

STATE-OF-THE-ART

Influenza in the neonatal intensive care unit

DJ Wilkinson¹, JP Buttery^{2,3,4,5} and CC Andersen¹

¹Neonatal Unit, Mercy Hospital for Women, Melbourne, Australia; ²NHMRC Centre for Clinical Research Excellence in Child and Adolescent Immunisation, Melbourne, Australia; ³Murdoch Children's Research Institute, Melbourne, Australia; ⁴Department of Paediatrics, University of Melbourne, Melbourne, Australia and ⁵Department of General Medicine, Royal Children's Hospital, Melbourne, Australia

Influenza has historically been an uncommon illness in the newborn period, although epidemic outbreaks in neonatal intensive care units have been described. There is currently significant concern about the possibility of a new pandemic of influenza in the near future. During a pandemic neonates are likely to be exposed, with significant illness more likely in pre-term newborns due to reduced levels of passively transferred protective maternal antibodies. While newer therapies have been shown to be effective in reducing the severity of illness in adults and children, such therapies are untried in neonates. Supportive care and measures to contain and prevent spread of infection may well be the most important measures in the event of a neonate acquiring influenza, including the avian variety.

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Biology of influenza

Influenza is an RNA virus of the *orthomyxoviridae* family, classified into types A, B or C. Type A affects many animal species, and is responsible for most clinical infection in humans. Type B is responsible for about 11% of non-pandemic influenza in humans, whereas Type C causes only a mild coryzal illness.⁴ Influenza A nomenclature is further subdivided on the basis of the surface glycoproteins hemagglutinin (H) and neuraminidase (N), for example, 'H1N1'. At least 15 hemagglutinins and nine neuraminidases have been described and all are antigenically distinct. These glycoproteins are major virulence factors. Hemagglutinin mediates viral binding to cell receptors, whereas neuraminidase has a crucial role in the release of virus from the cell following viral replication.⁵ Minor changes in surface antigens (antigenic drift) contribute to seasonal epidemics of influenza A, whereas major changes (antigenic shift) have been associated with pandemics.

Introduction

There is widespread concern about a potential new pandemic of influenza A of avian origin with increasing reports of H5N1 avian influenza affecting birds and humans across multiple continents.^{1,2} Pandemic planning has focused for the most part on adults and older children.³ While influenza is an uncommon illness in newborn infants, it would seem timely to review the clinical features and management of influenza in the newborn. This paper will also review the epidemiology of influenza in newborn infants, anti-viral therapy, vaccination and control measures in a neonatal intensive care unit in the event of an outbreak. The rarity of influenza in this population, and the lack of controlled trials of therapy, of necessity means that recommendations are based largely upon level 4 and 5 evidence.

Influenza pandemics and newborn infants

There were three pandemics of influenza in the 20th century, in 1918, 1957 and 1968,³ but the most recent of these occurred before the development of modern neonatal intensive care. There are few descriptions of the effect of those pandemics on newborn infants. It is clear however that the 1918 to 1919 pandemic was associated with an increase in neonatal and post-neonatal infant mortality (as well as an increase in pre-term delivery).⁶

In more recent times, outbreaks of influenza have been described in neonatal intensive care units,^{7–10} and these have sometimes coincided with community-wide epidemics. Furthermore, recent avian influenza (H5N1) disease has been particularly severe in infants and young children.² Transmission of H5N1 influenza to date has been almost entirely owing to direct acquisition from birds. The fear is that change in the viral genome, potentially by genetic mixing with coinfecting human influenza strains, could make human to human transmission possible, thereby setting the scene for rapid spread within the population.¹

Correspondence: Dr DJ Wilkinson, Neonatal Unit, Mercy Hospital for Women, 163 Studley Road, Heidelberg, Victoria 3084, Australia.

E-mail: dwilkinson@mercy.com.au

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When the next pandemic arrives, it is likely that newborn infants will be exposed and develop clinical illness.

