26 **Tiemessen MM**, Van Hoffen E, Knulst AC, *et al.* CD4 CD25 regulatory T cells are not functionally impaired in adult patients with IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2001;**110**:934–6.
27 **Bellinghausen I**, Klostermann B, Knop J, *et al.* Human CD4+CD25+ T cells derived from the majority of atopic donors are able to suppress TH1 and TH2 cytokine production. *J Allergy Clin Immunol* 2003;**111**:862–8.
28 **Ling EM**, Smith T, Nguyen XD, *et al.* Relation of CD4+CD25+ regulatory T-cell suppression of allergen-driven T-cell activation to atopic status and expression of allergic disease. *Lancet* 2004;**363**:608–15.
29 **Woo EY**, Yeh H, Chu CS, *et al.* Cutting edge: Regulatory T cells from lung cancer patients directly inhibit autologous T cell proliferation. *J Immunol* 2002;**168**:4272–6.
30 **Bennett CL**, Christie J, Ramsdell F, *et al.* The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. *Nat Genet* 2001;**27**:20–1.
31 **Brunkow ME**, Jeffery EW, Hjerrild KA, *et al.* Disruption of a new forkhead/winged-helix protein, scurfin, results in the fatal lymphoproliferative disorder of the scurfy mouse. *Nat Genet* 2001;**27**:68–73.
32 **Hori S**, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. *Science* 2003;**299**:1057–61.
33 **Fontenot JD**, Gavin MA, Rudensky AY. Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. *Nat Immunol* 2003;**4**:330–6.
34 **Khattri R**, Cox T, Yasayko SA, *et al.* An essential role for scurfin in CD4+CD25+ T regulatory cells. *Nat Immunol* 2003;**4**:337–42.
35 **Walker MR**, Kasprowicz DJ, Gersuk VH, *et al.* Induction of FoxP3 and acquisition of T regulatory activity by stimulated human CD4+CD25- T cells. *J Clin Invest* 2003;**112**:1437–43.
36 **Bruder D**, Probst-Kepper M, Westendorf AM, *et al.* Neuropilin-1: a surface marker of regulatory T cells. *Eur J Immunol* 2004;**34**:623–30.
37 **O'Garra A**. Cytokines induce the development of functionally heterogeneous T helper cell subsets. *Immunity* 1998;**8**:275–83.
38 **Eisenbarth SC**, Piggott DA, Huleatt JW, *et al.* Lipopolysaccharide-enhanced, toll-like receptor 4-dependent T helper cell type 2 responses to inhaled antigen. *J Exp Med* 2002;**196**:1645–51.
39 **Pasare C**, Medzhitov R. Toll-like receptors: balancing host resistance with immune tolerance. *Curr Opin Immunol* 2003;**15**:677–82.
40 **Pasare C**, Medzhitov R. Toll pathway-dependent blockade of CD4+CD25+ T cell-mediated suppression by dendritic cells. *Science* 2003;**299**:1033–6.
41 **Akbari O**, Freeman GJ, Meyer EH, *et al.* Antigen-specific regulatory T cells develop via the ICOS-ICOS-ligand pathway and inhibit allergen-induced airway hyperreactivity. *Nat Med* 2002;**8**:1024–32.
42 **Umetsu DT**, McIntire JJ, Akbari O, *et al.* Asthma: an epidemic of dysregulated immunity. *Nat Immunol* 2002;**3**:715–20.
43 **Baldini M**, Lohman IC, Halonen M, *et al.* A polymorphism in the 5′ flanking region of the CD14 gene is associated with circulating soluble CD14 levels and with total serum immunoglobulin E. *Am J Respir Cell Mol Biol* 1999;**20**:976–83.
44 **Eder W**, Klimecki W, Yu L, *et al.* Toll-like receptor 2 as a major gene for asthma in children of European farmers. *J Allergy Clin Immunol* 2004;**113**:482–8.
45 **Platts-Mills T**, Vaughan J, Squillace S, *et al.* Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet* 2001;**357**:752–6.
46 **Jiang S**, Camara N, Lombardi G, *et al.* Induction of allopeptide-specific human CD4+CD25+ regulatory T cells ex vivo. *Blood* 2003;**102**:2180–6.
