcomes assessed in the review**
For each of the strategies analysed, the authors assessed: the prevalence of pneumococcal bacteremia; the probability of infectious complications (bone/joint infection, cellulitis, meningitis, persistent bacteremia, and pneumonia); the probability of neurologic sequelae from meningitis; the probability of death from meningitis; the probability of fever with and without antibiotics; the efficacy of the antibiotics for bone/joint infection, cellulitis, meningitis, persistent bacteremia, and pneumonia; the probability of antibiotic complications associated with rash/diarrhoea and anaphylaxis; the probability of false-positive BC; the probability of hospitalisation for false-positive BC; the sensitivity and specificity of WBC, considering different WBC cut-offs: 10, 15, 16, 17, 18, 19, and 20x10^9/L; and the sensitivity and specificity of clinical judgement. These outcomes were included as input parameters in the decision analytic model.

**Study designs and other criteria for inclusion in the review**
The authors did not state the criteria for the inclusion of the studies in the review. Only one randomised clinical trial and one meta-analysis were included, among a total of, at least, 39 primary studies included in the review.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
Not stated.

**Methods used to judge relevance and validity, and for extracting data**
Number of primary studies included
At least 39 primary studies were included in the review.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
The results of the review were as follows:

The prevalence of pneumococcal bacteremia was 0.0145.

The probability of bone/joint infection complications was 0.01.

The probability of cellulitis complications was 0.02.

The probability of meningitis in bacteremic patients was 0.01 in treated patients and 0.04 in untreated patients.

The probability of persistent bacteraemia complications was 0.18.

The probability of pneumonia complications was 0.05.

The probability of neurologic sequelae from meningitis was 0.30.

The probability of death from meningitis was 0.06.

The probability of fever without antibiotics was 0.64.

The probability of fever with antibiotics was 0.21.

The antibiotic efficacy for bone/joint infections was 0.0.

The antibiotic efficacy for cellulitis was 0.25.

The antibiotic efficacy in preventing meningitis was 0.75.

The antibiotic efficacy for persistent bacteraemia was 0.95.

The antibiotic efficacy for pneumonia was 0.70.

The probability of antibiotic-complications associated with rash/diarrhoea was 0.14.

The probability of antibiotic-complications associated with anaphylaxis was 0.0005.

The probability of false-positive BC was 0.01.

The probability of hospitalisation for false-positive BC was 0.26.

The sensitivity of WBC, considering different WBC cut-offs (10, 15, 16, 17, 18, 19, and 20x10^9/L) was: 10 = 0.98, 15
= 0.86, 16 = 0.77, 17 = 0.72, 18 = 0.64, 19 = 0.56, and 20 = 0.48.
The specificity of WBC, considering different WBC cut-offs (10, 15, 16, 17, 18, 19, and 20x10^9/L) was: 10 = 0.44, 15 = 0.77, 16 = 0.81, 17 = 0.84, 18 = 0.87, 19 = 0.90, and 20 = 0.92.
The sensitivity of clinical judgement was 0.28.
The specificity of clinical judgement was 0.82.

Methods used to derive estimates of effectiveness
Authors’ assumptions were used to derive an estimate of the sensitivity of BC.

Estimates of effectiveness and key assumptions
The authors assumed the sensitivity of BC to be 100%.

Measure of benefits used in the economic analysis
In order to estimate the number of life-years saved by each of the strategies, the authors assumed a life expectancy of 75 years. The total number of life-years saved was calculated for the lifetime of a cohort of 100,000 patients.

From the results of the decision analytical model, the authors assessed, per strategy: the number of life-years saved compared with the comparator 'no work-up'; the number of children needed to treat to prevent a case of meningitis; the cases of: meningitis, bone/joint infection, cellulitis, persistent bacteremia, and pneumonia; the number of false-positive cultures considering different WBC cut-offs: 10, 15, and 20x10^9/L; the cases of antibiotic-associated rash/diarrhoea; and the cases of anaphylaxis.

