Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CORRESPONDENCE

e-mail submissions to correspondence@lancet.com

Personal view of SARS: confusing definition, confusing diagnoses

Sir—The diagnosis of severe acute respiratory syndrome (SARS) is based on a clinical definition. Overdiagnosis or underdiagnosis could happen, although to estimate the extent of this occurrence is difficult.

Overdiagnosis might lead to anxiety and fear associated with confinement and isolation, especially in children. In Hong Kong's public hospitals, health-workers are unable to provide a room for every patient with suspected or probable SARS. Patients diagnosed with SARS may or may not have the SARS virus(es), but they are at risk of contracting the infection if they are grouped with infected patients. Over-diagnosis also leads to inconvenience in the workplace or at school. The case of a young girl who developed fever during her visit to Taiwan is a good example. She had no SARS contact and chest radiograph was normal. However, the Taiwan government labelled her as a suspected SARS case, and she was transported back to Hong Kong where she was declared free from the infection, but the experience for her was not a memorable one.

Conversely, underdiagnosis of SARS could lead to cases of the infection being unrecognised, with the potential for pathogen to spread in the community. Imprecise definition therefore has serious public-health consequences.

WHO has done little to alleviate the confusion surrounding the terminology. SARS is an ambiguous term. The clinical features of many patients are neither severe nor respiratory in nature. SARS was initially labelled as atypical pneumonia with the outbreak in China, and this definition also caused much confusion with the so-called typical atypical pneumonia due to mycoplasma and chlamydia. Also, the acronym SARS is closely similar to that of ARDS for acute respiratory distress syndrome, but has a totally different meaning. Indeed, SARS typically kills patients not via the virus but by complications of ARDS.

WHO defines SARS as either suspected or probable. The case definition of suspected SARS is (1) fever, (2) respiratory symptoms including cough and difficulty breathing, and (3) close contact with people with SARS or a history of travel to an epidemic area.[1] Probable SARS is a suspected case with radiographic evidence of pneumonia or respiratory distress syndrome. Thus, diagnosis of the cause of SARS was not required in these clinical definitions. However, to not obtain chest radiographs for a patient suspected as having SARS is not practical, neither is it sensible to label a patient as having suspected SARS in the absence of change on chest radiograph. Therefore, to differentiate suspected SARS from probable SARS on the basis of radiographic changes alone is not logical. Furthermore, any child in Hong Kong who has a cold with fever and cough would be diagnosed as suspected SARS by WHO definition. WHO has now revised their definition of a probable case of SARS to include a suspected case of SARS that is positive for SARS coronavirus.

In Hong Kong, the infection can be diagnosed by several definitions, official or otherwise. Suspected SARS, for instance, is now defined as SARS infection that is serious enough that ribavirin is started. The modification is a practical one and partly avoids overdiagnosis of mild febrile symptoms that are probably not SARS. This modification, however, could lead to underdiagnosis of otherwise mild SARS cases. For example, a teenage girl was identified with symptoms of SARS and chest radiographic changes in accordance with the infection, but no definite history of contact was reported. She was started on ribavirin. Coronavirus was subsequently detected in her throat gargle and stool specimens by reverse transcriptase-PCR. She was labelled as suspected SARS in the absence of contact history. However, WHO would probably judge this case probable SARS because she resides in an epidemic area. If definite contact history is needed, this case is one of coronavirus pneumonia, not SARS at all. We have also seen other cases of SARS without fever and those with diarrhoea but no pneumonia.

To confuse matters further, the Chinese translation of probable SARS is confirmed SARS. In the Chinese media, confirmed SARS really means a person has been confirmed to have probable SARS. The local media must be reminded that SARS is really not the same as atypical pneumonia but rather a subset of this disease. For example, people can have atypical pneumonia but not SARS.

