SARS: systematic review of treatment effects

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CRD summary
This review assessed treatment options for severe acute respiratory syndrome (SARS). The authors concluded that there was insufficient evidence to determine whether patients with SARS benefit from treatments currently used, and that some treatments might be harmful. The review appeared to be well conducted and the authors’ conclusions are likely to be reliable.

Authors’ objectives
The wider objective was to summarise the evidence of effects of treatment options for severe acute respiratory syndrome (SARS). This included clinical effectiveness and in vitro studies of viral replication inhibition.

Searching
MEDLINE, EMBASE, BIOSIS Previews and the Cochrane CENTRAL Register were searched in February 2005 for published studies; the search strategies are available on the PloS Medicine website (accessed 26/11/2007). See Web Address at end of abstract. No language restriction was reported (the review included English and Chinese literature). Unpublished studies were not sought.

Study selection
Study designs of evaluations included in the review
Eligible SARS study designs were randomised controlled trials (RCT), prospective uncontrolled studies, retrospective cohort, case-control studies and case series. Eligible ARDS studies were RCTs and systematic reviews. In vitro assays of viral replication in human or animal cell lines were also eligible for inclusion.

Specific interventions included in the review
Studies of ribavirin, lopinavir and ritonavir (LPV/r), corticosteroids, type I interferon, intravenous immunoglobulin and SARS convalescent plasma were eligible for inclusion. Combination therapy was given in almost all of the included clinical studies. The treatment regimens, where reported, varied widely in dose, duration and route of administration.

Participants included in the review
Studies of at least 10 patients with SARS and studies of at least 20 patients with acute respiratory distress syndrome (ARDS) or acute lung injury were eligible for inclusion. The SARS case definition in most of the included studies was based on clinical and epidemiological criteria established by the World Health Organization (WHO), Centers for Disease Control and Prevention, or equivalent (13% of those studies had laboratory confirmation of infection).

Outcomes assessed in the review
Inclusion criteria for the outcomes were not reported. The outcomes of interest appeared to include mortality, measures of morbidity and adverse effects. The outcomes reported in the studies reviewed included death, ventilation, admission to the intensive care unit, infectious complications, discharge and adverse effects.

How were decisions on the relevance of primary studies made?
Each study identified was obtained in full and examined by two reviewers independently. Any disagreements were resolved by consensus.

Assessment of study quality
The clinical studies were critically appraised, but the authors did not state the criteria or how the validity assessment was performed. Aspects that were assessed included study design, the possibility of bias in the selection of the control group and treatment allocation, and whether the treatment regimen and reporting of outcomes was consistent.
Data extraction
Two reviewers independently extracted the data from English language publications and resolved any disagreements by consensus. One reviewer extracted the data from Chinese language publications with the help of a translator. Data extracted from the clinical studies included the number treated with each intervention, outcomes reported, adverse effects measured or reported, and the investigators' inferences or conclusions. Two reviewers independently applied predefined criteria (defined in the report) to assign a level of evidence to each clinical study: inconclusive, possible harm, possible benefit, definite harm or definite benefit.

Methods of synthesis
How were the studies combined?
The studies were tabulated and summarised in a narrative, grouped by treatment type. As the interventions evaluated in the review were often used in combination, the studies were grouped according to the treatment given to all patients in a cohort or according to the treatment whose effects the investigators intended to study. The narrative summary was based largely on a tally of studies according to the level of evidence. Studies of SARS and ARDS were summarised separately. In vitro studies were summarised separately from the clinical studies.

How were differences between studies investigated?
Tables enabled comparisons of individual study characteristics and findings. Studies in English and Chinese were summarised separately.

Results of the review
Fifty-seven clinical studies (6,539 participants) and 15 in vitro studies were included. Five of the clinical studies were RCTs (428 participants), one was a case-control study, eight were prospective and the rest retrospective.

Clinical studies.
Twenty-six out of 30 studies of ribavirin treatment in SARS patients were inconclusive. Four studies provided evidence of possible harm: 36 to 61% of patients in 3 studies (n=392) developed haemolytic anaemia; in the fourth study (n=54) the number of patients with elevated alanine aminotransferase increased after treatment (the studies did not have control groups).

Two studies (n=1,204) of LPV/r treatment for SARS were inconclusive.

Twenty-five out of 29 studies of corticosteroid treatment in SARS patients were inconclusive. Four studies provided evidence of possible harm: a placebo-controlled RCT (n=16) reported delayed viral clearance; in a case-control study (n=45) patients with psychosis received higher cumulative doses of corticosteroids than those without psychosis; a retrospective study (n=132) reported diabetes onset; another retrospective study (n=40) reported avascular necrosis and osteoporosis.

Two out of 3 placebo-controlled RCTs of corticosteroid treatment in ARDS patients (n=198) showed no benefit (no statistically significant effect). One RCT (n=24) showed a possible benefit: 2 out of 16 patients died in the treatment group versus 5 out of 8 in the placebo group.

Three studies (n=308) of type I interferon treatment for SARS were inconclusive.

Seven studies (n=389) of SARS treatment with intravenous immunoglobulin or convalescent plasma were inconclusive.

In vitro studies.
Ribavirin, lopinavir and type I interferon inhibited the SARS virus in tissue culture.

Authors' conclusions
There was insufficient evidence to determine the benefit of the treatments used during the last SARS epidemic; some of the treatments might be harmful.

**CRD commentary**

The review had a clear purpose: to help the WHO identify research priorities in the treatment of SARS. The scope and inclusion criteria were defined in a protocol (although not all of the inclusion criteria were reported clearly in the paper). The search covered several large electronic databases, although the named sources would not have provided comprehensive coverage of Chinese literature. It was unclear if studies in languages other than English and Chinese were identified or eligible for inclusion. The decision to restrict to published studies was explained as partly pragmatic and partly based on opinion (which some may dispute). Steps were taken to minimise reviewer error and bias in the study selection and data extraction processes. The quality assessment appeared to be thorough but the procedure was not reported, which is unfortunate because it appeared to require some subjective judgment and provided the basis for the conclusions.

Details of the individual studies were tabulated clearly and the narrative approach to data synthesis was appropriate. Despite poor reporting of the criteria and procedure, the critical appraisal information shown for each study appeared to be consistent with the conclusion of 'inconclusive' assigned to most of the included studies. A conclusion of 'possible harm', however, only required the reporting of adverse effects consistent with any reported in the treatment of other conditions. The authors' conclusion about there being insufficient evidence of benefit and that some of the treatments might be harmful is probably reliable.

**Implications of the review for practice and research**

Practice: Use of ribavirin for SARS should be in the context of a controlled trial and close attention paid to adverse effects. Although clear recommendations on the use of corticosteroids could not be made, attention was drawn to the evidence of potential harm. In the event of another epidemic, treatment protocols and a standardised minimum data set should be developed.

Research: The authors stated that there is a great need for good quality RCTs. More trials of immunoglobulin are needed to provide evidence of an effect in SARS.

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