Direct costs
Resource quantities and unit costs were not given separately. The direct costs included in the analysis seem to have been those of the health service. The authors reported that the charges for the following services were included in the direct costs: laboratory studies, hospital rooms, emergency department visits, office visits, physician fees, antibiotics, average charges for hospitalisation, follow-up, and medical care for children with meningitis and subsequent neurologic disability. The Handbook of Fees and Fee Committee for the Department of Medicine from the hospital was used to obtain the charges for laboratory studies, hospital rooms, emergency department visits, office visits and physician fees. The average charges of hospitalisations were derived from the fiscal database at the hospital from 1991 to 1999. As the authors stated, the charges do not reflect the true opportunity costs to society of the resources used. In order to obtain a better estimator of the costs, they adjusted the charges by means of a cost-to-charge ratio of 0.66. The costs incurred in the future were discounted at an annual discount rate of 3%. The price year was 1999.

Statistical analysis of costs
No statistical analysis of costs was reported.

Indirect Costs
The authors included as indirect costs those related to the future impact of disability on a patient's time and resources, and the costs incurred by parents, such as time lost from work. They also appear to have included as indirect costs, those derived from the special education for children with meningitis. The costs related to time lost from work due to bacteremia and meningitis were based on a published study (see Lieu et al., ‘Other Publications Of Related Interest’). Using the results of this study and making some assumptions, the authors estimated the other costs arising from lost work. Resource quantities and costs were not reported separately. These costs were discounted at a 3% annual discount rate. The price year was 1999.
Currency
US dollars ($).

Sensitivity analysis
The authors performed a one-way sensitivity analysis on CE ratios to assess the impact of changes over the range of the variables related to both health outcomes and costs. Two-way sensitivity analyses were also performed to assess the interaction of 2 variables on the results of the model. The area of uncertainty investigated was therefore variability in data. The ranges considered in the sensitivity analyses were given in the article.

Estimated benefits used in the economic analysis
An annual discount rate of 3% was used to discount life-years saved. Other outputs from the decision model were fully reported in the paper.

The numbers of life-years saved were:

28 for CJ; 58 for BC;
101 for BC+T; 98 for CBC+BC+T when a cut-off of 10x10^9/L was considered;
86 for CBC+BC+T when a cut-off of 15x10^9/L was considered;
49 for CBC+BC+T when a cut-off of 20x10^9/L was considered;
100 for CBC+BC+ST considering a cut-off of 10x10^9/L;
94 for CBC+BC+ST, considering a cut-off of 15x10^9/L; and
78 for CBC+BC+ST, with a cut-off equal to 20x10^9/L.

Cost results
The total costs of each of the strategies proposed, calculated for a cohort of 100,000 patients, were (in millions of dollars):

$54.8 for 'no work-up';
$50.6 for CJ;
$58.7 for BC;
$51.6 for BC+T;
$47.8 for CBC+BC+T with a cut-off of 10x10^9/L;
$46.9 for CBC+BC+T with a cut-off of 15x10^9/L;
$52.4 for CBC+BC+T with a cut-off equal to 20x10^9/L;
$50.9 for CBC+BC+ST with a cut-off of 10x10^9/L;
$51.0 for CBC+BC+ST with a cut-off of 15x10^9/L; and
$54.5 for CBC+BC+ST with a cut-off equal to 20x10^9/L.
Synthesis of costs and benefits
Three different rates of bacteremia were considered by the authors to calculate the cost-effectiveness (CE) ratios. The authors stated that they eliminated strategies by dominance and extended dominance, and reported some of the incremental CE ratios for the remaining strategies.

The baseline case considered a rate of bacteremia of 1.5%. In this case, CBC+BC+T dominated no work-up using a cut-off equal to 15x10^9/L. Using a lower WBC cut-off of 10x10^9/L resulted in an incremental CE ratio of $72,300 per life-year gained.

When a rate of bacteremia of 1% was considered, CJ dominated no work-up. The use of CBC+BC+T (using a cut-off equal to 15x10^9/L) had an incremental cost-effectiveness ratio of $30,800 per additional life-year saved. The use of a lower WBC cut-off (10x10^9/L) resulted in a cost-effectiveness ratio of $236,500 per life-year saved.

