Effect of integrated traditional Chinese medicine and Western medicine on the treatment of severe acute respiratory syndrome: a meta-analysis

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CRD summary
The authors concluded that the treatment of severe acute respiratory syndrome with combined traditional Chinese medicine and Western medicine appears encouraging, but further investigations are required. The authors appear to have considered the limitations of the included studies, and their conclusion for further research into the use of traditional Chinese medicine appears reasonable.

Authors' objectives
To assess the effectiveness of combined traditional Chinese medicine (TCM) and Western medicine (WM) with WM alone for treating patients with severe acute respiratory syndrome (SARS).

Searching
MEDLINE, PubMed, EMBASE, the Cochrane Library, CNKI and Chinese Biomedical Database were searched from 2002 to August 2006; the search terms were reported. In addition, the references of retrieved articles were checked. Publications were restricted to those in English and Chinese.

Study selection
Studies including patients diagnosed with SARS, based on clinical signs and epidemiology suggested by the World Health Organization (WHO) were eligible for inclusion. The included studies involved patients with mild or critical SARS.

Studies comparing combined TCM and WM (TCM-WM) with WM alone in the treatment of SARS were eligible for inclusion. TCM could include raw herbs or refined herbal products in the form of single herbs, mixtures of different herbs, or herbal extracts. The included TCM studies used compound herbs of anti-SARS formulae (including gypsum, anemarrhena, atractylodes, aspidum, Artemisia/sweet wormwood herb, bupleurum, peony, scute, antelope horn powder, rhizaoma copitidis, golden thread, curcuma, re-rooted sage, fritillaria, coptis), other combinations of herbal medicines, or herbal extracts. The included WM studies used empiric antibiotics such as azithromycin (0.5 g/day), levofoxacin (0.4 g/day) and ceftriaxone (2 to 4 g/day); antiviral drugs such as ribavirin (0.5 to 1 g/day); corticosteroid such as methylprednisolone (80 to 320 mg/day); and/or thymosin (50 to 200 mg/day). Where reported, the duration of treatment ranged from 10 days to 3 weeks.

Included studies reported on mortality rates, cure rates, resolution of lung infiltrates, dosage of corticosteroid (average daily dose, cumulative dose and course of corticosteroid treatment), CD4+ cell count and time to defervescence. The mortality rate was defined as the proportion of deaths among SARS patients receiving treatment. The cure rate was defined as the proportion of patients whose fever remained normal (35.7 °C) for at least 7 days without using any anti-fever medications; symptoms of respiratory systems disappeared; and partial or complete resolution of the pulmonary infiltrates as demonstrated by chest radiographs. The time to defervescence was defined as the time from hospital admission to the patient’s temperature returning to the normal range and remaining so for at least 7 days.

Randomised controlled trials (RCTs) and non-randomised controlled trials (non-RCTs) were eligible for inclusion.

Two reviewers independently screened studies for relevance and any disagreements were resolved through discussion.

Assessment of study quality
Validity was assessed using the Jadad criteria, with items on method of randomisation, double-blinding, and the reporting of withdrawal and drop-outs for RCTs. A score of one was given for each item (maximum score of three). Studies were also assessed for estimation of sample size and intention-to-treat analysis.

The validity assessment process was not clear, but it appears that two reviewers may have assessed validity and resolved
any discrepancies through discussion.

**Data extraction**
Two reviewers extracted data on each outcome, ultimately to calculate the risk ratio (RR) with 95% confidence intervals (CIs). Rate differences (RDs) were calculated for dichotomous outcomes and weighted mean differences (WMDs) for continuous outcomes, along with 95% CIs. Formulae for the calculations were reported in the review. Any discrepancies between reviewers were resolved through discussion.

**Methods of synthesis**
RRs, RDs and WMDs were pooled using a random-effects model where heterogeneity was significant, otherwise a fixed-effect model was used. Heterogeneity was assessed using the $\chi^2$ test. Sensitivity analyses were carried out by excluding non-RCTs. Subgroup analyses were also conducted, based on sample size and the presence of adequate information on randomisation.

**Results of the review**
Fifteen (reported as 16) RCTs and 9 (reported as 8) non-RCTs were included in the review (n=1,668, reported as n=1,678). Studies reporting the severity of SARS included 547 patients with mild SARS and 519 with critical SARS. Sample sizes ranged from 12 to 237 patients.

Seven RCTs scored two points on the Jadad scale and the remaining studies scored one point. One RCT was reported as single-blinded, none of the studies reported on drop-outs or withdrawals or sample size estimation, and the authors reported that most studies did not provide adequate information for intention-to-treat analysis.

There was a significant difference in mortality rates (10 studies) between the treatment groups, with lower mortality among patients receiving TCM-WM than among patients receiving WM: 3.7% versus 10.9% (RR 0.38, 95% CI: 0.22, 0.63, p=0.0002).

There was a significant difference in cure rates (9 studies) between the treatment groups, with a higher cure rate for patients receiving TCM-WM than WM alone: 86.5% versus 76.8% (RD 0.10, 95% CI: -0.02, 0.22, p=0.05).

Partial or complete resolution of pulmonary infiltrate (8 studies) was significantly higher in the group receiving TCM-WM (80.9%) than in patients receiving WM alone: 80.9% versus 67.8% (RD 0.18, 95% CI: 0.07, 0.30, p=0.002).

The TCM-WM group used significantly lower doses of corticosteroids than the WM group (WMD -60.27, 95% CI: -70.58, -49.96; 10 studies). There was no significant difference between groups for average cumulative dose or course of corticosteroid treatment. Data were not presented in the review.

There was a significant difference in recovery of post-treatment CD4+ cell counts (4 studies) between treatment groups (pooled WMD 167.96, 95% CI: 109.68, 226.24). Details were not presented in the review.

There was a significant difference between groups for time to defervescence (8 studies), favouring the TCM-WM group (pooled WMD -1.06, 95% CI: -1.60, -0.53, p=0.0001).

Sensitivity analyses did not significantly alter the results for the different outcomes. However, subgroup analyses indicated that previously significant differences in mortality and cure rates became insignificant. There was evidence of heterogeneity between studies reporting cure rates and resolutions of lung infiltrate, which remained following sensitivity analyses.

**Authors' conclusions**
Treatment with combined TCM-WM appears encouraging and may have potential benefits for patients with SARS in terms of faster resolution of lung infiltrate, increasing the CD4+ cell counts, and reducing the time to defervescence. However, treatment with TCM requires further investigation.

**CRD commentary**
The review question was clear and supported by appropriate inclusion criteria relating to the participants, interventions and study designs. Attempts were made to identify relevant literature by searching several electronic databases and other appropriate sources. However, publications were restricted by language and, as there was no apparent search for unpublished material, it is possible that relevant papers were missed. Validity was assessed according to published criteria, and attempts appear to have been made to minimise bias and error at each stage of the review process. However, the methodological quality of the included studies was low. Given the heterogeneity between certain studies and the differences between treatment regimens, and potential uncertainty with diagnoses, it may not have been appropriate to pool the results. In addition, sample sizes were small and CIs appear wide. However, the authors appear to have considered such limitations, and their cautious conclusions and suggestion for further investigations into the use of TCM appear reasonable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that long-term research is required with any future outbreaks of SARS, and research into the benefits on CD4+ cell counts from using TCM-WM treatment is warranted. Improvements in the quality of future studies are needed and TCM treatment should be standardised.

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