Clinical features of influenza in newborn infants

Influenza is a significant cause of pediatric hospital admission,¹¹ with its highest attack rate in pre-school and school age children.^{4,12} The classic clinical features include high fever, myalgia, headache and malaise, whereas a small proportion have signs of pulmonary involvement.^{11,13} In comparison, influenza is an uncommon infection in the first 6 months of life with generally mild symptoms.¹² Community studies and studies of infants during epidemics have found that a high proportion of infections are asymptomatic.^{8,9,12} Where infants do manifest symptoms those most commonly described are abrupt onset of high fever and symptoms of upper respiratory tract infection.^{7-10,13} Such clinical features may be indistinguishable from bacterial sepsis.^{11,13,14} The milder illness in infants and newborns has been attributed to transplacental acquisition of protective antibodies (which can provide protection for 3 to 6 months after birth),^{9,11,15} as well as protection from breast milk.¹¹ However, epidemic and pandemic influenza is associated with significant mortality in infants.⁶ There were 153 influenza-related pediatric deaths reported during the US influenza season in 2003 to 2004, with the highest pediatric mortality rate in infants less than 6 months old.¹⁶ Severe influenza has been described in a small number of newborn infants (Figure 1).^{9,12,17,18} Glezen *et al.*¹² described an 11 day-old-term infant who died suddenly from pneumonitis presumed related to influenza A. That infant's mother had developed influenza A (H3N2) 6 days post-partum, and the infant had no detectable antibody to the epidemic virus in her cord serum. A 27-week gestation twin died during an epidemic described by Cunney *et al.*⁹



Figure 1 Influenza A pneumonitis in a 27-week gestation pre-term infant who became unwell on day 54 of life. Chest X-ray on day 3 of admission.

of influenza A virus-associated hemophagocytic syndrome. Van den Dungen *et al.*¹⁸ described a 29-week gestation infant who became unwell with a respiratory illness on day 17 of life (viral cultures grew influenza B), developed significant lung injury and neurological complications and subsequently died.

Epidemic influenza in the neonatal intensive care unit

Part of the reason that influenza is so uncommon in the newborn period is presumably related to the reduced contact neonates generally have with unwell adults or children. However, there have been several descriptions of nosocomial spread of influenza A within neonatal units.⁷⁻¹⁰ These outbreaks usually coincided with epidemics of influenza within the broader community, although in each case it was difficult to pinpoint the source. In the largest outbreak, 30 of 95 infants admitted to two neonatal units in Spain were positive for influenza A virus.⁸ Cunney *et al.*⁹ described a similar outbreak involving 19 out of 54 infants in a level III nursery in Canada. In both of these instances, the majority of newborns were asymptomatic. Furthermore, with the exception of one pre-term infant, all of the symptomatic newborns recovered completely. Mechanical ventilation, twin pregnancy, gestational age and birth weight were identified as risk factors for infection.⁹

Anti-viral agents in newborn infants

A number of different anti-viral therapies have been used for the treatment of influenza in children. However, in infants there is very limited evidence for either safety or efficacy of these agents. None of the M2 or neuraminidase inhibitors are licensed for use in young children either in Europe⁴ or in USA.¹⁹ Similarly, there have been no studies demonstrating safety of anti-viral therapies for influenza during pregnancy or breast-feeding, and they should be used only if the potential benefit to the mother outweighs the possible risks to the fetus or infant.²⁰

Ribavirin

Ribavirin is a nucleoside analog with some *in vitro* activity against influenza A and B. Its main use has been in the treatment of respiratory syncytial virus (RSV) infection.²¹ Ribavirin is usually administered by inhalation, but can be given by intravenous infusion, the latter having been described in adults with severe influenza,²² and a young child with influenza A and cardiomyopathy.²³ Ribavirin is teratogenic, making inhalational administration problematical owing to potential staff exposure.²⁴

