THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 10, Number 6, 2004, pp. 1041–1051

Chinese Herbal Medicine for Severe Acute Respiratory Syndrome: A Systematic Review and Meta-Analysis

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ABSTRACT

Objectives: To review randomized controlled trials (RCTs) evaluating the effects of Chinese herbal medicine for treating severe acute respiratory syndrome (SARS) systematically.

Design: Electronic and manual searches identified RCTs comparing Chinese medicine integrated to conventional medicine versus conventional medicine alone. Methodological quality of trials was assessed by generation of allocation sequence, allocation concealment, blinding, and intention-to-treat.

Results: Eight RCTs (488 patients with SARS) were included. The methodological quality was generally low. The combined therapy showed significant reduction of mortality (relative risk 0.32 [95% confidence interval {CI} 0.12 to 0.91]), shortened duration of fever, symptom relief, reductions in chest radiograph abnormalities, and reductions in secondary fungal infections among patients receiving glucocorticoids. There were no significant effects on quality of life or glucocorticoid dosage.

Conclusion: Chinese herbal medicine combined with conventional medicine may have beneficial effects in patients with SARS. The evidence is insufficient because of the low methodological quality of the included trials.

INTRODUCTION

Severe acute respiratory syndrome (SARS) emerged in November 2002 as a highly infectious disease associated with substantial morbidity and mortality. SARS caused 916 deaths before temporarily disappearing in the summer of 2003. Three new cases of laboratory-confirmed infection emerged in January 2004 (www.who.int/csr/don/2004_01_31/en/). The World Health Organization (WHO) estimates that the case fatality rate varies depending on age group: the rate is less than 1% in persons aged 24 years or younger; 6% in persons aged 25 to 44 years; 15% in persons aged 45 to 64 years; and greater than 50% in persons aged 65 years and older (Donnelly et al., 2003; World Health Organization, 2003b).

Caused by a novel coronavirus, SARS is predominantly spread by infected water droplets across short distance among close contacts, although indirect transmission is also possible (Mora et al., 2003; Peiris et al., 2003; Rota et al., 2003). Medical personnel are among those commonly infected because of their close contact with symptomatic and highly infectious cases. The advent of SARS poses an immense challenge to the affected health care communities and economies.

There is no consensus on the preferred treatment for SARS. Treatments used to date have been based on pathophysiologic rationale or on the experience obtained from case series collected during the early stages of the epidemic. Glucocorticoids and ribavirin have been administered most frequently during the early stages of the epidemic, yet in-

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sufficient evidence exists for their efficacy (Wenzel and Edmond, 2003; Wong and Hui, 2003). Antibiotics, other antiviral drugs (e.g., interferon, neuraminidase inhibitor), and other supportive treatments have also been widely used. Based on the anecdotal experience of traditional Chinese doctors in Guangzhou, different herbal medicines were combined with the conventional drugs, and this combined approach was claimed to be more effective than conventional drugs alone (Anonymous, 2003; Lin et al., 2003; Ma, 2003).

In April 2003, China's State Administration of Traditional Chinese Medicine (TCM; 2003) and the Chinese Ministry of Health coannounced an advocacy for the use of herbal medicines in the treatment of SARS. Eight specific herbal formulations were recommended after a screening of more than 30 herbal medicines used for SARS patients (Duan, 2003; Wang, 2003). The eight formulae are *Banlangen Keli* (*Baphicacanthi* granule), *Jinlian Qingre* granule, *Xinxue* granule, and *Dengzhan Xixin*, *Fufang Kushen*, *Qingkailing*, *Xiangdan*, and *Yuxingcao* injections. More than half of patients with SARS in Beijing received treatment with herbal medicine plus conventional drugs, according to the State Administration of TCM (Duan, 2003).

Clinical studies, ranging from case reports and case series to controlled observational studies and randomized clinical trials, have been conducted and reported. Clearly, there is a critical need to investigate systematically the beneficial and harmful effects of TCM approaches for treating SARS.