In view of the above confusions, we propose the term epidemic viral pneumonia (EVP) to replace suspected and probable SARS, and the classification shown in the table, which might be useful for index surveillance and in epidemiological and prognostication studies. The classification is not intended for triage of patients because any radiographic abnormality might not be noted at presentation. Virological results might also be available a few days after presentation. When we applied this classification to ten children previously reported,[2] six could be grouped under EVP [C+, Coronavirus+] and four under EVP [C+, V–]. The teenage girl mentioned above would be classified as EVP [C–, Coronavirus+]. EVP [C–, V–] represents an overdiagnosed group of patients with various typical and atypical pneumonitis syndromes.

Our classification also helps to guide health-workers on patient's management. Newly admitted patients with persistent fever and pneumonia should be isolated, preferably in a single room, and be eventually classified into one of the four forms of EVP. Patients with EVP [C+, V+], EVP [C+, V–], and EVP [C–, V+] need to be isolated for at least 14 days, whereas those with EVP [C–, V–] could be discharged once their symptoms improve.

Classification	Definition
EVP [C+, V+]	EVP with positive contact history and virus identified
EVP [C+, V–]	EVP with positive contact history but no virus identified
EVP [C–, V+]	EVP with negative contact history but virus identified
EVP [C–, V–]	EVP with negative contact history and no virus identified

Proposed classification system.

We thank Prof T F Fok for his help with this letter.

*K L E Hon, A M Li, F W T Cheng, T F Leung, P C Ng

*Department of Paediatrics, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong Special Administrative Region, China (KLEH, AML, TFL, PCN); and Department of Paediatrics, Prince of Wales Hospital, Shatin, Hong Kong SAR, China (FWTC)
(e-mail: b103892@cuhk.edu.hk)

1 World Health Organization. Case definitions for surveillance of severe acute respiratory syndrome (SARS). Geneva: WHO, 2003. Available at http://www.who.int/csr/sars/casedefinition (accessed May 21, 2003).
2 Hon KLE, Leung CW, Cheng WTF, et al. Clinical presentations and outcome of severe acute respiratory syndrome in children. *Lancet* 2003; **361:** 1701–03. Published online April 29, 2003. http://image.thelancet.com/extras/03let4127web.pdf.

Lymphopenia in SARS

Sir—A common observation in patients with severe acute respiratory syndrome (SARS) has been pronounced lymphopenia with reported prevalence of 69·6%[1] and 54%.[2] Glucocorticoids have a profound effect on circulating T lymphocytes,[3] which may involve their movement out of the intravascular compartment.[4] Glucocorticoids are also used therapeutically in lymphoproliferative diseases, because of their cytolethal actions. In the study by Lee and colleagues,[1] use of steroids may account for the decreasing trend in lymphocyte count over the 7 days of treatment. Booth and colleagues[2] only used steroids in 40% of the patients, less than half of whom received them during the first 48 h. Therefore, some of the lymphopenia reported by Booth and colleagues[2] may be associated with use of steroids, but it does not account for all the patients, and certainly not for the lymphopenia at the initial presentation.

Any critical illness is accompanied by the activation of the hypothalamic-pituitary-adrenal axis resulting in increased adrenocorticotropic hormone (ACTH) and cortisol to maintain the integrity of the vasculature and modulate the actions of proinflammatory and anti-inflammatory cytokines.[5] In a healthy person under severe stress, pituitary ACTH can easily cause the adrenal cortex to release 225–440 mg per day of cortisol,[5] which is equivalent to the dosage of methylprednisolone used by Lee and colleagues[1] that can drive T lymphocytes out of the peripheral circulation. Therefore, is the lymphopenia seen in some of the SARS patients an indication of the integrity of the status of the hypothalamic-pituitary-adrenal axis? More importantly, are the patients without lymphopenia, adrenal insufficient?

The answers to these questions need to be addressed urgently, because they may have a bearing on whether to use glucocorticoids in the treatment of SARS. Thompson[5] has provided a helpful review of glucocorticoids and acute lung injury.

