The Management of the 2009 pandemic Influenza A H1N1 virus infection

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By far the most important step in the management of a new pandemic viral illness is the availability of a rapid and accurate diagnostic test. Within 1 week of the announcement by the Word Health Organization of the outbreak in Mexico, rapid diagnostic tests based on reverse transcriptase-polymerase chain reaction (RT-PCR) was designed to differentiate this novel influenza A H1N1 virus from the lately circulating seasonal H1N1 and H3N2 virus, and the sporadic avian H5N1 and H9N2 virus (1). This allowed the institution of infection control measures to reduce nosocomial and household transmission. Using the quantitative version of such diagnostic test, the viral load of the respiratory secretions of these infected patients can be measured. Such diagnostic test allowed clinicians to objectively gauge the response to various antiviral or immunomodulating therapy of infected patients. As expected, the early use of oseltamivir therapy can reduce the viral load slightly more rapidly than our immune system with earlier resolution of symptoms (2,3). However we still do not know whether early institution of oseltamivir or other neuraminidase inhibitor can really prevent normal healthy individuals, pregnant women, obese patients and those with chronic underlying illness from progressing to severe illness. The majority of these patients suffered from mild disease and recover without any specific antiviral treatment or with only symptomatic treatment. However some suffered and died from very severe illness with primary viral pneumonia and sometimes secondary bacterial pneumonia which progressed to acute respiratory distress syndrome. These severe cases had delayed viral load clearance with concomitant marked activation of plasma proinflammatory cytokines and chemokines. The mortality is up to 30% even in patients with no underlying illness and despite oseltamivir treatment (4,5). They may have extrapulmonary manifestations such as myocarditis, vascular thrombosis and reactive haemophagocytosis as in the case of avian H5N1 infection. This is not completely unexpected as the new virus is very well adapted to many human cell lines of different organ origins though the lung and intestinal cell lines such as Caco2 appeared better as they can produce endogenous trypsin-like proteases which can enhance proteolytic cleavage of the haemagglutinin for cell entry by membrane fusion (6). Furthermore this new virus can produce a D225G mutant (or D222G with H1 numbering) of haemagglutinin which is associated with severe illness and has a predilection for the α2,3-linked sialic acid receptors more abundantly found in the lower respiratory tract of human (7-10). Interestingly this mutant was also associated with viraemia as demonstrated by RT-PCR (11).

No potential conflict of interest.

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Zhong NS *et al.* has produced a very comprehensive guideline for the diagnosis and treatment of influenza which can serve Chinese patients who choose to be treated with either Western medicine or traditional Chinese medicine (12). In the former case of antiviral treatment, the adamantanes including the amantadine and rimantadine are not useful for the 2009 pandemic H1N1 virus because of the S31N mutation of the matrix M2 protein. Moreover it has been reported that oseltamivir resistance through the H275Y mutation of the haemagglutinin can emerge in patients without any exposure to oseltamivir as the quasispecies of resistant mutant have the advantage to outgrow sensitive wild type in cell culture (13). It is also important to note that such oseltamivir resistance will result in cross resistance to another neuraminidase inhibitor peramivir. Thus for the treatment of severe cases, other agents such as oro-inhaled or intravenous zanamivir have to be considered. However if the patient has severe pneumonia, inhaled agents will have difficulty of penetrating pulmonary consolidation. The role of sialidase DAS181 is still uncertain. As for polymerase inhibitors such as ribavirin, viramidine and T705, only ribavirin is commercially available but has significant side effects. Though interferons are active in-vitro and in animals, their pro-inflammatory side effects are severe and will not be considered in the clinical setting of severe pneumonia. In fact none of these agents including double-dose oseltamivir has ever been shown to decrease mortality in patients with influenza pneumonia and respiratory failure. Therefore further antiviral targets are being searched such as the nucleozin analogues which aggregate the viral nucleoprotein which is a non-surface and non-enzymatic antiviral target (14). Because elderly patients who have previous exposure to the 1918 pandemic H1N1 virus were relatively protected from the new pandemic 2009 H1N1 virus (15,16), it is conceivable that passive immunotherapy with convalescent plasma or hyperimmune immunoglobulin harvested by plasmapheresis from convalescent patients may be an important treatment option (17,18). Since protective antibody titer is lower after vaccination than natural infection, the convalescent plasma should be collected only from patients with natural infection (19). It is of note that patients with severe disease had a significantly lower serum IgG2 level than those with mild influenza (20). In a case control study, patients with severe influenza pneumonia have a lower mortality, serial viral load and proinflammatory serum cytokine level if treated with convalescent plasma (21). Further randomized control trials should be performed on patients with severe influenza pneumonia to ascertain the role of different treatment options.

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