47 **Walker LS**, Chodos A, Eggena M, *et al.* Antigen-dependent proliferation of CD4+ CD25+ regulatory T cells in vivo. *J Exp Med* 2003;**198**:249–58.
48 **Barrat FJ**, Cua DJ, Boonstra A, *et al.* In vitro generation of interleukin 10-producing regulatory CD4(+) T cells is induced by immunosuppressive drugs and inhibited by T helper type 1 (Th1)- and Th2-inducing cytokines. *J Exp Med* 2002;**195**:603–16.
49 **Robinson DS**, Nguyen XD. Fluticasone propionate increases suppression of allergen-driven T cell proliferation by CD4+CD25+ T cells. *J Allergy Clin Immunol* 2004;**113**(suppl):1190 (abstract).
50 **Groux H**, O'Garra A, Bigler M, *et al.* A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. *Nature* 1997;**389**:737–42.
51 **Cottrez F**, Hurst SD, Coffman RL, *et al.* T regulatory cells 1 inhibit a Th2-specific response in vivo. *J Immunol* 2000;**165**:4848–53.
52 **Sundstedt A**, O'Neill EJ, Nicolson KS, *et al.* Role for IL-10 in suppression mediated by peptide-induced regulatory T cells in vivo. *J Immunol* 2003;**170**:1240–8.
53 **Chen Y**, Kuchroo VK, Inobe J, *et al.* Regulatory T cell clones induced by oral tolerance: suppression of autoimmune encephalomyelitis. *Science* 1994;**265**:1237–40.
54 **Durham SR**, Walker SM, Varga EM, *et al.* Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;**341**:468–75.
55 **Walker SM**, Pajno GB, Lima MT, *et al.* Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol* 2001;**107**:87–93.
56 **Francis JN**, Till SJ, Durham SR. Induction of IL-10+CD4+CD25+ T cells by grass pollen immunotherapy. *J Allergy Clin Immunol* 2003;**111**:1255–61.
57 **Jutel M**, Akdis M, Budak F, *et al.* IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. *Eur J Immunol* 2003;**33**:1205–14.
58 **Ling EM**, Calderon M, Nguyen D, *et al.* Allergen immunotherapy increases suppressive activity by CD4+CD25-, IL-10 producing T cells but does not affect suppression by CD4+CD25+ T cells. *J Allergy Clin Immunol* 2004;**113**(suppl): 330 (abstract).
59 **BSACI Working Party**. Position paper on allergen immunotherapy. *Clin Exp Allergy* 1993;**23**(Suppl 3):1–44.
60 **Haselden BM**, Kay AB, Larche M. Immunoglobulin E-independent major histocompatibility complex-restricted T cell peptide epitope-induced late asthmatic reactions. *J Exp Med* 1999;**189**:1885–94.
61 **Oldfield WL**, Larche M, Kay AB. Effect of T-cell peptides derived from Fel d 1 on allergic reactions and cytokine production in patients sensitive to cats: a randomised controlled trial. *Lancet* 2002;**360**:47–53.
62 **Oldfield WL**, Kay AB, Larche M. Allergen-derived T cell peptide-induced late asthmatic reactions precede the induction of antigen-specific hyporesponsiveness in atopic allergic asthmatic subjects. *J Immunol* 2001;**167**:1734–9.
63 **Smith TRF**, Alexander C, Kay AB, *et al.* Cat allergen peptide immunotherapy reduces $CD4^+$ T cell responses to cat allergen but does not alter suppression by $CD4^+CD25^+$ T cells. *Allergy* 2004 (in press).
64 **Tighe H**, Takabayashi K, Schwartz D, *et al.* Conjugation of immunostimulatory DNA to the short ragweed allergen amb a 1 enhances its immunogenicity and reduces its allergenicity. *J Allergy Clin Immunol* 2000;**106**:124–34.
65 **Zuany-Amorim C**, Sawicka E, Manlius C, *et al.* Suppression of airway eosinophilia by killed Mycobacterium vaccae-induced allergen-specific regulatory T-cells. *Nat Med* 2002;**8**:625–9.
66 **Pajno GB**, Barberio G, De Luca F, *et al.* Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy* 2001;**31**:1392–7.
67 **Moller C**, Dreborg S, Ferdousi HA, *et al.* Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002;**109**:251–6.

