Review

Pro/con clinical debate: Steroids are a key component in the treatment of SARS

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Published online: 26 January 2004 *Critical Care* 2004, **8:**105-107 (DOI 10.1186/cc2452)
This article is online at http://ccforum.com/content/8/2/105

Abstract

SARS (severe acute respiratory syndrome) proved an enormous physical and emotional challenge to frontline health care workers throughout the world in late 2002 through to mid 2003. A large percentage of patients (many being health care workers themselves) became critically ill. Unfortunately, clinicians caring for these individuals did not have the advantage of previous experience or research data on which to base treatment decisions. As a result, at least early in the outbreak, a 'best guess approach' and/or anecdotes drove therapy. In many centres systemic steroids, which carry many potential downsides, became a mainstay of therapy. In this issue of *Critical Care*, two groups that have frontline experience of SARS debate the role of steroids. Let us hope and pray together that we never have the patient population needed to resolve the questions the two sides raise.

Keywords critical care, respiratory failure, SARS, steroids, viral pneumonia

The scenario

Unfortunately, in the winter of 2004 SARS (severe acute respiratory syndrome) emerges in the world once again, and health care workers in your institution begin to develop the illness. Patients with SARS start to develop critical illness and you are asked to become involved in their care. You have read that during the first outbreak of SARS steroids were a commonly employed therapy. Despite this you worry about the adverse effects of steroid therapy, especially in critically ill patients.

Pro: Yes, steroids are a key component of the treatment regimen for SARS

Charles D Gomersall

SARS is a potentially life-threatening disease caused by infection with SARS coronavirus. The early phase of the disease appears to be due to the virus itself whereas the later phase is thought to be due to an inflammatory response. Quantitative reverse transcriptase polymerase chain reaction of nasopharyngeal aspirates has shown that the viral load peaks at about 10 days from symptom onset [1], and serum concentrations of IL-6, IL-8, IL-16 and tumour necrosis factor-α are most markedly raised 8–14 days from disease onset [2]. In addition, the histological changes in the lungs of patients who died from SARS suggest cytokine dysregulation [3]. Thus, the available data suggest that the clinical manifestations of SARS in the second week of illness are predominantly due to an excessive immune response to viral infection rather than to infection itself. Because admission to the intensive care unit (ICU) occurs 8–9 days after symptom onset and the median duration of ICU stay is 8.5–14.5 days [4–6], it is likely that most critically ill patients are in this immunological phase. Therefore, a logical approach is to modify the immune response with anti-inflammatory agents such as corticosteroids.

ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IL = interleukin; SARS = severe acute respiratory syndrome.

The majority of critically ill patients with SARS develop acute respiratory distress syndrome (ARDS); not only do the vast majority meet the criteria for ARDS [4–6] but also computed tomography of the lungs 22–54 days after the onset of ARDS shows changes consistent with late phase ARDS [7]. Data from other patients with ARDS suggest that high-dose corticosteroids may have a beneficial effect in those who fail to improve by day 7 of respiratory failure [8]. Other ARDS data indicate that steroids do not worsen outcome despite the inclusion of patients with ARDS due to sepsis, and that the incidence of infectious complications is unaffected by the administration of very high doses of corticosteroid [9].

Finally, in other viral pneumonias corticosteroids may be of benefit. In a rat model of respiratory syncytial virus pneumonitis the histological changes of pneumonitis were significantly less marked in animals treated with an antiviral and corticosteroids than in control animals treated with an antiviral alone [10]. Human data on the effect of corticosteroids in viral pneumonia are limited, but in a retrospective study of patients with severe varicella pneumonia the patients treated with steroids had a shorter hospital and ICU stay despite having a lower arterial oxygen tension/fractional inspired oxygen ratio on admission to the ICU [11].

In the absence of randomized clinical trials, intensivists have the choice of providing only supportive treatment (almost none of which is based on randomized controlled trials) or treating patients on the basis of the pathophysiology of SARS. The severe respiratory failure, which occurs in the later phase of SARS and results in critical illness, appears to be due to an excessive inflammatory response to infection with SARS coronavirus. This suggests that corticosteroids have a role to play in the treatment of critically ill patients with SARS, namely to ameliorate the inflammatory response and possibly decrease the progression to fibrosis in those who develop ARDS.

