The treatment of rheumatic carditis: a review and meta-analysis

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Authors' objectives
To undertake a literature review and meta-analysis of the existing studies, attempting to demonstrate the superiority of salicylates or corticosteroids in preventing the sequelae of active carditis valvular heart disease.

Searching
MEDLINE was searched from 1966; Index Medicus was also searched but the search dates were unclear.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) reporting the uses of salicylates and corticosteroids in rheumatic fever or rheumatic carditis were included in the meta-analysis if they fulfilled the following criteria: adequate case definition as determined by use of the Jones criteria; proper randomisation of patients to treatment with either salicylates or some form of corticosteroids; non-overlap of patients with other studies included in the meta-analysis; and follow-up for at least 1 year for determination of an apical systolic murmur.

Specific interventions included in the review
The interventions studied included variable doses of prednisolone, hydrocortisone, cortisone, adrenocorticotropic hormone (ACTH) and acetylsalicylic acid.

Participants included in the review
The participants included children and male airmen, patients with and without carditis at entry, patients experiencing a first attack of acute rheumatic fever and patients with pre-existing heart disease.

Outcomes assessed in the review
The outcome assessed was the presence of an apical systolic murmur at 1 year post-entry, or the presence of a new apical systolic murmur at 1 year in patients with pre-existing disease.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The quality of the included trials was assessed using the guidelines published by Chalmers et al. (see Other Publications of Related Interest no.1). The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction. The treatment effect for each study was expressed as the estimated relative odds of having a pathological apical murmur at 1 year. This was calculated separately for all patients and for those patients who had carditis at entry.

Methods of synthesis
How were the studies combined?
A summary OR was calculated using the fixed-effect model of Wolf (see Other Publications of Related Interest no.2), and the Cochran semi-weighted estimator using the random-effects model of DerSimonian and Laird (see Other
How were differences between studies investigated?
The chi-squared test was used to assess heterogeneity between studies. A sensitivity analysis was performed by repeating the analysis after removing each of the studies in turn.

Results of the review
Five RCTs (N=1,027,905) were used to assess the odds ratio (OR) of having a pathological apical murmur 1 year post-event. Eleven non-randomised and 6 further RCTs were also reported, but were not included in the meta-analysis. [A: Reasons are given for the exclusion of these trials from the meta-analysis]

Overall OR: when using the fixed-effect model, the OR was 0.99 (95% confidence interval, CI: 0.74, 1.31) and the chi-squared test for heterogeneity was 9.01 (P>0.05); using the random-effects model, the OR was 0.88 (95% CI: 0.53, 1.46). Removing any one of the studies did not alter the conclusions appreciably.

Patients with carditis at entry: when using the fixed-effect model, the OR was 0.96 (95% CI: 0.69, 1.35) and the chi-squared test for heterogeneity was 11.73 (P<0.025); using the random-effects model, the OR was 0.78 (95% CI: 0.39, 1.55). Removing any one of the studies did not alter the conclusions appreciably.

Authors’ conclusions
The question of whether corticosteroid therapy is marginally superior to salicylates for the prevention of valvular disease from rheumatic fever remains open.

CRD commentary
By limiting the literature search to two sources some relevant studies may have been omitted. The inclusion criteria for studies were defined but there were no details of the methods used to either select the studies or to extract the data. The main outcome assessed was the presence of an apical systolic murmur, but although the authors mentioned that this auscultatory outcome may be less than satisfactory, there was no consideration given to measuring the agreement between assessors. The authors acknowledged that a more sensitive means of detecting carditis, such as echocardiography, may improve the definition of carditis but highlighted the lack of such facilities in developing countries where rheumatic fever is a significant health problem. The authors stated in the discussion that the lack of homogeneity between studies may make aggregation of the trials questionable.

The authors suggested possible sources for the heterogeneity, e.g. differences in patient populations, differences in dosing regimes and bias in observation of the outcome, but concluded that the reasons remain unclear. In view of this heterogeneity, it would have been helpful to have had baseline comparisons of patient characteristics including severity of disease, concurrent therapy and time from onset of illness to intervention. Other problems with the primary studies included the following: a lack of blinding, though this is stated as being impossible given the nature of the interventions; the cushioned side-effects of the steroid; inadequately powered studies; analysis not based on the intention to treat principle; and the transfer of patients allocated to salicylates to steroid treatment. In view of the withdrawals it may have been justified to repeat the analysis using a worst scenario assumption. [A: However, we do not feel that intent to treat analyses on the part of the investigators would have affected the results very much since there were few lost to follow-up or crossed over]. The quality of the included studies was assessed but results of this assessment and details of the methodology were not reported.

In summary: the literature search was limited; there was insufficient detail given of the primary studies, and the methodology used to select studies, extract data and assess quality; unaccounted for heterogeneity between studies; a lack of intention to treat analysis; and the trials were conducted between 1955 and 1965. Given these factors, the question of the superiority of steroids or salicylates remains unanswered.

The authors state that the incidence of the disease has altered spontaneously over the last half century and it is uncertain what relevance trials conducted 30 to 40 years ago have for patients with rheumatic fever today. Different populations may experience different attack rates and different risks of valvular heart disease.

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Implications of the review for practice and research
In view of the changing nature of rheumatic fever and uncertainties of the most efficacious therapy for rheumatic carditis, further research is required.

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Other publications of related interest

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.