Treatment of SARS

Antiviral agents and corticosteroids in the treatment of severe acute respiratory syndrome (SARS)

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Systematic evaluation of treatment modalities for SARS is still needed

The epidemic of severe acute respiratory syndrome (SARS) of 2003 caught the medical profession by surprise. The accumulated global total number of cases was 8098 with 774 deaths, a case-fatality ratio of 9.6%.[1] Although the novel coronavirus (SARS-CoV) was discovered within weeks,[2] treatment was inevitably empirical as controlled clinical trials were not possible during the epidemic of this new and serious illness. Many antiviral and immunomodulatory drugs, as well as other treatments such as convalescent patient plasma and traditional Chinese medicines, have been tried. Ribavirin and corticosteroids are by far the most widely used treatments for SARS. In the later phase of the epidemic lopinavir and ritonavir in combination were also used in Hong Kong.

ANTIVIRAL AGENTS

Ribavirin

Ribavirin is used extensively for the treatment of SARS and was given to over 90% of patients in Hong Kong. It is a nucleoside analogue that has activity against a number of DNA and RNA

viruses in vitro.[3] The mechanism of action of ribavirin has been studied for decades and is still under active debate.[4] In early March 2003, before the isolation of the SARS-CoV, many experts believed that the mysterious severe illness was due to an unknown virus and ribavirin was empirically given because of its broad spectrum antiviral activity. Furthermore, corticosteroids were increasingly prescribed for the treatment of SARS and some believed that such treatment would be dangerous if not covered with an antiviral agent. The published reports on the effectiveness of ribavirin were mostly retrospective case series with intrinsic methodological issues and it is difficult to draw conclusions. The major side effect of ribavirin is anaemia which occurs in 27–59% of patients.[5–9] Anaemia reduces oxygen transport and potentiates the existing problem of oxygenation and tissue hypoxia. Other significant side effects include raised transaminases and bradycardia,[5] as well as hypocalcaemia, hypomagnesaemia, and risk of teratogenicity.[10] In a detailed study on the clinical course and viral load, Peiris *et al*[11] reported that 14 patients given a standard regimen of ribavirin and steroids showed a peak viral load at day 10 from onset of illness. This study, although involving a small number of subjects, clearly indicated the inability of ribavirin to clear SARS-CoV from patients with SARS. The result of this study also explained why patients treated with ribavirin early in the illness were able to infect healthcare workers when they subsequently required endotracheal intubation. The lack of in vitro activity of the drug against SARS-CoV[12–14] cast further doubts on the usefulness of ribavirin in SARS. The use of ribavirin in SARS has been reviewed elsewhere.[15 16]

Lopinavir and ritonavir

Lopinavir and ritonavir (LPV/r) are protease inhibitors which, in combination, have been licensed for the treatment of HIV disease. Ritonavir has little antiviral activity and its role is to inhibit CYP3A mediated metabolism of lopinavir, thus increasing the serum concentration of lopinavir. In the laboratory lopinavir and ribavirin have significant synergism in inhibiting SARS-CoV[6] and, on that basis, this combination—together with steroids—have been used in some centres in Hong Kong since mid April 2003. In this retrospective study the authors found that the 12 patients who received early treatment with LPV/r together with ribavirin and steroids had significantly fewer 21 day adverse clinical outcomes (acute respiratory distress syndrome or death) than 111 historical controls receiving ribavirin and steroids. Other benefits of the LPV/r group included favourable viral load profiles (in six patients), early rise of lymphocyte counts, and a reduced need for ''rescue'' pulse steroid doses. Adverse events attributable to LPV/r were minimal. Similar findings were reported in a case controlled study involving more patients from Hong Kong.[17] Randomised controlled trials are being planned in Hong Kong to confirm these results should SARS re-emerge.