Con: No, steroids are not a key component of the treatment regimen for SARS

Marcus J Kargel and Stephen E Lapinsky

Systemic steroids have been used in the treatment of SARS based on the hypothesis that disease manifestations are in part due to the host's inflammatory response. Many questions regarding the use of steroids in the treatment of SARS remain unanswered, including the efficacy of this treatment, the appropriate timing of initiation of treatment, and the dose and duration of therapy.

Steroid therapy causes significant adverse effects, and this remains true in patients with SARS. Wang and coworkers [12] described a case of fatal aspergillosis, and recent press reports indicate that a large number of SARS survivors in Hong Kong are now suffering from steroid-induced avascular necrosis [13,14]. Myopathy and polyneuropathy occur in ARDS patients treated with steroids [15], and this has been noted in follow up of SARS patients (S Herridge, personal communication, 2003).

Currently, there is no published evidence demonstrating an improvement in morbidity or mortality with steroid treatment in SARS. None of the case series that evaluated predictors of outcome have demonstrated an association between the lack of steroid use and poor clinical outcome [4,16,17]. Lew and coworkers [5] found no significant difference in outcome between 15 patients treated with immunoglobulin and methylprednisolone and 30 patients who were not administered those agents. A report from China [18] suggests that a regimen including high-dose steroids was associated with reduced mortality, but that study exhibits a potentially biased randomization scheme, nonblinded assessments, and significant cross-over between treatment groups.

SARS can progress to ARDS [4,5]. Steroid treatment in ARDS remains controversial, with two negative meta-analyses [19,20]. One small trial of steroids administered late in the course of unresolving ARDS found improvement in lung injury and mortality [8]. Given these conflicting results, steroid therapy is not generally accepted for the treatment of ARDS and larger trials are in progress.

The appropriate timing of steroid therapy needs to be clarified. Steroids have been advocated for the late immune-mediated phase of the disease, although patients progressed to this later stage despite receiving early steroids [1]. The appropriate dosing of steroid therapy for SARS is unknown. Reported doses have varied from no therapy to pulse doses of methylprednisolone with up to 1 g/day [4,5,16,18,21,22]. Ho and coworkers [21] compared patients treated with high-dose steroids with those treated with more conventional steroid doses (methylprednisolone $<$ 500 mg/day) and found no significant difference in mortality or duration of mechanical ventilation at 21 days. In the Toronto cohort only 40% of patients received steroids [16], but mortality was similar to that in reports from Hong Kong [17,21], where high doses were commonly used.

SARS clinicians prescribed steroids under desperate circumstances based on anecdotal experience and on a rudimentary understanding of the role of host inflammatory damage in this condition. We would not recommend the routine use of steroids in all SARS patients with respiratory failure. Large randomized clinical trials are needed to help resolve the many unanswered questions regarding the role, dose and timing of corticosteroids for SARS.

Pro response: How great is the risk of adverse effects?

Charles Gomersall

First, none of the studies that evaluated predictors of outcome were adequately powered to exclude a clinically important effect of steroids [4,5,16]. Second, what is at issue is the incidence of steroid-related complications in SARS patients, not whether steroids have adverse effects. The incidence has not been reliably determined. It is inconsistent to ask for evidence of benefit from randomized controlled trials yet accept evidence of harm from the popular press. Third, agreement between results of meta-analyses and large randomized controlled trials is poor [23].

Con response: Research first

Marcus J Kargel and Stephan E Lapinsky

The existing anecdotal and retrospective literature does not conclusively support the use of corticosteroids for treatment of SARS. Although steroids are often used in desperate and life-threatening situations, no benefit has been proven for this disease or related conditions such as ARDS or other viral pneumonias. History has shown that therapy based on anecdotes, even with sound pathophysiological support, may not prove to be beneficial in formal studies [24]. Given the potential severe side effects of steroid therapy, it is essential that randomized controlled trials be performed. Research protocols should be pre-developed to be initiated promptly, should SARS return.

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