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Avian influenza A/H5N1 virus: management in human and bird

The high mortality of over 50% in Hong Kong patients with pneumonia caused by the influenza A/H5N1 virus in 1997 was found to be quite consistent in subsequent outbreaks in South-East Asian countries.\textsuperscript{1,2} Our initial clinical observation was that this disease was not simply a viral pneumonia, and that all other major organs could be affected due to a cytokine storm caused by virus-induced aberrant immune activation. Fatalities were often associated with severe lymphopaenia, pancytopenia, impaired coagulation profiles, impaired liver and renal functions in addition to oxygen desaturation on admission. Besides diffuse alveolar damage in the lungs, lymphoid atrophy and necrosis were prominent in the spleen and lymph nodes with reactive haemophagocytosis, also evident in bone marrow.\textsuperscript{3} Unlike seasonal influenza caused by the human virus, which usually can only be isolated in the respiratory secretions, the A/H5N1 virus can also be found in the blood, faeces, and cerebrospinal fluid.\textsuperscript{4} Thus, this so-called cytokine storm could be the end result of uncontrolled systemic viral infection as in severe septic shock due to poorly treated Gram-negative bacteraemia.

Human vaccination to prevent the A/H5N1 virus is not commercially viable because of the low number of human cases and the rather rapid viral antigenic drift. The option of antiviral therapy is very limited, because resistance to adamantanes is widespread in A/H5N1 isolates from Vietnam and Thailand. Zanamivir is only likely to be useful for prophylaxis in health care workers, because it is delivered by inhalation and not expected to reach therapeutic concentrations in extrapulmonary tissues or hypoventilated areas of lung consolidation. Treatment with oseltamivir did not obviously result in improved survival, but there was a trend towards better survival if given early in the course of illness.\textsuperscript{5} Though the poor response may have resulted from delayed treatment initiation, other factors might be equally important. These include: the non-specific initial manifestations of A/H5N1 infection, the high initial viral load, poor oral bioavailability of oseltamivir in seriously ill patients, lack of a parenteral preparation, and the ready emergence of resistance. Since the lymphopaenia and serum pro-inflammatory cytokine levels correlate directly with the viral load in respiratory secretions,\textsuperscript{6} it is also reasonable to consider giving immunomodulators to dampen the cytokine storm. However, the use of steroids did not improve survival and was associated with significant complications such as hyperglycaemia and superinfection.\textsuperscript{7} In fact, after knockout of pro-inflammatory chemokine and cytokine genes or treatment with steroids, A/H5N1 virus–infected mouse models showed no significant improved survival.\textsuperscript{8} Due to the low incidence of this important disease, randomised controlled clinical trials are unlikely to be conducted. However, data from mice models suggest that high dose of oseltamivir therapy prolonged to more than 8 days,\textsuperscript{9} combination of oseltamivir with amantadine,\textsuperscript{10} and use of high titres of neutralising monoclonal antibody or convalescent plasma, may improve survival.\textsuperscript{11}

Recently, we combined the systemic administration of zanamivir with the COX-2 inhibitor celecoxib and mesalazine to treat mice inoculated with a high dose of A/H5N1 virus.\textsuperscript{12} Despite delayed therapy initiation of up to 48 hours after inoculation, this combination significantly reduced the viral load, production of pro-inflammatory cytokines, chemokines, leukotrienes, as well as mortality. The inhibitory activities of these non-steroidal anti-inflammatory agents against the pro-inflammatory response, together with the anti-apoptotic activities of the aminosalicylate, reduced cell death and tissue damage in the host. The concomitant use of an effective antiviral is essential, not only to limit the extent of viral replication that drives the cytokine dysfunction triggered by the infection, but also to counteract the possible increase in viral load after COX-2 inhibition. Notably, these drugs are widely available and intravenous zanamivir has been used in humans with little in the way of side-effects.\textsuperscript{13-15}