CORTICOSTEROIDS

Corticosteroids have been used widely to treat SARS, first in mainland China and then in Hong Kong. The main rationale for their use in SARS is that, in acute viral respiratory infections, early response cytokines such as interferon gamma (IFN-γ), tumour necrosis factor, interleukin 1 (IL-1), and interleukin 6 (IL-6) contribute to tissue injury,[18 19] and corticosteroid treatment may suppress the ''cytokine storm''.[20] Peiris *et al* hypothesised that the clinical worsening often observed during the second phase of illness is the result of immunopathological damage from an overexuberant host response.[13] In a newly published report Wong *et al*[21] showed in 20 consecutive adults with SARS that there was a marked increase in the Th1 cytokine IFN-γ, inflammatory cytokines IL-1, IL-6, and IL-12 for at least 2 weeks after disease onset. The chemokine profile showed a significant increase in IL-8, monocyte chemoattractant protein-1 (MCP-1), and IFN-γ inducible protein-10 (IP-10). Corticosteroids significantly reduce IL-8, MCP-1, and IP-10 concentrations 5–8 days after treatment. The data confirmed the Th1 cell mediated immunity and hyperinnate inflammatory response in SARS through the accumulation of monocytes/macrophages and neutrophils. Another rationale for use of steroids in SARS is the necroscopic finding of features of acute respiratory distress syndrome (ARDS),[22 23] and there have been reports of successful use of steroids in the treatment of ARDS[24] and septic shock.[25] In addition, systemic steroids have been used in the treatment of some infections with variable success.[26–29] On the other hand, the potential for corticosteroids to suppress the innate host defence against SARS-CoV resulting in increased viral replication has to be considered. Chu *et al* reported an increase in viral load in one patient following pulse methylprednisolone therapy.[6] Increased replication of other respiratory viruses has also been reported following steroid therapy.[26 30–32]

Whereas ''low dose'' steroids at 0.5–1.0 mg/kg/day prednisolone (or equivalent) have been used in infections, ARDS and septic shock, ''pulse doses'' at 0.5–1.0 g/day methylprednisolone have generally not been recommended for these conditions but were used extensively in SARS, particularly in the second week of illness when patients often show acute clinical deterioration. The efficacy of pulse steroids in SARS remains to be determined, but it is conceivable that higher steroid doses will result in a higher incidence and severity of side effects.

Published case series examining the clinical efficacy of steroid treatment in SARS[7 9 33–40] suffer the same methodological problems as those of ribavirin. In addition, there is a wide variety of steroid dosing schedules making retrospective analysis of steroid efficacy exceptionally difficult. There is so far no systematic review of the efficacy of corticosteroid treatment in SARS based on the numerous published studies. Some investigators do feel that judicious use of corticosteroids is beneficial, but randomised controlled studies are needed to confirm the beneficial effects as well as to give insight into the optimal regimen. The possible beneficial effects, however, have to be balanced against the significant side effects including nosocomial infections,[7 9 40 41] hyperglycaemia, hypokalaemia, hypertension, and gastrointestinal haemorrhage.[7–9] Avascular necrosis of bone (AVN) is perhaps the most distressing medium term side effect of steroids in patients with SARS. Preliminary data on a cohort of 330 adult patients from Princess Margaret Hospital, Hong Kong who received various doses of steroids and in whom magnetic resonance imaging was performed at an average of 7.5 months from illness onset showed that AVN was present in 48 of them (14.5%, (unpublished data). Of the 48, 16 (33%) had unilateral involvement of the femoral head and 19 (40%) had bilateral involvement of the femoral head. Univariate analysis showed that the total steroid dose was significantly associated with development of AVN (unpublished data).