MATERIALS AND METHODS

Search strategy

To identify relevant studies, we searched the following databases from November 2002 through December 2003: The Cochrane Library, PubMed, Chinese Biomedical Database, Chinese Journals Full-text Database, Chinese Scientific Journal Database, trials database of the Cochrane Collaboration Complementary Medicine Field, and the Allied and Complementary Database. We used the search terms "atypical pneumonia," "severe acute respiratory syndrome," "SARS," "Traditional Chinese Medicine," "herbal medicine," and "integrative medicine." Various combinations of the terms were used, depending on the database searched. Relevant Chinese newspapers and Internet websites such as WHO, U.S. Centers for Disease Control (CDC), and China CDC were also screened, and reference lists of identified papers and review articles were checked.

Inclusion criteria

We included randomized clinical trials comparing herbal medicines plus conventional drugs versus placebo/no intervention plus conventional drugs in patients with SARS on clinical outcomes. In an exploratory analysis, we included nonrandomized controlled studies on medicinal herbs compared to placebo/no intervention to investigate the potential impact of study design on the primary outcome measure (death). Eligible studies had to include patients meeting the WHO criteria for a confirmed or suspected case of SARS (www.who.int/csr/sars/) (during the earliest stage of the SARS epidemic, patients with SARS were diagnosed as "atypical pneumonia" in China, and the diagnostic criteria of "atypical pneumonia" conformed to the WHO criteria). Published and unpublished studies were included irrespective of languages or masking. When more than one publication described a single study, we extracted data from the one providing the most detailed information.

Validity assessment

The methodological quality of trials was assessed using the generation of the allocation sequence, the allocation concealment, double blinding, and withdrawals/dropouts (Clarke and Oxman, 2003; Kjaergard et al., 2001; Moher et al., 1998; Schulz et al., 1995).

Data abstraction

Two reviewers (J.L. and Y.S.) extracted the data independently, and any disagreement was resolved by discussion. The following study characteristics were tabulated from trials: design, participants and diagnosis, intervention regimen, and clinical outcomes. Outcome measures to be extracted included death, number of complications, symptoms, quality of life, use of glucocorticoids, findings on chest radiograph, biochemistry, and adverse events.

Data synthesis

We used the statistical package (RevMan 4.2.3) provided by The Cochrane Collaboration for data analyses. Dichotomous data were presented as relative risk (RR) and continuous outcomes as weighted mean difference (WMD), both with 95% confidence interval (CI). We assessed data by both random effects and fixed effect analyses, but only reported the fixed effect analysis if the overall conclusion was the same with both analyses. We assessed heterogeneity by the I^2 statistic and used $p < 0.10$ as a significance limit for heterogeneity (Higgins et al., 2003). An exploratory analysis was performed using data from the nonrandomized studies. Publication bias was examined by funnel plot, that is, a graphical display of sample size plotted against effect size, if data allowed (Egger et al., 1997).

RESULTS

Description of studies

We identified 193 records on SARS from electronic and manual searches (Fig. 1). By reading titles and abstracts, we

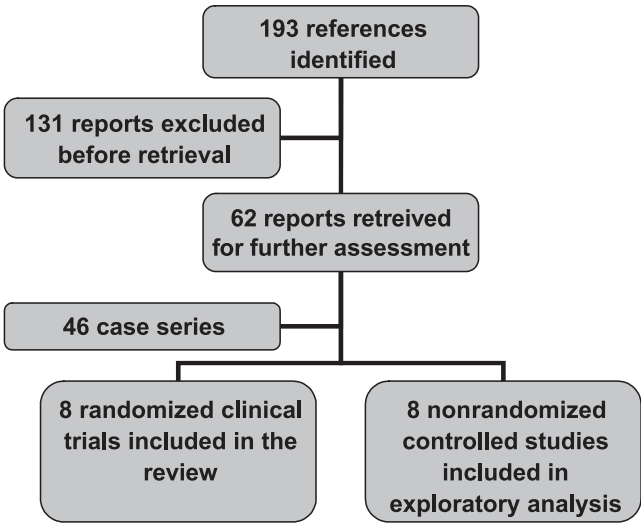


FIG. 1. Flow chart of study selection.

