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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.\(^1,2\) 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.\(^3\) 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.\(^4\) 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.\(^5\) 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,\(^6\) 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.\(^7\) 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.\(^8\) 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,\(^9\) combination of oseltamivir with amantadine,\(^10\) and use of high titres of neutralising monoclonal antibody or convalescent plasma, may improve survival.\(^11\) 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.\(^12\) 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.\(^13-15\)

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, perimetric 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. 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.

References


10. Ilyushina NA, Hoffmann E, Salomon R, Webster RG, Govorkova EA. Amantadine-oseltamivir combination therapy for H5N1

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1/AH5N1禽流感病毒：人和禽的處理

1997年香港因AH5N1流感病毒導致禽流感的病人，死亡率超過50%，而東南亞國家後來的情況則與此相去不遠。據我們的初期觀察，這種疾病並不僅僅是一種病原性流感，因病毒引起的免疫系統異常活躍而導致的細胞激素風暴，也可能影響到所有其它重要器官。致命的原因，往往是人體淋巴細胞嚴重減少，全血細胞減少，凝血狀態損傷，肝和腎功能損傷，以及氧平衡低下等。除了廣泛的肺泡受損之外，淋巴細胞的嚴重破壞和壞死的情況在有呼吸系統作業的肺泡組織和淋巴組織中，乃至在骨髓中，都可觀察到。與此同時，病患體內抗體的產生能力，通常只能存在於呼吸道分泌物中的人類病毒所導致的季節性流行，AH5N1病毒可以在血液、脅腺和腦組織中找到。因此，這種所謂的細胞激素風暴只不過是一種失控的系統性細胞激素的預期結果，情況正如革蘭氏陰性菌性血症處理不當時引致的敗血症一樣。

由於人類的感染個案不多，以及病毒抗原的迅速變異，所以難以預防AH5N1病毒的疫症，而必須依循商業原則，抗病毒治療的方法不多，因為盤克和禽類分離出來的AH5N1對於金銅有廣泛的抗藥性。扎那米韋只有有利於維持每日作預防，因為這種藥物是口服吸收，而且不能夠導致被肺泡過度濡潤或換氣不足的肺泡或肺外組織，而奧司他韋治療沒有明顯提高患者存活的機會，但若在發病初期便使用這種藥物，則存活的機會較大。在後期或症狀性疾病反應不佳或延遲開始使用所致，但其原因因素可能同時重要，這些因素包括AH5N1感染初期病徵不明確、初期病毒量大、嚴重患者口服奧司他韋的吸收率低及沒有靜脈注射的方針，以及治療期間產生的抗藥性。由於被瑞拉細胞減少和血清促炎性因子的水平，以及呼吸道病毒的消長至相當然，所以除了給予抗病毒藥物之外，加入免疫調節劑以減低細胞激素的消長，亦是合理的處理方法。然而，使用類固醇沒有提高病者的存活機會，反而會引起血糖過高和重複感染等併發症。事實上，受病毒感染被剝除了促炎因子和細胞因子的實驗鼠，或接受類固醇處方後，存活機會也沒有明顯提高。由於這種重要疾病的發病率低，不大可能進行臨床的監控及臨床試驗。不過，從實驗數據所顯示，較高劑量的奧司他韋和延長至8天以上的治療及奧司他韋與金銅的組合使用，以及使用高濃度和單劑或複合血清，可能提高患者的存活機會。近期，我們把扎那米韋用脈沖注射來治療受高濃AH5N1病毒的實驗鼠，再配合COX-2抑制劑塞洛昔布和美沙拉診，治療結果延緩至禽痘注射後48小時才開始。這種治療方法顯示了禽痘敏感，減低了細胞因子、促炎因子和白細胞的產生，以及動物的死亡。這些非類固醇抗炎劑對抗炎反應的抑制力，加上改善血流和氧供，減少了組織的死亡和組織擴張，由自然反應所造成病毒複製，引致細胞功能障礙，因此必須伴隨使用有效的抗病毒藥物，以限制病毒的複製程度。除此以外，這些藥物也可用以抗衡COX-2抑制作用後病毒量的上升。還有應該指出的是，這些藥物供應充足，而且扎那米韋靜脈注射在人體內副作用不多。

1998年禽流感的治療，和1918年那樣的流感做好準備。2009年AH5N1病毒沒有出現致命人傳人之前，預防人類禽流感大暴發的措施，主要是監督病毒發病症狀地點，預防和迅速處理家禽的爆發，禽舍分隔以減少禽流感病人的可能，以及適當處理人類的禽流感感染。1997年香港禽流感峰期時，濕潤市場205家禽受禽流感感染。控制措施是宰殺香港全部150萬隻家禽；濕潤市場禁止活禽活賣。因為這些家禽可以在無現狀的情況下排放病毒；本地農場積極執行生物安全措施；濕潤市場家禽後に每隔兩周實施一次清潔消毒；供應家禽的家禽的本地和大陸農場均須進行AH5流感疫症防疫。這些嚴格的措施多年來有效防止了病毒入侵本地農場和市場。可惜，預期的抗原變異無法阻止，而可能導致家禽禽流感的保護力不足。另外，非法入口的家禽之中可能有来自大陸非註冊農場的受感染家禽，要完全消除這些非法入口亦困難重重。重要的是，濕潤市場的活禽業務實際上是個小農場，由於空間所限，不可能實施農場的生物安全措施。因此，最後的政策便是在中央宰屠之上，唯有這樣才可避免活家禽與公眾接觸。在中央宰屠實行之前，2005年活禽節假日則可阻止小禽流感的病毒排放，避免病毒在這些市場期間經疫力成為潛伏病毒。但是，這種做法不能防止已受感染的非法入口雞禽的病毒排放。

發展中國家控制家禽禽流感，面臨更為嚴峻的問題。東南亞的經濟不斷改善，帶來禽肉蛋白質消費的不斷上升。為了應付這項需求，必須大量增加飼養家禽。可是，農場和市場中的生物安全措施卻沒有相應改善，而半數家禽是在家居後院的農場上飼養的。全國範圍的家禽和病毒監控，在疫區周邊宰殺可能受感染的家禽，使用適當的疫苗作防疫，分離禽類，市場定期禁止售鵝家禽，農場、市場和個人門面實行生物安全和衛生措施，凡此種種皆可控制這種禽鳥傳染病。但在發展中國家這些措施卻常常很少執行。如果在病毒檢測中沒有過量的家禽死亡，則在本地層面上可以考慮採取相當有限的措施，因為病毒排放在無禽流感的農場中相當罕見。為了降低禽流感的病毒量，從而減少農場家禽再次感染的風險，那麼按數學模型的計算結果，在年熱量期的月份一次過去三周，也許是一種重要的措施。後來農場事後將新飼養來自無病毒疫巢的所有家禽和幼禽，以確保環境不受病毒污染。給後院農場所有家禽設立禽流感免疫工作，亦可以，免疫工作應針對工業農場的鵝、鵝、鴨。而只有在這些家禽帶有足夠濃度的抗H5N1病毒中和抗體的時間，才允許鵝類在欄外自由走動。