CONCLUSIONS

As SARS has only recently appeared and a limited number of patients have been managed in different locations, it is understandable that there has been a lack of systematic and critical evaluation of treatment in the form of randomised controlled trials. Nonetheless, the enormous effort that researchers put into looking for effective treatments for SARS is highly commended. The recent re-emergence of SARS did not result in secondary spread, but is nevertheless a reminder that it could strike again. What may be even more threatening

is the deadly avian influenza A (H5N1) which has repeatedly demonstrated its ability to infect humans, and may acquire the ability for efficient human to human transmission in the future. It is hoped that, when epidemics of new disease strikes, a systematic way of evaluating treatment modalities would be in place to provide answers to important questions in the shortest possible time.

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REFERENCES

1 **World Health Organization: SARS: cumulative number of reported probable cases**. http://www.who.int/csr/sars/country/en/ (accessed 24 January 2004).
2 **Ksiazek TG**, Erdman D, Goldsmith CS, *et al.* A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 2003;**348**:1953–66.
3 **Sidwell RW**, Huffman JH, Khare GP, *et al.* Broad-spectrum antiviral activity of virazole: 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide. *Science* 1972;**177**:705–6.
4 **Cameron CE**, Castro C. The mechanism of action of ribavirin: lethal mutagenesis of RNA virus genomes mediated by the viral RNA-dependent RNA polymerase. *Curr Opin Infect Dis* 2001;**12**:261–72.
5 **Booth CM**, Matukas LM, Tomlinson GA, *et al.* Clinical features and short term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA* 2003;**289**:2801–9.
6 **Chu CM**, Cheng VC, Hung IF, *et al.* The role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004;**59**:252–6.
7 **Chan JWM**, Ng CK, Chan YH, *et al.* Short term outcome and risk factors for adverse clinical outcomes in adults with severe acute respiratory syndrome. *Thorax* 2003;**58**:686–9.
8 **Choi KW**, Chau TN, Tsang O, *et al.* Outcomes and prognostic factors in 267 patients with severe acute respiratory syndrome in Hong Kong. *Ann Intern Med* 2003;**139**:715–23.
9 **Sung JJ**, Wu A, Joynt GM, *et al.* Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak. *Thorax* 2004;**59**:414–20.
10 **Knowles SR**, Phillips EJ, Dresser L, *et al.* Common adverse events associated with the use of ribavirin for severe acute respiratory syndrome. *Clin Infect Dis* 2003;**37**:1139–42.
11 **Peiris JS**, Chu CM, Cheng VC, *et al.* Clinical progression and viral load in an outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003;**361**:1767–72.
12 **Huggins JW**. Severe acute respiratory syndrome (SARS) and coronavirus testing—United States. *MMWR* 2003;**52**:297–302.
13 **Health Canada**. *Management of severe acute respiratory syndrome (SARS) in adults: Interim guidance for healthcare providers*, http://www.hc-sc.gc.ca/(accessed 24 January 2004).
14 **Cinatl J**, Morgenstern B, Bauer G, *et al.* Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. *Lancet* 2003;**361**:2045–6.
15 **van Vonderen MGA**, Bos JC, Prins JM, *et al.* Ribavirin in the treatment of severe acute respiratory syndrome (SARS). *Neth J Med* 2003;**61**:238–41.
16 **Zhaori G**. Antiviral treatment for SARS: can we draw any conclusions? *Can Med Assoc J* 2003;**169**:1165–6.
17 **Chan KS**, Lai ST, Chu CM, *et al.* Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. *Hong Kong Med J* 2003;**9**:399–406.
18 **Van Reeth K**, Van Gucht S, Penseart M. Correlations between lung proinflammatory cytokine levels, virus replication, and disease after swine influenza virus challenge of vaccination-immune pigs. *Viral Immunol* 2002;**15**:583–94.