excluded 131 citations that were clearly duplicates, review articles, or nonclinical studies. A total of 62 articles published in Chinese or English were retrieved for further assessment. Of these, 46 articles were excluded because they were noncontrolled clinical studies including case reports and case series. In total, 8 randomized clinical trials (Bian et al., 2003; Kang et al., 2003; Lei et al., 2003; Li et al., 2003d; Wang et al., 2003; Zhang, 2003; Zhang et al., 2003; Zhao et al., 2003) were identified and they reported to allocate SARS patients randomly ($n = 488$) to herbal medicine plus conventional drugs or to conventional drugs alone. The characteristics of 8 randomized trials are summarized in Table 1. Two of the trials had been published twice (Wang et al., 2003; Zhang et al., 2003). We also identified 8 nonrandomized controlled studies (Dai et al., 2003; He et al., 2003; Jiao et al., 2003; Li et al., 2003a, 2003b; Sun et al., 2003; Zhang et al., 2003) that compared herbal medicine plus conventional drugs to conventional drugs alone for SARS patients ($n = 605$) (Table 2). One of the studies had been published four times in different journals (Li et al., 2003c).

All eight randomized trials were small, ranging from 40 to 91 participants per trial. All trials included Chinese patients with SARS. The trial reports did not state whether the diagnosis was confirmed by laboratory testing. The types, constituents, dosages, and methods of administration of the herbal medicines used for treating SARS varied, and most of the trials used several different herbal medicines during the disease course (Table 1).

Methodological quality of included studies

Of the eight trials, only two described the method to generate the allocation sequence (both used random number tables) (Bian et al., 2003; Wang et al., 2003). No trial provided information on allocation concealment, double blinding, withdrawals/dropouts, intention-to-treat, or prior sample size estimation. Accordingly, the included trials had generally low methodological quality (Bian et al., 2003; Kang et al., 2003; Lei et al., 2003; Li et al., 2003e; Wang et al., 2003; Zhang et al., 2003a, 2003b; Zhao et al., 2003). Four of eight trials failed to provide baseline data for the comparability between groups (Lei et al., 2003; Zhang et al., 2003a, 2003b; Zhao et al., 2003).

The eight nonrandomized studies that were compared in an exploratory analysis also had poor quality in terms of design, methodology, and reporting (Table 3) (Dai et al., 2003; He et al., 2003; Jiao et al., 2003; Li et al., 2003a, 2003b, 2003c; Sun et al., 2003; Zhang et al., 2003). Outcomes are summarized in Tables 3 and 4.

Mortality

A meta-analysis of five randomized trials (Li et al., 2003e; Wang et al., 2003; Zhang et al., 2003a, 2003b; Zhao et al., 2003) showed that a statistically significant difference in mortality existed between the combined therapy and the conventional drugs in patients with SARS (RR 0.32 [95% CI 0.12 to 0.91]; $n = 294$). The I^2 statistic indicated no significant heterogeneity among the trials. Three trials did not provide data on death. Pooling data from six non-randomized controlled studies (Dai et al., 2003; He et al., 2003b, 2003c; Sun et al., 2003; Zhang et al., 2003) showed a statistically significant beneficial effect of combined therapy compared to conventional drugs (0.27 [0.12 to 0.61]; $n = 486$) with no significant heterogeneity.

Fever and symptom

Three randomized trials (Lei et al., 2003; Li et al., 2003e; Zhao et al., 2003) showed a significant benefit of the combined therapy versus conventional drugs in shortening the duration of fever. A pooled result of two trials (Lei et al., 2003; Li et al., 2003e) showed significant benefit from the combined therapy versus conventional drugs in shortening the time to symptom relief. One trial (Bian et al., 2003) evaluated quality of life in 40 patients with SARS at the convalescent stage, and the scales used included limitation in activity, difficulty in breathing, and emotion. The results showed no significant difference in the overall scores of quality of life comparing combined therapy versus conventional drugs.

