



Position Statement on Diagnostic tests and Antiviral treatment for children with influenza infection

Hong Kong College of Paediatricians

7th June 2016

Introduction

A recent media report on the death of a young child due to Acute Necrotizing Encephalopathy (ANE) associated with influenza infection has fueled vigorous discussions among medical professionals and the community on the use of diagnostic tests and antiviral treatment for children with influenza infection. There has been widespread public concern about the optimal clinical management of our young children infected with influenza. Questions are also raised among medical professionals about the relevance of existing clinical guidelines on the management of influenza in Hong Kong children considering the cultural context in our healthcare system.

The Hong Kong College of Paediatricians is part of the Hong Kong Academy of Medicine, and a statutory body established since 1991. It plays a critical role in developing and maintaining good practice in Paediatrics for medical professionals by ensuring the highest professional standards and high quality postgraduate training for the benefit of child and adolescent health in Hong Kong. It has a stated official duty to provide expert advice and education on key child health issues and to protect the wellbeing of Hong Kong children. In response to the public concern, the College organized a medical forum on 7th June 2016, with scientific presentations by Drs. Susan Chiu and David Lung and active discussion among participants from both public and private sectors. The forum was well attended by over 60 paediatricians, including practitioners in General Paediatrics, Paediatric Immunology and Infectious Diseases (PIID) subspecialty fellows and paediatric trainees from different training units. In-depth discussions were conducted about the latest scientific evidence in the literature about diagnostic tests and the use of neuraminidase inhibitors (NAI) in children with influenza infection.

Below is a summary of the forum and the consensus of participants after a thorough discussion.

Latest scientific evidence on the use of NAI for children with influenza infection

The fact sheet on antiviral therapy against influenza published by the Hospital Authority Central Committee on Infectious Disease and Emergency Responses (CCIDER) in January 2015 is a piece of important information on antiviral therapies for serious influenza infection. Professionals should be aware that the fact sheet is based on data from both paediatric and adult studies. Clinical judgment, based on the patient's disease severity and progression, presence of risk factors for complications of influenza, and likelihood of influenza, is important when making decisions on antiviral treatment for children with influenza infection (1).

For those paediatric patients a majority of whom were infected with pH1N1 admitted to a Paediatric Intensive Care Unit (PICU), use of NAI was associated with decreased mortality (2). But this benefit in reduced mortality rate was not found in a meta-analysis of 9218 paediatric influenza patients admitted to hospital with a different spectrum of disease severity (3).



In a Cochrane Review of NAI for preventing and treating influenza in 2356 children, NAI appears to have a modest benefit in reducing the duration of illness in otherwise healthy children with influenza by about one day (4, 5). It reduced the incidence of acute otitis media in children aged one to five years but was associated with a significantly increased risk of vomiting (around 15%). Currently there is no evidence that NAI treatment prevents serious complications (e.g. pneumonia) in children with influenza infection. The majority of influenza infections in children are mild and most of them would recover without any complications on conservative treatment. There is no scientific evidence to recommend the use of NAI in all children with influenza infection.

Experience from the Department of Paediatrics and Adolescent Medicine, The University of Hong Kong

From 2002 to 2016, about 10% (n=262) of the 2538 laboratory confirmed paediatric influenza patients hospitalized in Queen Mary Hospital received NAI during their hospitalization. Eighty-seven (33%) of them were given during the first phase of the 2009 pandemic as required by the Centre for Health Protection, 53 (20%) were given for severe or complicated influenza disease and 104 (39%) were given because of conditions at high risk of developing severe or complicated influenza infections e.g. malignancy. There were only 3 unrelated fatalities out of the 2538 patients due to their underlying conditions i.e. MELAS, Wilm's tumour and mediastinal malignancy. No serious medical complications arising from the infection were noted in the 90% of cases who did not receive NAI.

