Response to Letter by Kwan et al

We appreciate the interest of Dr Kwan and colleagues in our recent work analyzing the clinical consequences of systemic infection in patients with acute stroke.1 In their Letter to the Editor these authors request some clarifications about the methods used in the study, and make some criticisms that we pass to address.

Kwan et al demand whether the clinical outcome of the patients was measured in hospital discharge or at day 7, and how the clinical score was handled in patients discharged before day 7. We agree that a variable time-point for the evaluation of the patients would have biased the results of the study. Thus, patients with a protracted outcome score would have been allowed more time for recovery than patients with shorter observations, but also to longer exposure to invasive maneuvers and secondary risk of infection. To avoid this heterogeneity we did all outcome assessments at day 7, except in patients with stable symptoms for at least 48 hours, who were discharged before day 7. The Last Observation Carried Forward approach was the method selected for analysis in these cases. Therefore, we are confident that we did not introduce an attrition bias in our clinical evaluation.

Kwan and colleagues criticize the nonspecific definition of acute bronchitis used in the study, and the inclusion of acute bronchitis as an end point for it might minimize the relevance of infection because its systemic impact might not be as great as that of bacterial pneumonia. Nevertheless, we established a quite clear definition of acute bronchitis: fever (≥37.5°C in 2 separate determinations or ≥37.8°C in 1 single determination), bronchial purulent secretions, blood leukocyte count >11×10⁹/L or <4×10⁹/L, and normal chest x-ray films. In a population such as the one reported in the study, these criteria confidently predict bacterial bronchitis. Kwan et al buttress their criticism based on observations obtained in previously healthy and young patients, and in which cough and rhonchi were the only requisites for the diagnosis of viral bronchitis.2 Contrarily, fever, bronchial purulent secretions, and abnormal white cell counts were not mandatory. To extrapolate these results to our population is not justified.

The clinical meaning of acute bronchitis was recently analyzed in old patients (mean age 70) with suspected pneumonia.3 In this study, the mortality rates of patients with normal or abnormal chest x-rays were similar: 10% and 8%, respectively. In the same line, patients with acute respiratory infection and “normal” chest x-rays may harbor pneumonia in about 30% of the cases, if a high resolution lung tomography is performed.4 Therefore, these results endorse the appropriateness of including acute bronchitis as an infectious end point in patients with acute stroke.

Kwan et al also claim that the modified Rankin Scale (mRS) used in the study was not sensitive to detect small clinical changes. They also criticize that outcome assessment was dichotomized, and that longer-term outcomes were not performed. Certainly, a refinement in the neurological assessment and a longer-term evaluation would have shown a greater rate of recovery, but it is unclear how this would facilitate the detection of the small size effects of infection during the acute phase of stroke. Alternatively, infections might have clouded the neurological examination performed at day 7, and a longer-term examination might have emphasized even further the harmlessness of early infection. We also performed daily National Institutes of Health Stroke Scale (NIHSS) exams in the patients, and we did not disclose any deleterious effect of infection. In a recently reported randomized controlled trial of antibiotic prophylaxis in acute stroke,5 we found a lack of association between infection and poor outcome at 3 months. Outcome in this study was a global measure that integrated the scores in the mRS, the NIHSS, and the Barthel Index,6 reinforcing that infection after stroke has not either short- or long-term outcome effects.

We concur with our colleagues that further research on stroke-related infection is needed. A better understanding of infection might provide clues of the biology of brain ischemia, and it may unravel the clinical meaning of the cross-talk between the nervous system and the immune system, essential to maintaining homeostasis. Meanwhile, our findings indicate that infection should be addressed as a marker of the severity of ischemic brain injury, a view not in conflict with the recommendation of preventing, detecting, and treating poststroke infection appropriately.8

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