M2 inhibitors

Amantadine and rimantadine inhibit the replication of influenza A by acting on the viral protein M2 (they have no activity against influenza B).²⁵ They have been used for some years for prophylaxis and treatment of influenza infection,¹⁹ but resistance may develop rapidly, and in addition they are associated with reversible central

nervous system side effects.^{10,19} There are no randomized placebo-controlled trials of either agent for the treatment of influenza in children.¹⁹ They are not effective against some of the possible pandemic strains (e.g. H5N1).³ Amantadine and rimantadine have been shown to be teratogenic at high dose in animal studies and should not be used in pregnant women or while breast-feeding.²⁰

Neuraminidase inhibitors

The most recently developed agents are the neuraminidase inhibitors oseltamivir and zanamavir. They are effective against both influenza A and B, and have been shown to reduce duration of illness in previously healthy children²⁶ and adults.²⁷ They are also associated with less adverse events than the M2 inhibitors.⁴ Treatment (as with any of the above agents) must be started within 48 h of the onset of symptoms to be effective.¹¹ For prophylaxis, neuraminidase inhibitors and M2 inhibitors are effective in adults in preventing influenza when started within 48 h of exposure, but there have been few studies in children.^{25,26} Zanamavir and oseltamivir cross the placenta and are excreted in breast milk in animals, but have not been found to be teratogenic.⁵ Their safety in humans during pregnancy or breast-feeding has not been established.

Specific safety concerns about the use of neuraminidase inhibitors in infants were raised after the release of a US Food and Drug Administration animal trial of oseltamivir in 2003.²⁸ Seven-day-old rats were fed 1000 mg/kg of oseltamivir (250 times the dose recommended in children). The treatment led to the death of many of the rats, with brain levels 1500 times higher than adult animals exposed to the same dose.²⁸ The clinical relevance of this is unclear, however it has led to recommendations that neuraminidase inhibitors not be used in infants.²⁸ Nevertheless, in Japan, where the rate of encephalopathy after influenza in childhood is high, many children and infants have been treated with oseltamivir.²⁹ Two case series of a total of 150 infants younger than 1 year treated with oseltamivir found no association between oseltamivir use and mortality or encephalopathy.^{29,30}

The other limiting factor for the use of anti-viral agents in critically ill neonates relates to the method of administration. Zanamavir and ribavirin are usually administered by inhalation.¹⁹ Oseltamavir, amantadine and rimantadine are only administered

orally, with suspensions available for each.¹⁹ The only intravenous preparation is that of ribavirin.

Influenza vaccination

Influenza vaccination is the primary means of prevention of influenza in the community, and has been shown to be safe and effective in preventing significant illness in adults and children.²⁰ Inactivated and live attenuated forms are available. Inactivated influenza vaccine has been approved for use in infants older than 6 months, and is routinely recommended in the US (although not currently in Europe or Australia) in infants aged 6 to 23 months.^{4,20,31} The vaccine is not thought to be immunogenic in infants less than 6 months.^{20,32} Live attenuated vaccines are not recommended for children younger than 5 years.²⁰

Vaccination is safe throughout pregnancy and while breast-feeding.²⁰ Influenza infection during pregnancy is associated with increased morbidity, and consequently influenza vaccine is recommended for women who will be pregnant during an influenza season.²⁰ Additionally, vaccination may provide protection for the neonate during the first 6 months of life.³³ All current vaccines are grown initially in embryonated hens' eggs, and consequently there is a risk of hypersensitivity reactions in individuals with severe egg allergy.²⁰ There are candidate pandemic vaccines in development, some of which have been shown safe and immunogenic; however, there are no efficacy data to date.²

Prevention of nosocomial influenza

Given the lack of proven and safe treatment for influenza in neonates, prevention of spread of infection may be the most effective measure in the context of an epidemic or pandemic (Table 1).