Latest scientific evidence on the use of diagnostic tests for children with flu-like symptoms

There are different rapid antigen detection tests (RADT) available for rapid diagnosis of influenza virus infection in Hong Kong. But some of them have sub-optimal sensitivity in the range of 50 – 70% and a low negative-predictive value during influenza season when the prevalence of influenza infection is high. A negative (RADT) result does not exclude influenza virus infection and influenza should still be considered in a patient if clinical suspicion is high based upon history, signs and symptoms and clinical examination. (6) PCR based influenza testing with high sensitivity and specificity is available in most of the public and private hospitals laboratories. Despite the high sensitivity, the yield is still dependent on the quality of the specimen, and the test would not be able to differentiate between viable and dead virus.

As described in different guidelines, the use of NAI in children with flu-like symptoms should be based on clinical judgment of the medical doctor, not on the influenza test results. Children at risk or presented with features of serious influenza infection or complications should be given the priority for treatment with NAI (1). There is currently no evidence to support universal influenza tests for all children with flu-like symptoms.

It is recommended by the Centre for Disease Control (CDC) of the United States that laboratory test of influenza infection should be performed in state or local public health laboratories if there is **risk of avian influenza infection** e.g. a travel history to endemic area with close poultry contact before symptoms onset. (7) There has been imported cases of H7N9 from China since 2014 (8) and, together with the recent local reports of H7N9 in poultry market, the public health risk of human avian influenza infection should be carefully considered before implementation of point of care test (POCT) in community clinics in Hong Kong.



For office or clinic based near-patient POCT, proper specimen handling guidelines on collection, testing, storage and disposal of the infectious specimens should be strictly followed. Specially-trained personnel are essential for these procedures to avoid cross contamination of specimens or spreading the virus. Amplicon contamination precautions must be implemented for PCR based POCT to prevent false positive results in office or clinics.

Acute necrotizing encephalopathy (ANE)

Initially described by Mizuguchi et al. from Japan in 1995(9), ANE is a host-mediated encephalopathy triggered by viral infection. Previously reported triggers of ANE include different viruses such as influenza A and B, parainfluenza, varicella, rubella, HHV-6 and HHV-8, enterovirus and coxsackie A9. There are published reports of ANE in Hong Kong, Taiwan and Korea. There are two types of ANE: a sporadic form (ANE) and a recurrent/familial form related to mutations in the RANBP2 gene (10). It is a very serious illness with initial mortality as high as 70% and less than 10% survive intact (survival without permanent disability).

ANE is not considered an inflammatory encephalitis as evidenced by the fact that there is usually minimal inflammation in the autopsy findings and pleocytosis is usually absent in the cerebrospinal fluid.

There is currently no evidence-based effective treatment for ANE patients and, based on the available literature, immune-modulatory therapy in the form of steroid or intravenous immunoglobulin should be considered in the management of children with ANE in view of the poor prognosis. Antiviral therapy e.g. NAI should be given for children at risk or presenting with serious complications of influenza. The absence of evidence of direct viral invasion of the central nervous system in most cases of ANE i.e. no virus in the cerebrospinal fluid in most cases (11), suggests it is unlikely for NAI to alter the clinical course of ANE.

Forum discussions

The rate of gastrointestinal side effects such as vomiting can be as high as 15% in children put on NAI. Although the risk of neuropsychiatric side effects of NAI is not common (< 1%), participants have shared a number of personal experiences of suicidal or self-injurious gestures in their influenza patients treated with NAI in which further hospital admissions were required because of the imminent threat to their lives. It was emphasized that prudent use of NAI in children with psychiatric problems or suicidal behavior is important.

There was a surge of hospital admissions for children with flu-like symptoms after the media coverage on the ANE case and the bed occupancy went up to 130% at some point in many major paediatric units across the territory. Frontline healthcare workers are under stress in handling such a large number of admissions and in alleviating the stress and concern of the paediatric patients and their families. It is a general consensus that such panic in the community could be better soothed by provision of timely information and evidence-based recommendations to the public by statutory body like the Hong Kong College of Paediatricians.



