Frequency and risk factors of anthracycline-induced clinical heart failure in children: a systematic review
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Authors' objectives
To evaluate the existing evidence of the frequency and risk factors of anthracycline-induced clinical heart failure (A-CHF) in children.

Searching
MEDLINE was searched from 1966 to December 2000 (search terms were reported) and the reference lists of relevant articles and reviews were checked. Only studies published in the English language were considered eligible.

Study selection
Study designs of evaluations included in the review
No inclusion criteria relating to study design were reported. The included studies were cohort studies that monitored patients from the start of the anthracycline treatment, cohort studies of patients who survived childhood cancer, and subgroups of these cohorts.

Specific interventions included in the review
Studies of anthracycline therapy (doxorubicin, daunorubin or epirubicin) were eligible for inclusion. Details of the anthracycline therapy used in the included studies were incomplete.

Participants included in the review
Studies that included more than 50 children were considered for inclusion. Studies in which it was not possible to separate adults and children were excluded. Details of the participants in the included studies were incomplete.

Outcomes assessed in the review
Studies that reported on the incidence of heart failure with clinical symptoms were considered for inclusion.

How were decisions on the relevance of primary studies made?
Two reviewers assessed the validity of the included studies.

Assessment of study quality
Validity was assessed using the criteria for prognostic studies described by the Evidence-Based Medicine Group. These included the use of a well-defined representative sample with similarity at baseline, adequate follow-up, complete follow-up, objective and unbiased outcome criteria, and adjustment for important prognostic factors. Each study was graded on the basis of meeting each of these criteria to give a total score ranging from zero to five. Two reviewers assessed the validity of the included studies.

Data extraction
Two reviewers abstracted the data and resolved any disagreements by consensus. The frequency and cumulative incidence of A-CHF and their 95% confidence intervals (CIs) were calculated for each study. For studies that reported the number of patients with and without certain risk factors, and the number of patients with and without A-CHF, the relative risk (RR) and 95% CI for the risk factors were calculated.

Methods of synthesis
How were the studies combined?
The relation between potential predictive factors and A-CHF were analysed across studies using a multivariate linear regression model with a backward selection strategy. Possible predictive factors included in the model were study design, the validity of the study, type of anthracycline treatment, cumulative dose of anthracycline, and maximal dose of anthracycline within one week. Only studies that reported data on all these factors were included in the model. A logistic transformation of the cumulative incidence of A-CHF was used, with 0.5 being added to each incidence figure (because 2 studies reported 0% incidence) prior to logistic transformation.

How were differences between studies investigated?
Differences between the included studies were discussed in the text.

Results of the review
Thirty studies described in 25 articles met the inclusion criteria; 12,507 children were treated with anthracyclines. Nineteen studies recruited children at the start of anthracycline therapy and 11 studies included survivors.

The inter-observer agreement for selecting the studies for inclusion was 95%.

All studies were found to have methodological limitations (median quality score 3; range: 0 to 4).

The reported frequency of A-CHF varied between 0 and 16%.

The RR of possible risk factors of A-CHF were assessed in 10 studies. The following factors were found to be statistically significant: a higher cumulative dose (4/5 studies, i.e. 4 of the 5 studies), radiation therapy in the heart region (3/4 studies), age less than 4 years (1/1 study), children (1/2 studies), a higher maximal dose in 1 week (2/2 studies), daunorubicin (1/1 study), amsacrine (1/1 study), black race (1/1 study), female (1/1 study) and trisomy 21 (1/1 study).

The multivariate regression analysis showed that anthracycline type and the maximal dose in 1 week explained a considerable part (66%) of the variation in A-CHF frequency. The predictive frequency of A-CHF for patients treated with doxorubicin was 3.1% higher than for those treated with daunorubicin (95% CI: 0.6, 11.2). The predictive frequency of A-CHF for patients treated with a maximal dose of greater than 45 mg/m2 within 1 week was 5.8% higher than for those treated with a dose of less than 45 mg/m2 (95% CI: 1.7, 14.1).

Authors' conclusions
Doxorubicin and a dose above 45 mg/m2 within 1 week seemed to increase the frequency of A-CHF. Well-designed and executed studies are needed to accurately estimate the frequency of A-CHF and reliably assess the importance of potential risk factors.

CRD commentary
The review question was clear in terms of the interventions, participant and outcomes of interest. However, the authors did not state which study designs were eligible for inclusion. Only one electronic database was searched and no attempt was made to look for unpublished studies. The limited search and the restriction to studies published in English means that some important information may have been missed, as the authors acknowledged. The study selection, data extraction and quality assessment processes were carried out in duplicate, which helps to reduce errors and reviewer bias.

The authors appear to have analysed the data appropriately, although they noted that the results of the review were limited by the serious methodological limitations and poor reporting within the included studies. Potential risk factors were not well defined in the studies and some risk factors are still unknown. Only 10 studies reported sufficient data to calculate the RR for potential risk factors, and most of these studies only reported data on one or two factors. The authors also noted that the regression analysis was limited by the possible influence of confounding due to the use of non-randomised comparisons, and by there being no evaluations of the influence of factors such as age, gender distribution, radiation therapy and duration of therapy. The authors' conclusions appear to follow from the results presented.
Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that further well-designed and executed studies are needed to accurately estimate the frequency of A-CHF and reliably assess the importance of potential risk factors.

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