Chest radiograph abnormalities

Seven trials reported outcome of lung radiograph (Kang et al., 2003; Lei et al., 2003; Li et al., 2003e; Wang et al., 2003; Zhang et al., 2003a, 2003b; Zhao et al., 2003). A meta-analysis showed significant benefit of the combined therapy versus conventional drugs in shortening the average time to resolution of the lung inflammation from three trials (Lei et

Table 1. Characteristics of Included Randomized Clinical Trials

Study[a]	*Location*	*No. pts*	*M/F*	*Age (year)*	*Baseline data*	*Herbal medicines*	*Conventional medicines*	*Primary outcomes*
Bian et al.	Beijing	40	14/26	40 (18–70)	Gender, age, Disease duration, severity	Herbal compounds No. I (*Yiqi Yangyin*), No. II (*Bufei Jianpi*), No. III (*Yangyin Qingre*), depending on the differentiation of patients' syndrome by TCM practitioners; decoction, one dosage daily, for treatment of 21 days	Bedrest, symptomatic treatments, nutrient and other support therapy	Quality of life
Kang et al.	Taiyuan	63	29/34	18–55	Gender, age	Herbal compounds *Qingre Jiedu Shufeng Xuanfei* or *Yiqi Huayu Qingre Jiedu*; depending on patient's syndrome; decoction, one dosage daily, for 12 days	Antibiotics, antiviral drugs, glucocorticoid, immunomodulation	Fever, symptom, chest radiograph, dosage of glucocorticoid, secondary fungal infection
Lei et al.	Guangzhou	91	36/55	1–78	NA	*Qiankunning* (herbal compound of 14 herbs), 6 tablets/time, 4 times daily, for 14 days	Antibiotics, ribavirin, methylprednisolone (for severe patients), oxygen	Symptoms, fever, chest radiograph
Li et al. (2003e)	Tianjin	28	17/11	34.5 (11–65)	Gender, age, temperature, chest radiograph	*Chuanhuning* (herbal extracts) and *Shenmai* (herbal extracts) intravenously; *Hufei Qingsha Yin, Jiedu Zhitong* capsule, and *Zhuyinsan* capsule orally; Qingshaling spray; for 7–10 days	Antibiotics, ribavirin, methylprednisolone, immunoglobulin, thymosine, supportive treatment, mechanical ventilation	Death, fever, symptom, chest radiograph, dosage of glucocorticoid, complications
Wang et al.[b]	Beijing	65	19/46	37.4 (18–65)	Gender, age, diasease duration, severity	Herbal compounds '*Guoyao*' No. 2, 3, or 4, depending on disease duration, one dosage daily; *Qingkailing injection* (herbal extracts), and *Xuesaitong* injection (ingredients of ginseng) intravenously; for over 14 days	Azithromycin, levofloxacin, ribavirin, methylprednisolone, thymosine	Death, chest radiograph, fungal infection
Zhang et al.	Beijing	61	NA	NA	NA	Chinese herbal medicine 'SARS No. 4', one bag, two times a day; duration of use not reported	Antibiotics, antiviral agents, glucocorticoid, oxygen supplementation	Death, symptoms, chest radiograph, dosage of glucocorticoid

Zhang et al.	Beijing	63	34/29	41 (18–65)	temperature	Herbal compounds '*Feidian*' No. 1, 2, 3, used for different stage of disease; decoction, one dosage daily, for 21 days	Antibiotics, gancyclovir, methylprednisolone, thymosine, and symptomatic treatment	Death, fever, symptoms, dosage of glucocorticoid, chest radiograph, biochemical tests
Zhao et al.	Beijing	77	31/46	37 (14–78)	NA	Herbal compounds '*Feidian*' No. 1, 2, 3, used for different stage of disease; decoction, one dosage daily, for 14–21 days	Methylprednisolone, thymosine	Death, chest, radiograph, symptoms, duration and dosage of glucocorticoid

NA, not available; TCM, Traditional Chinese Medicine; SARS, severe acute respiratory syndrome.

[a]References are in Reference section and cited in text except as marked and provided here.

[b]Wang RB, Liu JM, Jiang YY, Wu YZ, Wang XJ, Chi PP, et al. Preliminary study on clinical efficacy of integrative Chinese and western medicine in treating severe acute respiratory syndrome (SARS). Chin J Integr Trad West Med 2003;23:492–493.