Nirmal S Panesar

Department of Chemical Pathology, Chinese University of Hong Kong, Shatin, New Territories, Hong Kong Special Administration Region, People's Republic of China
(e-mail: nspanesar@cuhk.edu.hk)

1 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.
2 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. http://jama.ama-assn.org/cgi/content/full/289.21.JOC30885 (accessed May 22, 2003).
3 Slade JD, Hepburn B. Prednisone-induced alterations of circulating human lymphocyte subsets. *J Lab Clin Med* 1983; **101:** 479–87.
4 Cupps TR, Fauci AS. Corticosteroid-mediated immunoregulation in man. *Imm Rev* 1982; **65:** 133–55.
5 Thompson BT. Glucocorticoids and acute lung injury. *Crit Care Med* 2003; **31:** S253–57.

ASCOT-LLA: questions about the benefits of atorvastatin

Sir—We have no doubts about the benefit of lipid-lowering drugs on cardiovascular morbidity and mortality. However, we dispute the conclusions of Peter Sever and colleagues (April 5, p 1149)[1] about the beneficial effects of atorvastatin as presented in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA). As Lars Lindholm and Ola Samuelsson report in the accompanying Commentary (p 1144),[2] the additional benefit of lipid-lowering treatment upon antihypertensive treatment was rather low in ASCOT-LLA.

The benefit of atorvastatin was not significant in patients with diabetes, left-ventricular hypertrophy, and previous vascular disease. Among women, placebo even had non-significantly better results than atorvastatin. The positive results for atorvastatin were not significant in patients aged 60 years or younger, those without renal dysfunction, and in those who had metabolic syndrome.

The disappointing results among women accord with the findings of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT),[3] in which pravastatin did not reduce all-cause mortality, myocardial infarction, or fatal coronary heart disease. One explanation for this finding could be that in ALLHAT-LLT, almost 50% of the participants were women and a high proportion of patients in the control group used statins. The ASCOT investigators argue that the number of events among women and participants with diabetes was too small, because of the inadequate power of the study. However, we doubt the usefulness of lipid-lowering treatment in a population of women with such a low incidence of cardiovascular events (36 for almost 6500 patient-years).

The finding that atorvastatin had no effect on total mortality accords with the results of previous primary prevention studies. However, an effect on cardiovascular mortality would be expected in view of the high number of risk factors among ASCOT-LLA participants.

Why was ASCOT-LLA stopped prematurely after 3·3 years when no significant reduction in mortality could be shown? During the first 3 years of the study, there was no decreasing trend in mortality. In addition, there was even a non-significant trend towards a disadvantage with atorvastatin for fatal and non-fatal heart failure, peripheral arterial disease, and development of diabetes mellitus or renal impairment.

The reason why atorvastatin did not show a similar beneficial effect to simvastatin or pravastatin might be found in the low dose of atorvastatin used in ASCOT-LLA. A higher dose might have shown better results. But there is also a substantial difference in the biochemical structure of the different statins. Lovastatin and pravastatin are natural statins of fungal origin, whereas simvastatin is a semisynthetic derivative of lovastatin. Atorvastatin and fluvastatin are fully synthetic statins.[4] In addition, Cromwell and Ziajka[5] found that the long-term use of atorvastatin led to tachyphylaxis (a decreasing response to a physiologically active agent), which resulted in an increase of LDL cholesterol over time despite optimum treatment. By contrast, all other statins showed no evidence of tachyphylaxis.[5]

Atorvastatin offers no additional benefit above antihypertensive treatment for the reduction of fatal and non-fatal cardiovascular events in women, patients with diabetes, and those with left-ventricular hypertrophy or previous vascular disease—and all this without affecting mortality.

Dirk Devroey received travel expenses from Merck Sharp and Dohme Belgium, for whom he has served as a consultant, he received research funds from Novartis Belgium and Bristol-Myers Squibb Belgium, and Pfizer Belgium sponsored some research meetings.