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.10 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

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A/H5N1禽流感龍毒：人禽畜的處理

1997年香港因A/H5N1流感病毒致禽流感的病人，死亡率超過50%，而東南亞國家後來的情況與此相當一致。據我們的初步觀察，這種疾病並不僅僅是一種禽流感疫情，由病毒引發的免疫系統異常活躍而導致的細胞激昂風暴，也可能影響到所有其有重要器官。致命的原因，往往與人感染禽流感數顯嚴重減少，全血細胞減少，凝血酶濃度減低，肝和腎功能損傷，以及氧和細胞下降有關。除了濁慣的肺泡浸潤之外，淋巴細胞和死實的情況在有時有抗感染的血球被吞食現象的肺部和淋巴結之內，甚至在骨骼之內，腸胃和腎亦靈到。因此，這種所謂的細胞激昂風暴不但是多種失常的細胞激昂風暴，而且也是多種失常的細胞激昂風暴，以及這些細胞激昂風暴之因的處置結果，情形正如革蘭氏陰性菌血病處理不明時引致敗血症之原因。

由於人類的感染個案不多，以及抗菌療法的迅速深務，所以基於防止A/H5N1禽流感病毒的疫苗並非符合理事原則。抗病毒治療的方法不多，因為越南和泰國分離出的A/H5N1對於金剛烷胺有鈍化的抗藥性。扎那米韋只有利於禽流感人員作預防，因為這種病毒會經鼻口吸入，而且不能夠達到被肺部組織引導了或換氣不足的肺部或肺外組織，而奧司他韋治療沒有明顯提高病者存活的機會，但若在發病初期便使用這種藥物，則存活的機會較大。對奧司他韋反應不佳者可能再延遲開始用藥所致，但其他的因素可能同樣重要，這些因素包括A/H5N1感染初期病徵不明，初期病毒量高，嚴重病者口服奧司他韋的吸收率及沒有靜脈注射的方剤，以及治療期間產生的抗藥性。

由於細胞細胞和減少細胞激昂風暴因子的水平，以及細胞激昂風暴的病徵直接相連，所以除了給予抗病毒藥物之外，加入免疫調製以減低細胞激昂風暴的處理，以及細胞激昂風暴因子沒有提高病者的存活機會，反而會引發纖維過高和重複感染等併發症。事實上，受病毒激昂風病被剝除了促炎因子和細胞因子素的產生，或接受類固醇處方者，存活機會也會有明顯提高。由於這種重要疾病的發病率低，不大可能進行隨機的監控治療試驗。不過，從實驗資料和臨床治癒病例顯示，較高劑量的奧司他韋和延長至8天以上的治療期。奧司他韋與金剛烷胺的結合使用，以及使用高逐漸增加的抗病毒藥物，可提高病者的存活機會。近期，我們把扎那米韋用於靜脈注射治療受H5N1禽流感病毒的實驗，再配合COP-2抑制劑塞米普和布美沙拉鈉。嘗試治療減緩至病毒注射後48小時才開始，這種治療結果減少了病者，細胞反應因子、促炎因子和細胞因子的產生，以及動物的死亡。這些治療的促進對抗抗炎反應的抑制力，加上塞米普類固醇的抗炎死亡，減少了骨髓的細胞激昂風暴的機率，因自然激昂細胞的細胞激昂，引起細胞激昂功能障礙，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。除此之外，這些藥物亦用以抗衡COP-2抑制作用後病毒量的上升。有應該指出的是，這些藥物物供應充足，而且扎那米韋靜脈注射在人體內副作用不多。

預防永遠勝於治療。在世界上沒有一個已發展國家真正為1918年那樣的流感做好準備。在A/H5N1病毒還沒有出現首個傳人之前，預防人類感染大爆發的措施，主要是監控病毒發現地點，預防和迅速處理家禽的爆發，人禽分離以減少禽禽感染的可能，以及適當處理人類的禽流感感染。1997年香港禽流感高峯期時，湧現市場205家禽受到感染。控制措施是宰殺全香港全部150萬隻家禽；潑洗市場禁止活禽活飼，因為這些家禽可以在無患病的情況下排放病毒；本地農場執行生物安全措施；潑洗市場家禽攜帶每周實施一次清潔消毒；供應家禽的本地及大廈農場均必須進行A/H5流感防疫注射。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，預防的抗病突變無法阻止，而可能導致家禽禽流感的保護力下降。另外，非法入口的家禽之中可能有來自大陸不同農場的受感染家禽，但要完全消除這些非法入口亦困難重重。重要的是，潑洗市場的活禽操作實際上是個小農場，由於空間所限，不可能實施農場的生物安全措施。因此，最後的政策是在中央屠宰業之上升高橋可避免活禽與公眾接觸。在中央屠宰業實行之前的過渡時期，活禽不過週的食呢可以阻止新禽類的病毒排放，避免病毒在進市期間經濱幸的潛在。但是，這種做法不能防止已感染的非法入口禽隻的病毒排放。

發展中國家控制家禽禽流感疫情，面對更為嚴峻的問題。南亞的經濟不斷改善，帶來獵肉蛋白質需求的不斷上升，為應付這種需求，只得大量增加禽舍飼養。可是，農場和市場的生物安全措施卻沒有相應改善，而半數禽舍是在農家後院的農場上飼養的。理論上，全國範圍的禽和禽流感監控，在疫區周邊屠宰可能受染的家禽，使用適當的疫苗作防疫，分離禽類，市場定期禁止活禽飼養，死亡家禽、市場和個人居間實行衛生和衛生保健，凡此種種皆是控制這種禽流感傳染病，但在發展中國家這些措施卻在許多場合未必可行，如果在疫苗檢測中沒有過量的家禽死亡，則在疫區界面上可以考慮採取更少的措施，因為病毒排放在無桿菌的水禽中相當普遍。為了降低環境的病毒量，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，在年內最熱的月份一次過高二周，也許是一種重要的指標。流行期農場績可將飼養場的自身禽流感無卵和分離家禽的飼養，以保證環境不受病毒污染。給農場業所有家禽做全面的禽流感免疫工作並可可行，免疫工作應針對工業農場的鴨、鵝、雞。而只有在這些禽鳥有足夠程度的抗H5N1病毒中和抗體的狀態，才允許飼養在欄外自由走動。