Reducing transmission of virus

Influenza virus is primarily spread from person to person by respiratory droplets.^{34,35} Consequently cohorting and isolation of affected infants is recommended by most authorities. The relative importance of airborne (droplet nuclei) spread is unclear, and in general negative pressure isolation is not required.^{34,35} In a nosocomial RSV epidemic in a pediatric intensive care unit droplet

Table 1

Key measures in the event of an outbreak of influenza.^{37,43}

Screen patients using a rapid diagnostic test to enable cohorting of pre-symptomatic or asymptomatic infants.

Affected infants should be cohorted and droplet precautions taken to minimize spread.

Infants admitted from home and other units should be isolated until screening test results are available.

All staff and parents should be immunized.

Staff or parents who are unwell should not enter the unit, or should be sent home.

Anti-viral prophylaxis should be provided for staff and parents if unvaccinated, or if infection has occurred with a strain not covered by the vaccine.

precautions were more important than a physical barrier.³⁶ Influenza can survive on a variety of fomites and in the environment, and although the clinical significance of direct contact spread is unclear, good hand-washing is likely to reduce transmission.³⁵

Timely diagnosis is essential for effective cohorting. Traditional methods of detection have included immunofluorescence or rapid diagnostic tests (using immunoassay or viral neuraminidase detection).¹⁹ The use of rapid diagnostic tests for influenza enabling detection and cohorting of infected infants has been associated with reduced nosocomial transmission in pediatric hospitals.³⁷ Detection of viral RNA by polymerase chain reaction (PCR) is the most sensitive technique, and the recent development of real-time PCR³⁸ has led to this becoming the method of choice for rapid, reliable diagnosis of influenza.

To avoid exposure of infants to influenza, staff are recommended not to work when unwell; however, compliance with this by medical and nursing staff has historically been poor.^{9,34,39} Other measures to reduce spread are of unknown benefit. For example, the application of viral filters to the expiratory arm of ventilator circuits has been described in the neonatal setting (in the context of an outbreak of severe acute respiratory syndrome (SARS)),⁴⁰ and may be useful for ventilated infants with influenza. During one of the aforementioned neonatal intensive care outbreaks procedures for changing ventilator tubing were altered in order to reduce aerosol spread.⁹

Immunization

To prevent transmission of influenza to vulnerable populations, it is recommended that health-care workers should be immunized annually against influenza.²⁰ Again compliance rates amongst staff in neonatal units (and elsewhere in hospitals) have been low.^{9,10} Routine immunization of parents of high-risk infants in the neonatal unit in addition to that of pregnant mothers has also been advocated.⁴¹ It is unclear how much protection vaccines will provide in the event of a novel strain.

Chemoprophylaxis

During epidemics, prophylactic treatment with anti-viral agents for unimmunized parents and staff has been suggested by some authorities.²⁰ They are an adjunct to immunization and should not replace it.^{20,42} Most reported experience has been with M2 inhibitors. Amantadine use has been described in the two larger neonatal intensive care outbreaks.^{8,9} It remains to be seen whether neuraminidase inhibitors will be more effective and better tolerated.³⁴

Conclusions

It is likely that some newborn infants will be affected in the setting of a new pandemic of influenza. Mortality rates in previous

outbreaks within neonatal units have been surprisingly low. However, pandemic influenza may well be more severe in this population because of the lack of antibody protection to a novel strain. Although anti-viral agents have been shown to be effective in children and adults, there are no agents with proven efficacy or safety in infants, and the available formulations limit their use in pre-term infants. This may lead to difficult decisions about whether to use unproven therapy in the context of life-threatening illness. If such agents are used, parents should be informed of the limited evidence and provide informed consent. Careful follow-up may provide useful information for future infants.

The most important measures in a neonatal intensive care unit in the event of a pandemic are likely to be preventive ones (Table 1). If an effective vaccine is available, staff and parents should be immunized. Anti-viral prophylaxis of staff, parents and even newborns may have a role, although despite stockpiling, availability of these agents during a pandemic may well be limited. Isolation of affected infants and strict adherence to infection-control precautions are critical to control spread within a unit.

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