There has always been a low influenza vaccination coverage in Hong Kong children; however, in the interim analysis of this past influenza season of a vaccine effectiveness (VE) study conducted in Queen Mary Hospital, Princess Margaret Hospital and Yan Chai Hospital, Cowling, Kwan et al. found that the VE against influenza A or B hospitalization in children was 79.2 % (95% CI: 42.0%-92.4%). (12)

All of us agree that influenza vaccination is the best method for prevention of influenza infection and its complications.

Conclusions

1. There is scientific evidence that early use of NAI in children with influenza infection could modestly reduce the duration of illness by around one day and reduce the risk of acute otitis media.
2. There is insufficient evidence to support universal testing for influenza infection in all children with flu-like illness or universal use of NAI in all children with influenza infection.
3. The potentially serious uncommon neuropsychiatric side effect of NAI use in children should be underscored and prudent use of NAI is important in the management of children with influenza infection.
4. Influenza vaccination is the best method for the prevention of influenza infection and its resulting complications.

References:

- (1) The fact sheet on antiviral therapy against Influenza in January 2015. Published by the Hospital Authority Central Committee on Infectious Disease and Emergency Responses (CCIDER).
- (2) Louie JK, Yang S, Samuel MC, Uyeki TM, Schechter R. Neuraminidase inhibitors for critically ill children with influenza. *Pediatrics* 2013 Dec;132(6):e1539-45.
- (3) Muthuri SG, Venkatesan S, Myles PR, Leonardi-Bee J, Al Khuwaitir TSA, Al Mamun A, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *The Lancet Respiratory Medicine* 2014 May;2(5):395-404.
- (4) Wang K, Shun-Shin M, Gill P, Perera R, Harnden A. Neuraminidase inhibitors for preventing and treating influenza in children (published trials only). *Cochrane Database of Systematic Reviews* 2012;4:002744.
- (5) Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ* 2014;348:g2545.
- (6) CDC Guidance for Clinicians on the Use of Rapid Influenza Diagnostic Tests. Content source: Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases. Page last updated: May 26, 2016 (NCIRD) http://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm
- (7) CDC Health Update: Interim Guidance for Laboratory Testing of Persons with Suspected Infection with Avian Influenza A (H5N1) Virus in the United States, Health Alert Network, June 2006, available at <http://www2a.cdc.gov/han/ArchiveSys/ViewMsgV.asp?AlertNum=00246>
- (8) Leung YH, To MK, Lam TS, Yau SW, Leung OS, Chuang SK. Epidemiology of human influenza A(H7N9) infection in Hong Kong. *J Microbiol Immunol Infect.* 2015 Jun 30. pii: S1684-1182(15)00772-0. doi: 10.1016/j.jmii.2015.06.004.
- (9) Mizuguchi M, Abe J, Mikkaichi K, et al. Acute necrotising encephalopathy of childhood: a new syndrome presenting with multifocal, symmetric brain lesions. *J Neurol Neurosurg Psychiatry.* 1995;58:555-561.



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- (10) Anand G, Visagan R, Chandratre S, Segal S, Nemeth AH, Squier W, et al. H1N1 triggered recurrent acute necrotizing encephalopathy in a family with a T653I mutation in the RANBP2 gene. *Pediatr Infect Dis J* 2015 Mar;34(3):318-320.
- (11) Singh RR, Sedani S, Lim M, Wassmer E, Absoud M. RANBP2 mutation and acute necrotizing encephalopathy: 2 cases and a literature review of the expanding clinico-radiological phenotype. *European Journal of Paediatric Neurology* 2015 Mar;19(2):106-113.
- (12) Cowling BJ, Kwan MYW, Wong JSC, Feng S, et al. Interim estimates of the effectiveness of influenza vaccination against influenza-associated hospitalization in children in Hong Kong, 2015-16. *Influenza Other Resp Viruses* (accepted)