Chronic kidney disease after hematopoietic cell transplantation: a systematic review
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CRD summary
This review concluded that chronic kidney disease after haematopoietic stem cell transplantation was likely to be common and affect a significant proportion of patients who survived beyond 100 days post transplantation, but further confirmation was required. The authors’ conclusions appeared cautious, but the review findings may not be reliable considering the numerous limitations in the review methods and study data.

Authors' objectives
To determine the incidence and risk factors for the development of chronic kidney disease after haematopoietic cell transplantation (HCT). A secondary aim of the review was to determine the incidence of other renal-related outcomes including end-stage renal disease, hypertension and proteinuria.

Searching
MEDLINE, EMBASE and Science Citation Index were searched for English-language publications up to February 2007. Search terms were reported. Abstracts from the American Society of Nephrology and American Society of Hematology were searched between 2000 and 2006. Reference lists of retrieved studies were screened for further studies.

Study selection
Cohort studies of at least 10 patients who underwent HCT and survived for at least 100 days after transplantation were eligible for inclusion in the review. Eligible studies had to report the assessment of one or more renal function outcomes such as serum creatinine (SCr), estimated or actual glomerular filtration rate (GFR) and creatinine clearance (CrCl).

Included studies evaluated cohorts of patients from 57 different institutions in nine countries (79.3% North America, 18.9% Europe, 1.2% Japan and 0.6% Australia). Studies spanned the period from 1970 to 2004. Studies assessed mixed groups of adults and children (43%), solely adults (32%) and solely children (25%). Types of HCTs varied and included allogeneic transplants only (32.1%), autologous transplants (21.4 %) and mixed transplant types (46.4%). Patients were followed up for between three months and nine years. Chronic kidney disease was defined differently across the studies. All of the studies specified that chronic kidney disease occurred after at least 100 days following HCT. Kidney function was assessed using a variety of measures that included: formulaic estimations (such as Schwartz formula, Cockcroft-Gault equation and the Modification of Diet in Renal Disease equation); SCr measures; urinary CrCl or urinary clearance of 51creatinine-ethylenediaminetetracacetic acid; and direct measures that used inulin clearance. Some studies used multiple methods. Other types of outcomes assessed outcomes in the studies included incidence of end-stage renal disease that required haemodialysis and proteinuria. Studies investigated various risk factors for chronic kidney disease, such as acute renal failure, graft versus host disease (GvHD), long-term use of cyclosporine-A (CsA) and total body irradiation exposure.

Studies were screened for inclusion by two independent reviewers. Discrepancies were resolved through consensus.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Incidence of chronic kidney disease after HCT and mean change in estimated GFR/CrCl from pre- to post-transplant were reported. For the analysis of risk factors, the number of patients with and without chronic kidney disease who were exposed to each risk factor were extracted and used to calculate odds ratios (ORs) with 95% confidence intervals (CIs).

Two reviewers independently extracted data from each included study. Discrepancies were resolved through consensus. Primary study authors were contacted for clarification and missing data if required.
Methods of synthesis
Studies were grouped by outcome. Proportions of patients with chronic kidney disease were compared using two sample tests on the equality of proportions using large-sample statistics. Pooled weighted mean differences were calculated for eGFR/CrCl; mean values were pooled regardless of whether or not they were standardised to body surface area. Risk factor odds ratios were pooled with 95% CIs using a random effects model.

Statistical heterogeneity was assessed using the Q-statistic and the $I^2$ statistic. Potential sources of heterogeneity were investigated using subgroup analyses according to the type of transplant (autologous versus allogeneic) and the patient group (adult versus child).

Results of the review
Twenty-eight cohorts reported in 26 publications (n=9,317 patients; 7,317 survived at least 100 days and 5,337 survived at least 100 days and had kidney function assessed) were included in the review. Many of the studies were retrospective and uncontrolled (number not reported). The number of assessed patients ranged from 17 to 1,635.

Risk of chronic kidney disease after allogeneic HCT was 27.8% in comparison with 25.2% after autologous HCT (difference 2.6%, $p=0.40$). When allogeneic and autologous HCT patients were combined, incidence of chronic kidney disease was 13.9% (difference 11% to 14%, $p<0.0001$) in comparison with autologous and allogeneic transplants alone. Pooled risk of chronic kidney disease for allogeneic versus autologous HCT showed no significant difference between the two groups of patients. Incidence of chronic kidney disease was higher for adults (30.2%) than children (18.2%); the incidence in mixed populations of adults and children was 14.3%.

Approximately 16.6% of HCT patients developed chronic kidney disease with a decrease in glomerular filtration rate of 24.5mL/min/1.73m$^2$ after 24 months. The glomerular filtration rate decreased more moderately for allogeneic patients versus autologous patients (-40.0 versus -18.6mL/min/1.73m$^2$). Data from further analyses were reported in the review.

Numerous risk factors associated with development of chronic kidney disease after HCT were reported in the studies. The most frequently reported factors were acute renal failure (four cohorts), long-term use of CsA (five cohorts), cGvHD (six cohorts) and cumulative dose of total body irradiation (seven cohorts). The pooled estimate for cGVHD as a risk factor was OR 1.75 (95% CI 1.08 to 2.84) with significant heterogeneity ($I^2>50\%$). All of the risk factor analyses showed significant heterogeneity. Three risk factors showed no significant associations with the development of chronic kidney disease after HCT.

Other outcomes included 7.8% of patients with proteinuria and 0.8% of patients with end-stage renal disease; hypertension was reported in 12.4% of patients.

Authors’ conclusions
Chronic kidney disease after haematopoietic stem cell transplantation was likely to be a common problem that affected a significant proportion of patients who survived beyond 100 days post haematopoietic stem cell transplantation, but this observation required further confirmation.

CRD commentary
This review assessed a clearly defined research question. The authors searched relevant sources for data. Some studies in languages other than English were excluded and only published studies were eligible for inclusion, so the review was at risk of language and publication biases. Conference abstracts were searched. The risk of reviewer error and bias was low, as two independent reviewers were involved in all stages of the review process. The reliability of the review data was difficult to assess, as the authors did not perform a validity assessment. The small sample size in many studies and frequent use of retrospective and uncontrolled designs meant that data were likely to be at risk of bias. Studies varied in terms of outcome measures, definitions, populations and study designs. Statistical heterogeneity was assessed and some attempt was made to investigate potential sources of clinical heterogeneity, but subgroup analyses were not always possible due to the limited number of studies. A lack of control groups limited the analysis and no comparison was reported for the rate of chronic kidney disease in normal healthy populations. The analysis of risk factors failed to take
into account the effect of confounders. The authors acknowledged that heterogeneity and other factors may have limited their findings and that further studies were required to confirm their findings.

The review conclusions appeared cautious, but may not be reliable because of limitations in the review methods and study data.

### Implications of the review for practice and research

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

**Research:** The authors stated that further controlled prospective studies to assess the long-term incidence of chronic kidney disease following haematopoietic stem cell transplantation were required. Studies needed to use consistent definitions of chronic kidney disease and standardised measures of renal function.

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