19 **Cheung CY**, Poon LL, Lau AS, *et al.* Induction of proinflammatory cytokines in human macrophages by influenza A (H5N1) viruses: a mechanism for the unusual severity of human disease? *Lancet* 2002;**360**:1831–7.
20 **Lee N**, Sung J. The use of corticosteroids in SARS. *N Engl J Med* 2003;**348**:2034–5.
21 **Wong CK**, Lam CKW, Wu AKL, *et al.* Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin Exp Immunol* 2004;**136**:95–103.
22 **Nicholls JM**, Poon LL, Lee KC, *et al.* Lung pathology of fatal severe acute respiratory syndrome. *Lancet* 2003;**361**:1773–8.
23 **Franks TJ**, Chong PY, Chui P, *et al.* Lung pathology in severe acute respiratory syndrome (SARS): a study of 8 autopsy cases in Singapore. *Hum Pathol* 2003;**34**:743–8.
24 **Meduri GU**, Headley AS, Golden E, *et al.* Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1998;**280**:159–65.
25 **Keh D**, Boehnke T, Weber-Cartens S, *et al.* Immunologic and hemodynamic effects of ''low dose'' hydrocortisone in septic shock. *Am J Respir Crit Care Med* 2003;**167**:512–20.
26 **Buckingham SC**, Jafri HS, Bush AJ, *et al.* A randomized, double-blind, placebo-controlled trial of dexamethasone in severe respiratory syncytial virus (RSV) infection: effects on RSV quantity and clinical outcome. *J Infect Dis* 2002;**185**:1222–8.
27 **Pareja JG**, Garland R, Koziel H. Use of adjunctive corticosteroids in severe adult non-HIV Pneumocystis carinii pneumonia. *Chest* 1998;**113**:1215–24.
28 **Smego RA**, Ahmed N. A systematic review of the adjunctive use of systemic corticosteroids for pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2003;**7**:208–13.
29 **Wormser GP**, Horowitz H, Dworkin B. Low-dose dexamethasone as adjunctive therapy for disseminated Mycobacterium avium complex infections in AIDS patients. *Antimicrob Agents Chemother* 1994;**38**:2215–7.
30 **Gustafson LM**, Proud D, Hendley JO, *et al.* Oral prednisone therapy in experimental rhinovirus infection. *J Allergy Clin Immunol* 1996;**97**:1009–14.
31 **Domachowske JB**, Bonville CA, Ali-Ahmad D, *et al.* Glucocorticoid administration accelerates mortality of pneumovirus-infected mice. *J Infect Dis* 2001;**184**:1518–23.
32 **Puhakka T**, Makela MJ, Malmstrom, K, et al. The common cold: effects of intranasal fluticasone propionate treatment. *J Allergy Clin Immunol* 1998;**101**:726–31.
33 **Tsang KW**, Ho PL, Ooi GC, *et al.* A cluster of cases of acute severe respiratory syndrome in Hong Kong. *N Engl J Med* 2004;**348**:1977–85.
34 **Lee N**, Hui D, Wu A, *et al.* A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 2003;**348**:1986–94.
35 **So LK**, Lau AC, Yam LY, *et al.* Development of a standard treatment protocol for severe acute respiratory syndrome. *Lancet* 2003;**361**:1615–7.
36 **Zhao Z**, Zhang F, Xu M, *et al.* Description and early treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China. *J Med Microbiol* 2003;**52**:715–20.
37 **Ho JC**, Ooi GC, Mok TY, *et al.* High-dose pulse versus nonpulse corticosteroid regimens in severe acute respiratory syndrome. *Am J Respir Crit Care Med* 2003;**168**:1449–56.
38 **Tsui PT**, Kwok ML, Yuen H, *et al.* Severe acute respiratory syndrome: clinical outcomes and prognostic correlates. *Emerg Infect Dis* 2003;**9**:1064–9.
39 **Wu W**, Wang J, Liu P, *et al.* A hospital outbreak of severe acute respiratory syndrome in Guangzhou, China. *Chin Med J* 2003;**16**:811–8.
40 **Li N**, Ma J, Nie L, *et al.* Retrospective analysis of corticosteroid treatment in severe acute respiratory syndrome (SARS). *Beijing Da Xue Xue Bao* 2003;**35**(Suppl):16–18.
41 **Wang H**, Ding Y, Li X, *et al.* Fatal aspergillosis in a patient with SARS who was treated with corticosteroids. *N Engl J Med* 2003;**349**:507–8.