Table 2. Characteristics of Nonrandomized Control Studies

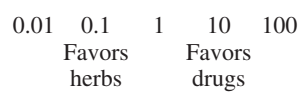
Study[a]	*Location*	*No. pts*	*M/F*	*Age (year)*	*Baseline data*	*Herbal medicines*	*Conventional drugs*	*Primary outcomes*
Dai et al.	Beijing	146	NA	NA	NA	*Qiankunning* (compound of 14 herbs), for 7–14 days	Antibiotics, methylprednisolone, ribavirin, oxygen supplement	Death, fever, symptoms, chest radiograph
He et al.	Beijing	91	52/39	34.4	Age, gender	Different herbal compounds prescribed based on the differentiation of symptoms of patients, duration of use not reported	Antiviral agents (ribavirin, ganciclovir, or interferon), azithromycin, levofloxacin, methylprednisolone, supportive treatment	Death, duration and dosage of glucocorticoid, chest radiograph
Jiao et al.	Beijing	49	16/33	35.5	Age, gender, WBC and CD cell count, temperature, severity, chest x-ray	TCM recipe I, II, III used in patients at different stage; plus *Zixue* powder, *Angong Niuhuang* bolus, *Qingkailing* injection, *Danshen* injection, *Shenmai* injection or *Shengmai* injection, based on different symptoms; for 3–20 days	Ribavirin, levofloxacin, azithromycin, methylprednisolone, thymopentin	Fever, symptoms, chest radiographic abnormalities, duration and dosage of glucocorticoid
Li et al. (2003a)	Beijing	80	40/40	35	Age, gender severity	*Shengmai Yin* plus *Zhuye Shigao Tang*, decoction; duration of use not reported	Antibiotics, antiviral agent, glucocorticoid, symptomatic treatment	Symptoms, chest radiograph, laboratory tests
Li et al. (2003b)	Beijing	59	45/14	31.6	Age, gender temperature symptoms, chest x-ray	*Qiankunning*, used until normalization of fever	Antibiotics, ribavirin, methylprednisolone, mechanical ventilation	Death, fever, symptoms
Li et al. (2003c)	Beijing	102	35/67	38.9	Age, gender	*Xingnao* injection, *Shenmai* injection,	Thymosin,	Death, fever,
Sun et al[a].	Tianjin	26	19/7	18–79	NA	*Yuxingcao* injection, *Qingkailing* injection; duration of use not reported	Pefloxacin, ribavirin, methylprednisolone, symtomatic management	Death, fever
Zhang et al[a].	Beijing	52	16/36	36.3	Age, gender severity, temperature, WBC and CD cell count, chest X-ray	Herbal medicine Nos. I, II, III, for patients at different stage, plus *Zixue* powder, *Angong Niuhuang* bolus, *Qingkailing* injection, *Danshen* injection, *Shengmai* injection or *Shenmai* injection; for 10–20 days	Ribavirin, levofloxacin, azithromycin, methylprednisolone	Death, fever, symptoms, chest radiograph, dosage of glucocorticoid

[a]References are in References section.
NA, not available; WBC, white blood cell count; TCM, Traditional Chinese Medicine.

Table 3. Comparison of Randomized and Nonrandomized Studies on Mortality

Review: *Chinese herbal medicine for severe acute respiratory syndrome*
Comparison: *01 Herbal medicine plus conventional drugs versus conventional drugs*
Outcome: *01 Mortality*

