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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. 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 lymphopenia, 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. 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. 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. 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 lymphopenia and serum pro-inflammatory cytokine levels correlate directly with the viral load in respiratory secretions, 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. 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. 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, combination of oseltamivir with amantadine, and use of high titres of neutralising monoclonal antibody or convalescent plasma, may improve survival. 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. 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.

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 proliferation of farms and markets, and only half of such poultry are reared in backyard premises. Theoretically, country-wide veterinary 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.

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A/H5N1禽流感病毒：人禽的处理

1997年香港因A/H5N1流感病毒致显肺炎的病人，死亡率超过50%，而东南亚国家此后的情况与此大同小异。按我们的初步观察，此病并不单纯是一种病毒性肺炎，由于病毒引起的免疫系统异常活跃而导致的细胞素风暴，也可能影响到所有其他重要器官。致命的原因，往往在于炎性肺泡细胞显著减少，全血细胞减少、凝血状态改变，肝和肾功能损害，以及呼吸功能下降或衰竭。除了肺部的损害外，淋巴结和脾脏的坏死，以及有潜在性作用的细胞内噬炎细胞的解体和结合中，甚至在骨骼肌，是显著的。与之相伴的是，存在与呼吸道分泌物内的人类病毒学资助的季节性循环不一，A/H5N1病毒可以在血液，粪便和脑脊液中找到，但因此，这虽是所谓的细胞素风暴只不过是一种非特异性免疫反应所引发的。目前，肺部，脓肿，肠管，细胶质体及肺出血时暴发的血症等。

由于人类的感染病案少，以及病毒抗原的迅速深变，所以推测A/H5N1病毒的疫苗或许不与上一个季节的覆盖率相同。抗病毒治疗的方法不多，因为越南和泰国分隔出来的A/H5N1对于金枪鱼来说是抗药的，当然，这是其他重要的抗病毒。扎那米韦是用于抑制病毒的复制物，因为这些药物是经口吸入的，而且不能达到被肺部炎性过程引致或损害应肺部的肺泡内皮细胞及肺门部。而氧他拉米治疗没有阻断病毒的存活的机会，除非在发病初期使用这些药物，寄存的机会才较大。对于急性呼吸道反应不佳可能是需要开始使用药物，但其他的影响因素可能不同，诸如可以阻断A/H5N1感染初期病情的预后，严重性患者口服氧他拉米的吸收率低及没有静脉注射的抗原，以及治疗期间产生的抗原性。由于静脉内注射减少和金枪鱼病原体细胞内的水平，与呼吸道分泌物的感染者和疫苗直接相联，所以除了给予抗病毒药物之外，加入免疫调节以减低细胞素风暴，也是合理的处理办法。然而，使用类固醇没有提高病人的存活机会，反而会引起血糖过低和二次感染等并发症。事实上，受病毒感染被剥除了促炎因子和细胞因子的宿主的实验，或接受类固醇前弗后，存活机会也没有明显的提高。由于这种重要疾病的发病率低，不大可能进行随机的监控实验。不同，从实验获得的数据显示，较高剂量的氧他拉米和延长至8天以上的治疗期，氧他拉米与金枪鱼的结合使用，以及使用高浓度度和单用类固醇抗炎和免疫血清，可提高病人的存活机会。近期，我们把扎那米韦用静脉注射治疗作为治疗高危A/H5N1病毒的干预策略，再配合COX-2抑制剂塞来昔布和美沙拉嗪，用以治疗延迟至病毒注射后48小时才开始，这种方法能显著减少流感症状，如发热、身体不适和肌肉酸痛，以及降低的死亡率。这些非类固醇抗炎剂对抑制炎性反应的抑制力，加上其容易剂量的抗炎剂，减少了病人的死亡和组织损伤。由自然感染形成的病毒复制，引致细胞功能障碍，因此必须伴随使用有效的抗病毒药物，以控制病毒的复制程度。除此之外，这些药物用以抗氧他拉米的抑制作用和病毒量的上升。因此，可预防的药物供应充足，而且扎那米韦静脉注射在人体内副作用不多。

预防永远胜于治疗。但世界上没有一个已发展国家真正为1918年那样流感做好准备。在A/H5N1病毒爆发前没有出现有效人传人前之后，预防人禽流感大爆发的措施，主要是监测病毒爆发地点，预防和迅速处理家禽的爆发，人禽分离以减少禽传人的可能，以及适当处理禽类的禽流感。1997年香港禽流感高峰时，爆发市场205家禽受到感染。控制措施是宰杀香港全部150万只家禽；爆发市场禁止活禽活卖。由于这些家禽可以在无症状的人群中情况下降解除，本地家禽场则继续执行生物安全措施；活禽市场的家禽继续每两周实施一次清水消毒；供应家禽的所在地本地和大农场均须进行A/H5流感监测试剂，进行严格合格的家禽。预防的抗菌剂气雾防治，可能将使家禽的保护率超过95%。另外，非法入口的家禽之中可能有来自大陆不注册农场的亲传禽流感，但要完全消使得这些非法入口家禽亦未能完全。主要是，爆发市场的活禽粪便管是间是小农场，由于空间所限，不可能实施农场的生物安全措施。因此，最后的答案是将中央实验室，有时情况才会避免活家禽与公众接触。在中央实验室在发生之前的爆发期，活禽不法不法的杀灭可阻止新感染禽的病毒扩散，避免病毒在该市市场期间迅速传播的危险。但是，除非阻止已感染的非法入口禽的病毒感染扩散。

發展中國家對鳥禽禽流感，面對更為嚴峻的問題。東南亞的經濟不斷改善，帶來的是人禽肉質需求的不斷上升，為了應付這種需求，只有大量增加家禽飼養。可是，農場和市場的生物安全措施在國內很少甚至為百就禽流感與禽流感。在中央政府實行之前的預期期，活禽不法不法的殺滅可阻止新感染禽的病毒擴散，避免病毒在該市市場期間迅速傳播的危險。但是，這種做法不能防止已受感染的非法入口禽的病毒擴散。

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