Considering a rate of bacteremia of 0.5%, CJ had the lowest cost-effectiveness ratio of $38,000 per life-year saved when compared to no work-up. The other strategies presented cost-effectiveness ratios higher than $300,000 per life-year saved.

The results of the other sensitive analyses showed that the results of the model were sensitive to changes in the probability of meningitis, probability of neurologic complications, probability of antibiotic efficacy in meningitis, sensitivity of CJ, and cost of CBC and BC. Two-way sensitivity analyses showed that strategies involving testing and treatment became significantly less cost-effective when the rates of bacteremia and meningitis, and the rates of bacteremia and efficacy of antibiotics declined.

Authors’ conclusions
Under the current estimate of bacteremia, CBC+CB+T (using a cut-off of 15x10^9/L) is a reasonably approach to treating febrile children. CJ becomes useful at a rate of bacteremia of 1%, although CBC+BC+T (using a cut-off of 15x10^9/L) generates more life-years saved at little additional costs. If widespread use of the conjugate pneumococcal vaccine reduces the overall rate of occult bacteremia to 0.5%, CJ remains a cost-effective strategy in the management of young febrile children, while strategies including empiric testing and treatment have very high CE ratios (greater than $300,000 per life-year saved).

CRD COMMENTARY - Selection of comparators
The authors did not provide an explicit justification for the comparators. However, no work-up is a widely used comparator in cost-effectiveness analysis. Moreover, 5 alternative strategies were compared with no work-up; another sixth strategy was excluded, and justification was given for its exclusion. Therefore, a positive aspect of the study was the consideration of a wide range of alternative strategies.

Validity of estimate of measure of effectiveness
The authors did not state whether a systematic review of the literature had been undertaken, which may have hindered the validity of the effectiveness results. Although at least 39 studies were used to obtain the effectiveness results, the authors did not state how they derived the effectiveness results from these studies, nor did they consider criteria to include previous studies in the review, reinforcing the previous limitations of the study. It seems that the authors used data from the available studies selectively, and they did not consider the impact of differences between the primary studies when estimating effectiveness. These limitations may have been reduced by means of the wide range of sensitivity analyses they performed. No justification was provided for the assumption about the sensitivity of BC.

Validity of estimate of measure of benefit
The estimation of benefits was modelled by means of a decision analytical model, which seemed appropriate for the analysis. Although the authors stated that two measures of health benefit were considered in the study (life-years gained and cases of meningitis prevented), they did not report the CE ratios related to the cases of meningitis prevented.
Validity of estimate of costs
A positive aspect of the study was that the authors adopted a societal perspective, which may be the most desirable in this context, since it attempts to consider all the benefits and costs of the strategies under study. It appeared that all the costs, both direct and indirect, related to the perspective adopted were included in the analysis. Resource quantities and unit costs were not reported separately, which hinders generalisability to other settings and reduces transparency. However, sensitivity analyses of costs were performed, the price year was given and discounting was appropriately undertaken. Although the authors adjusted the estimated charges by means of a cost-to-charge ratio in order to reflect the true opportunity costs of the interventions, they did not justify the value of the ratio used.

Other issues
The authors made appropriate comparisons of their results with those from other studies, showing some differences between their findings and the results obtained in other studies. The generalisability of the results to other settings appeared to have been, in part, addressed, since they reported results for different epidemiological characteristics of the population under study. Results were selectively reported, although it can be difficult to publish all results from a model with many outputs. The authors' conclusions regarding treatment being cost-effective must be viewed in the light of the opportunity cost, which such a study cannot show, i.e., we do not know what the cost and loss of benefit of displacing other technologies in order to fund any of those recommended would be.

Implications of the study
The authors recommend that, if the introduction and widespread use of the conjugate pneumococcal vaccine leads to a reduction of the rate of bacteremia to 10.5%, clinicians should re-evaluate their approach to highly febrile children and eliminate strategies that use empiric testing and treatment.

However, if such a reduction is not reached, clinicians must evaluate the epidemiologic characteristics and the costs of the alternative strategies within their setting, in order to establish the most appropriate strategy for highly febrile children. These conclusions should be viewed in the light of the caveats identified above, especially with regards to claims of being cost-effective.

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