Study[a] or subcategory	*Combined therapy n/N*	*Conventional drugs n/N*	*RR (fixed) 95% CI*	*Weight %*	*RR (fixed) 95% CI*
Randomized clinical trials					
Li et al.[a]	0/14	0/14			Not estimable
Wang et al.[b]	1/35	2/30		15.72	0.43 (0.04, 4.50)
Zhang (2003a)[a]	2/31	6/32		43.11	0.34 (0.08, 1.58)
Zhang et al.[c]	1/32	4/29		30.64	0.23 (0.03, 1.91)
Zhao et al.[a]	0/37	1/40		10.53	0.36 (0.02, 8.56)
Subtotal (95% CI)	149	145		100.00	0.32 (0.12, 0.91)
Total events: 4 (combined herapy), 13 (conventional drugs)					
Test for heterogeneity: $\chi^2 = 0.17$, $df = 3$ ($p = 0.98$), $I^2 = 0\%$					
Test for overall effect: $Z = 2.15$ ($p = 0.03$)					
Non-randomized controlled studies					
Dai et al.[a]	0/77	3/69		15.74	0.13 (0.01, 2.44)
He et al.[a]	2/43	2/48		8.06	1.12 (0.16, 7.59)
Li N et al.[a]	0/35	1/24		7.55	0.23 (0.01, 5.45)
Li XH[d,e,f]	2/73	9/39		50.06	0.12 (0.03, 0.52)
Sun et al.[a]	1/8	5/18		13.13	0.45 (0.06, 3.26)
Zhang et al.[a]	0/22	1/30		5.45	0.45 (0.02, 10.54)
Subtotal (95% CI)	258	228		100.00	0.27 (0.12, 0.61)
Total events: 5 (combined herapy), 21 (conventional drugs)					
Test for heterogeneity: $\chi^2 = 3.90$, $df = 5$ ($p = 0.56$), $I^2 = 0\%$					
Test for overall effect: $Z = 3.17$ ($p = 0.002$)					



RR, relative risk; CI, confidence interval.

[a]Reference is in References section.

[b]Wang RB, Liu JM, Jiang YY, Wu YZ, Wang XJ, Chi PP, et al. Preliminary study on clinical efficacy of integrative Chinese and western medicine in treating severe acute respiratory syndrome (SARS). Chin J Integr Trad West Med 2003;23:492–493.

[c]Zhang XM, Feng GL, Ma YM. Clinical recording of infectious atypical pneumonia (SARS) treated by integrated Chinese and western medicines. China's Naturopathy. 2003;11:4–6.

[d]Li XH, Hu JH, Zhang K, Ye J, Gou CY, Li Y, et al. Clinical effective observation on integrated traditional Chinese and western medicine in treatment of 51 severe SARS patients. Chin J Integr Trad West Med Intens Crit Care 2003d;10:259–261.

[e]Li XH, Zhang K, Hu JH, Guo XH, Hu ZJ, Yang Y, et al. Clinical observation on effects of treatment of severe acute respiratory syndrome (SARS) by integrative Chinese and western medicine. Chin J Integr Trad West Med 2003e;23:489–491.

[f]Li XH, Zhang K, Hu JH, Guo XH, Hu ZJ, Yang Y, et al. Clinical evaluation of integrative Chinese and western medicine in treating SARS. Chin J Integr Med 2003f;9:181–184.

al., 2003; Li et al., 2003e; Zhang et al., 2003a) and reducing the number of lung radiographic abnormalities from two trials (Kang et al., 2003; Zhang et al., 2003b). The remaining trials did not provide adequate lung radiographic data for analyses because of incomplete reporting.

Glucocorticoids and secondary fungal infections

Five trials (Kang et al., 2003; Li et al., 2003e; Zhang et al., 2003a, 2003b; Zhao et al., 2003) reported the dosages of methylprednisolone used in both intervention groups. The combined result of three trials (Li et al., 2003e; Zhang et al., 2003a; Zhao et al., 2003) did not show significant glucocorticoid-reducing effect of the combined therapy compared to conventional drugs using random effects model due to significant heterogeneity ($I^2 = 99.2\%$; $p < 0.00001$). Two trials (Kang et al., 2003; Zhang et al., 2003b) reported average daily dosage of methylprednisolone, and there was no significant difference between the treatment groups. A pooled result of two trials (Kang et al., 2003; Wang et al., 2003) showed significant benefit of the combined therapy versus conventional drugs on reducing the number of secondary fungal infections in patients with SARS treated with glucocorticoid (RR 0.35 [0.14 to 0.90]; $p = 0.03$).

No trial provided information on adverse events.