However, prevention is always better than cure. No developed nation in the world is really prepared for a 1918-like pandemic influenza. In the absence of efficient inter-personal spread of the A/H5N1 virus, preventing major outbreaks of human infection relies on controlling its endemicity in poultry. This entails prevention and prompt management of outbreaks in poultry, separation of poultry from humans to minimise transmission to them, and proper management of occasional human infections. At the height of the 1997 outbreak in Hong Kong, 20% of the poultry in wet markets were infected by the virus. Control of the outbreak ensued after culling of all the 1.5 million poultry throughout Hong Kong. Sale of live ducks and geese in wet markets was banned, as these birds can shed the virus asymptomatically. Biosecurity measures in local farms were strictly enforced, and a bi-weekly rest day with cleansing of all the poultry stalls was introduced to interrupt the transmission cycle in wet markets. Vaccination against influenza A/H5 infection was required for all poultry in local farms and farms supplying live poultry to Hong Kong from Mainland...
China. These stringent measures appeared successful in preventing the incursion of the virus into local farms and markets for several years. Unfortunately, we cannot prevent the expected antigenic drift which will overcome the protection conferred by the poultry vaccine and thus require changes in vaccine according to the dominant endemic viral strain at that time. Complete elimination of illegal poultry imports into Hong Kong from unregistered farms in the Mainland is unlikely to be successful. Moreover, chicken stalls in wet markets may be regarded as mini-farms, where biosecurity measures comparable to those imposed on recognised farms are impossible to implement. Thus, the final answer depends on central slaughtering, which eliminates any potential contact of live poultry with the general population. In the interim before central slaughtering is launched, daily culling of all unsold chickens can be expected to stop viral shedding from newly infected chickens. The latter may not stay in the market long enough to exceed the incubation period for viral shedding. However, such measures cannot stop viral shedding from illegally imported infected chickens.

Control of avian influenza outbreaks in poultry in developing countries poses even more formidable problems. The rising demand for meat protein associated with the improving open-door economy in South-East Asia is responsible for a tremendous increase in poultry farming. Regrettably, no corresponding improvement in the biosecurity measures have followed in the ensuing profligation of farms and markets, and over half of such poultry are reared in backyard premises. Theoretically, country-wide veterinary and virological surveillance of birds, perimeter depopulation of infected zones, and targeted immunisation of poultry with correct vaccines could all be helpful. Other potentially useful measures include: segregation of poultry species, regular moratoria of poultry in the markets, and the implementation of biosecurity and hygienic practices in farms, markets, and at a personal level might also help to control poultry pandemic. How many of these measures are practicable is questionable. Alternatively, lesser scale interventions at the district level can be considered in response to local virus detection even without evidence of excess poultry deaths, since virus shedding is common in asymptomatic water fowl. To reduce the environmental viral load and therefore the risk of re-infection of farmed poultry, a planned one-off moratorium of 3 weeks during the hottest months of the year may be an important measure, as shown by mathematical modelling.16 Backyard farms will then be re-populated by hatchlings from virus-free chickens and minor poultry to ensure a virus-free environment. Universal immunisation against avian influenza of all poultry in backyard farms is not feasible, and hence immunisation should be preferentially targeted to ducks, geese, and chickens in industrial farms. Free grazing of ducks and geese outside the pens should only be allowed if the birds carry adequate titres of neutralising antibodies against H5.

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A/H5N1禽流感病毒：人和禽的處理

1997年香港因A/H5N1流感病毒导致禽流人流感，死亡率超过50%，而东南亚国家后来的情况与此相当一致。根据我们的初步观察，这种疾病并不是一种病毒性流感，而是由于病毒的免疫系统异常活跃而导致的细胞激素风暴。也可能影响到所有其他重要器官。致命的原因，往往是在人体中变异严重，全血细胞减少、凝血功能异常、肝和肾功能异常，以及氧化应激下降。除了广泛的肺泡损伤外，淋巴细胞增加和坏死的情况在带有抗血浆作用的细胞在肺和淋巴结中，甚至在骨髓中，相当显著。即使抗血浆和抗炎蛋白质的其他表现，这种所谓的细胞激素风暴不过是一种失败的细胞激素风暴的预后结果，激素治疗无效的治疗，抗体治疗无效。激素和抗炎药物治疗无效。

由於人類的感染個案不多，以及抗病毒的迅速深覆，所以病毒抵抗A/H5N1禽流感的疫苗并不符合商業原則。抗病毒治療的方法不多，因為越南和泰國分離出來的A/H5N1對於金剛烷胺有抗藥性。扎那米筆有對禽流感患者作用，因為這麼一種藥物是經口吸收，而且能夠通過呼吸道肺部 Ordinary或中C而治療。然而，金剛烷胺的治療副作用包括神經系統的副作用，甚至長期服用可以導致神經系統的疾病，包括神經元的死亡。所以，這種药物的使用必须在临床医生的指导下进行，並且需要定期监测血药浓度。