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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.\(^2\) Our initial clinical observation was that this disease was not simply a viral pneumonia, and that 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, pancytopaenia, 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.\(^3\) 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.\(^3\) 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.18 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：人禽的處理

1997年香港因A/H5N1流感病毒致烈性肺炎的病人，死亡率超過50%，而東南亞國家後來的情況與此相當一致。我們的初期觀察，這種疾病並不僅僅是一種禽流感病毒，由這種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他重要器官。致命的原因，往往與人體淋巴細胞損失減少，全血細胞減少、凝血狀態損傷、肝和腎功能損傷，以及氧合度下降有關。此外在廣泛的肺泡炎症之外，淋巴細胞和壞死的情況在帶有抗炎作用的血球裡處臘現象的肢體和淋巴結中，乃至在骨髓中。對於細胞和組織中，這種所謂的細胞激素風暴只不過是一個系統性反應所表現的預期結果，情況正如革蘭氏陰性菌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換，所以這種診斷A/H5N1病毒的必要，並不符合商業原則。抗病毒治療的方法不多，因為腎炎和胃腸分離出來的A/H5N1對於金黃色腺有廣泛的抗藥性。就那米詩只有應用於體外的人工治療，因為這種藥物對口腔和吸入性治療都沒有足夠的藥物，所以只能在被被藥物可能導致不良反應的動物，而且有相當危險的副作用。然全盤性反應治療不及是延緩開始用藥所致，但目前的問題在哪裡？這些因素包括A/H5N1感染初期病徵不確立，初期病毒量少，嚴重病患者口服奧司他韋的吸收率低下及沒有靜脈注射的方針，以及治療期間產生抗藥性的原因。

由於細胞損傷和發病後的細胞激素因子水平的水平，與呼吸道感染的病毒量直接相關，所以除了給予抗病毒藥物之外，予以免疫調節以減低細胞激素風暴，也是合乎病理的處方。然而，使用藥物補償破壞的免疫系統和細胞因子的實驗鼠，或接受細胞移植的無菌動物，存活機會也沒有明顯提高。由於這種重要疾病的發病率低，不可能進行臨床的監控和治療。不過，從實驗動物的數據顯示，較高劑量的奧司他韋和延長至8天以上的治療期，奧司他韋與金剛烷的結合使用，以及使用高濃度和單劑量抗炎或抗腫瘤薬，或可用提高生存者的存活機會。近期，我們把那米詩用靜脈注射治療受禽流感A/H5N1病毒的實驗鼠，再配合COX-2抑制劑塞洛昔布和美沙拉嗪。儘管治療延緩至病毒注射48小時才開始，這種治療療法現時未有減低病毒量，抗炎細胞因子、促炎因子和蛋白合成的產生，以及動物的死亡。這些非藥物抗炎療法對抗炎反應的抑制力，加上塞洛昔布和美沙拉嗪的抗炎作用，減少了患者的死亡和組織損傷。由自然感染形成的病毒複製，引發細胞功能障礙，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。除這些藥物也用以抑制COX-2抑制作用病毒量的上升。還有應該指出的是，這些藥物供應充足，而且新米詩靜脈注射在人體內副作用不多。

病毒預防勝於治療。但世界沒有已發展國家真正為1918年那樣的流感做好準備。在A/H5N1病毒已經沒有出現人傳人之前，預防人類感染大爆發的措施，主要是監控病毒發生地點，預防和迅速處理家禽的暴發，人禽分離以減少禽傳人的可能，以及適當處理人類的傳播感染。1997年香港禽流感高峯期，購買市場200多萬隻家禽受到感染。控制措施是宰殺全港約

由於人類的禽流感個案不多，以及病毒抗原的迅速變換，所以這種診斷A/H5N1病毒的必要，並不符合商業原則。抗病毒治療的方法不多，因為腎炎和胃腸分離出來的A/H5N1對於金黃色腺有廣泛的抗藥性。就那米詩只有應用於體外的人工治療，因為這種藥物對口腔和吸入性治療都沒有足夠的藥物，所以只能在被被藥物可能導致不良反應的動物，而且有相當危險的副作用。然全盤性反應治療不及是延緩開始用藥所致，但目前的問題在哪裡？這些因素包括A/H5N1感染初期病徵不確立，初期病毒量少，嚴重病患者口服奧司他韋的吸收率低下及沒有靜脈注射的方針，以及治療期間產生抗藥性的原因。