Table 4. Summary for Outcome Variables of Randomized Clinical Trials

	No. of trials (references)[a]	*Herbal medicines (events/pts)*	*Conventional drugs (events/pts)*	*Relative risk (95% confidence interval)*	p *value*
Mortality	5 (Li et al., 2003e; Wang et al., 2003; Zhang et al., 2003a, 2003b; Zhao et al., 2003)	4/149	13/145	0.32 (0.12 to 0.91)	0.03
Incidence of secondary fungal infection	2 (Kang et al., 2003; Wang et al., 2003)	6/78	9/50	0.35 (0.14 to 0.90)	0.03
Abnormal chest radiograph	2 (Kang et al., 2003; Zhang et al., 2003)	10/74	24/52	0.29 (0.15 to 0.56)	0.0002
		No. of pts.	*No. of pts.*	*Weighted mean difference (95% confidence interval)*	
Duration to fever clearance (days)	3 (Lei et al., 2003; Li et al., 2003; Zhang et al., 2003)	95	87	−0.83 (−1.30 to −0.35)	0.0006
Duration to symptom relief (days)	2 (Lei et al., 2003; Li et al., 2003e)	64	55	−1.23 (−2.09 to −0.37)	0.005
Duration to resolution of chest radiograph	3 (Lei et al., 2003; Li et al., 2003e; Zhang et al., 2003a)	95	80	−2.27 (−3.16 to −1.39)	< 0.00001
Total dosage of glucocorticoids (mg)	3 (Li et al., 2003e; Zhang et al., 2003; Zhao et al., 2003)	60	59	−770.45 (−1798.47 to 257.58)[b]	0.14
Daily dosage of glucocorticoids (mg)	2 (Kang et al., 2003; Zhang et al., 2003)	74	52	−54.13 (−120.63 to 12.38)	0.11
Quality of life (score)	1 (Bian et al., 2003)	20	20	−2.20 (−4.93 to 0.53)	0.11

[a]References are in References section.
[b]Random effects model.

DISCUSSION

Based on this review and meta-analyses, herbal medicines given in combination with conventional drugs seem superior to conventional drugs alone for patients with SARS. Herbal medicines show benefit on mortality and on shortening the duration to temperature normalization, symptom relief, and resolution of chest radiograph abnormalities, as well as on reducing the incidence of fungal infections. We cannot draw conclusions about the safety of using herbal medicine because no trial provided information on adverse events.

Before accepting the findings of this review to form a basis for clinical practice, one must consider the following weaknesses. First, the randomized trials in this review had several methodological flaws in terms of generation of the allocation sequence, allocation concealment, and blinding. They provided limited descriptions of study design, and most trials stated only that patients were randomly assigned; thus the information does not allow a judgment of whether or not it was conducted properly. We therefore caution that the differences between the combined treatment and conventional drugs may be associated with the methodologically less rigorous trials (Clarke and Oxman, 2003; Kjaergard et al., 2001; Moher et al., 1998; Schulz et al., 1995). The number of trials identified limits us to perform meaningful subgroup or sensitivity analyses to illuminate robustness of the results in the review.

Second, epidemiologic studies on SARS have shown that age of the patients is strongly associated with mortality (Donnelly et al., 2003; World Health Organization, 2003b). None of the randomized trials used age as a stratification variable during randomization in spite of the fact that all trials were small. Furthermore a number of the trials and nonrandomized studies lack reporting of baseline data of the groups, including age. Therefore, unbalanced distribution of the important prognostic variable age between the intervention groups may partly explain the significant findings of the present systematic review.

Third, Vickers and colleagues (1998) found that some countries, including China, publish unusually high proportions of positive results, for which publication bias is a possible explanation. All identified studies for this systematic review was originating from China. The number of trials

identified in this review is too small for us to explore quantitatively the possibility of publication bias. But we note that some studies, both randomized and nonrandomized, have been published several times with the same data set.

Fourth, the use of herbal medicines varied both among the trials as well as during the conduct of the individual trials. This adds to the complexity of interpreting the present findings. TCM drug treatment, however, consists typically in complex prescriptions of combination of several components and uses such flexible administration of interventions so that they can be adjusted to reflect changes in the patient's condition or syndrome (Chan, 1995). The combination is based on the Chinese diagnosis that follows a completely different rationale than many Western herbal treatments.

Given the low methodological quality of the randomized trials, the risks of unbalanced distribution of prognostic factors and the publication bias, the multitude of different herbs used, and the small size of trials, we find it premature to conclude that the combination of herbal medicines and conventional drugs has been proven superior to conventional drugs alone for SARS patients. In spite of the fact that our exploratory analysis supported the findings from the randomized trials, nonrandomized studies may overestimate and underestimate intervention effects (Kunz et al., 2003). Hence, using nonrandomized studies in support of potentially biased clinical trials may be unreliable.

The use of glucocorticoids for patients with SARS remains controversial (Li et al., 2003d; Oba, 2003; Wang, 2003), and to date there is no randomized trial evidence to support or reject benefit or harm. Adverse effects from large doses of glucocorticoids are obvious, such as increased risks of secondary infection (Lionakis and Kontoyiannia, 2003). In the trials included in this review, we noticed that methylprednisolone was widely used for SARS in China, and the more severe the patients' conditions, the larger the dosage of glucocorticoids was used. However, the trials did not report long-term adverse effects from the use of glucocorticoids. Based on our personal contact with doctors who treated SARS patients in China and on information from the Internet (Xu, 2003), we have been informed that 20%–40% of SARS affected health professionals in Beijing had femoral head necrosis at discharge from the hospital. Early reports of case series in Guangzhou claimed that Chinese medicine combined with conventional drugs could reduce the dosage of corticosteroids (Lin et al., 2003). Our meta-analyses do not confirm this claim. However, findings from two trials show a benefit of the combined therapy in reducing the risk of secondary fungal infections, which may be related to the use of high doses of steroids. The mechanism of this benefit is not clear.

We also lack evidence from randomized trials that any of the conventional drugs, such as ribavirin or interferon (Loutfy et al., 2003), are effective. We have been unable to identify trials that compare either herbal medicines or conventional drugs to placebo for SARS patients. We only were able to identify one case series using herbal medicines alone for treatment of 16 SARS patients (Tong et al., 2003). In preparation for new outbreaks, investigators ought to develop international protocols for further well-designed clinical trials, which can be ready when new cases appear.

New treatment options are still needed, especially for an emerging disease such as SARS. Apart from this review on herbs, an *in vitro* study showed that glycyrrhizin (extract from liquorice root) may inhibit replication of the SARS-associated virus (Cinatl et al., 2003). Compared to the global case fatality rate of 11% (916/8422) by August 7, 2003, the fatality rates for Mainland China, Hong Kong, and Taiwan are 7% (349/5327), 17% (300/1755), and 27% (180/665), respectively (World Health Organization, 2003b). We do not know if these figures represent a potential benefit from the broad incorporation of herbal medicines into conventional treatment in Mainland China, or the lower case fatality rates reflect a cohort of healthier patients or the effect of different methods of fatality calculations in different regions (World Health Organization, 2003a).

ACKNOWLEDGMENTS

We thank Heather MacIntosh, Ph.D., and Heather Dubnick, Ph.D., for useful comments on our draft of the manuscript. We are grateful to Yunxia Liu, M.D., for assistance with searching for studies. Jianping Liu is supported by the Effective Health Care Alliance Programme (EHCAP) from the Department for International Development (DFID), UK. Eric Manheimer is supported by Grant Number 1 R24 AT001293-01 from the National Center for Complementary and Alternative Medicine (NCCAM), USA.

The authors have no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter of the review. The contents of the review are solely the responsibility of the authors and do not necessarily represent the official views of the authors' institutions.

J. Liu conceived, designed, drafted the review, and conducted the literature search, study selection, data extraction, analyses, and interpretation. E. Manheimer developed the search strategy, performed electronic searches, provided methodological perspectives, and revised the review. Y. Shi conducted the literature search, study selection, and data extraction. C. Gluud provided methodological perspectives and revised the review. All authors contributed to the writing of the review. J. Liu is a guarantor of the paper.

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