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American Society of Transplantation (AST) Infectious Diseases Community of Practice / Transplant Infectious Disease Section of The Transplantation Society (TTS) Guidance On Novel Influenza A/H1N1*

What's New In this Update?

- **New guidance on Antiviral Resistance**
- **Immunization guidance updated**
- **Antiviral dosing updated for infants < 1 year of age**

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Background and Significance

Influenza A and B are common causes of viral infections each year in transplant recipients, with predictable complications including viral pneumonia, secondary bacterial pneumonia and acute allograft rejection in the setting of weaning of immunosuppression [1]. Annual vaccination with inactivated influenza A/B vaccine, for recipients as well as close contacts, is the standard of care in transplant centers, in an attempt to mitigate and/or prevent infection.

In April 2009, a novel influenza A (H1N1) virus was initially detected in two children in the United States. Within weeks, this virus was determined to be the cause of outbreaks of disease in Mexico; within two months, infection had spread worldwide, causing the

World Health Organization to declare a pandemic on June 11, 2009. Infection has been noted to be most common in the young, with particularly severe disease in pregnancy as well as more traditional high-risk groups for influenza infection-including transplant candidates and recipients. While initially effective against this novel H1N1 strain, oseltamivir resistance was noted in two immunocompromised patients in August 2009 [2]. It is expected that infection will continue to spread across the globe. Reassortment with seasonal human influenza A strains and potentially with H5N1, with unpredictable virulence is a significant concern.

Reaction to this novel respiratory virus in the transplant community has been swift, with concern for prevention, diagnosis, and treatment of infection as public health data mount and the course of the pandemic evolves. Prior to the World Transplant Games in August 2009, athletes and supporters were advised to take prophylactic antiviral therapy preceding their travel to departure for Australia [3]. In May 2009 the International Society for Heart and Lung Transplantation developed guidelines for heart and lung transplant recipients in the pandemic setting, raising concern for transmission of novel H1N1 infection from thoracic organ donors [4]. These guidelines have now been published [5].

Animal and human autopsy studies have demonstrated that acute influenza A infection in the immunocompetent host may result in infection of multiple organs, including the brain, kidney, pancreas, spleen, liver and heart, in addition to the lungs [6-9]. Strain variation appears to be considerable, and data on the tropism of the novel H1N1 strain for various organs are limited. The impact of infection in potential donors (living and deceased), in those waiting on the transplant list with end stage organ disease, and in those undergoing and having undergone transplantation has implications for donor selection, peri-transplant management and the care of the transplant recipient.

The Infectious Diseases Community of Practice of AST and the Transplant Infectious Disease section of The Transplantation Society have developed the following guidelines for the prevention, diagnosis and treatment of novel H1N1 influenza A infection in the solid organ transplant setting, using available data on current patterns of infection, reports of resistance, and what is already known about the spread and control of influenza. The guidelines will be updated as new data become available about the course of H1N1 particularly data in the immunocompromised host population.

Diagnosis of Novel Influenza A/H1N1

- H1N1 should be suspected when patients present with flu-like symptoms (i.e., temperature ≥37.8°C, and cough and/or sore throat) and have suspected or confirmed evidence of exposure to H1N1 virus. This could include specific exposure to a confirmed case or evidence of H1N1 activity in the community. Novel H1N1 may also be associated with gastrointestinal symptoms like nausea, vomiting, and diarrhea in up to a third of cases. Atypical presentations may occur

in those with significant immunosuppression and/or lymphopenia (e.g. fever with no other symptoms or an afebrile patient with rhinorrhea alone).

- During epidemics, limiting routine office visits is recommended to avoid exposure to sick individuals in the waiting room. We recommend confirming a diagnosis by specific testing when H1N1 is suspected in a transplant patient.

    - *Suspected cases* of H1N1 are defined as those occurring in patients who have signs and symptoms consistent with influenza, potential exposure to H1N1 (i.e, presence of H1N1 activity in the community or exposure within the prior 7 days to a confirmed or probable case) in the absence of another defined cause of symptoms.
    - *Probable cases* are patients who have flu-like symptoms, positive testing for influenza A, and negative for H1 and H3 by influenza reverse transcriptase polymerase chain reaction (RT PCR).
    - *Confirmed cases* require confirmation of the presence of novel H1N1 (2009) by real-time RT-PCR or viral culture [10].

- Appropriate samples for testing include nasopharyngeal swab with or without an oropharyngeal swab, or a nasal aspirate. Endotracheal aspirates from intubated patients, bronchoalveolar lavage specimens, and sputum specimens may also be used. All specimens should be promptly placed in sterile viral transport media and kept at 4°C for transport to the microbiology laboratory (See collection technique for NP swabs) [10].

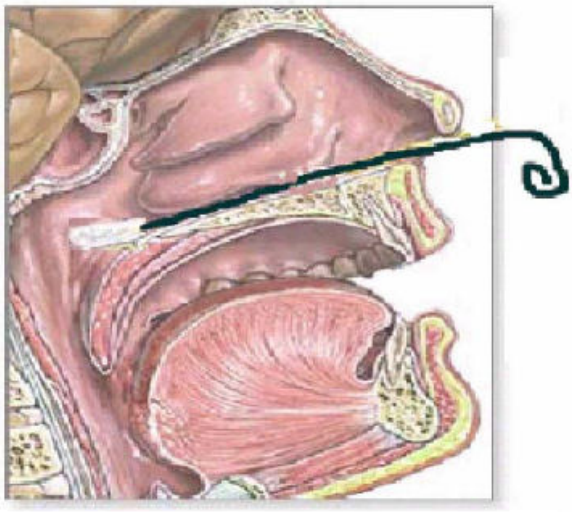
- Specific testing for H1N1 by standard methodology should be performed using real-time reverse transcriptase polymerase chain reaction (RT-PCR) or other nucleic acid based detection assay whenever possible. Samples that are positive for Influenza A and negative for seasonal H1 and H3 can be further tested at the CDC or state laboratories for definitive confirmation as H1N1. Alternative testing may include viral culture [11,12].

- If neither of these tests is available, rapid antigen detection may be acceptable for point of care testing, although will have lower sensitivity (estimated to range from 10-51%) and will not differentiate novel H1N1 from other strains of influenza A. Consequently, negative rapid tests cannot exclude the diagnosis [12]. Immunofluorescence by direct or indirect assays can also identify influenza A but will not differentiate novel H1N1 strains from seasonal influenza, In addition the rapid kits have variable sensitivity for novel H1N1; accordingly a patient with a negative test must have further testing with more a sensitive method [12-14]

I. **Collection of Nasopharyngeal Swab** [14]

a. Escort the patient into the collection room

> DO NOT collect the specimen when the patient is in a room with other people. The collection process may cause the patient to sneeze or cough, thus exposing others to infection.



b. Wash or sanitize your hands
c. Put on surgical mask with face shield or surgical mask with goggles.
d. Put on gloves

II. **Specimen Collection**

a. Seat or recline the patient comfortably
b. Explain the procedure to the patient. Emphasize that it is NOT painful but may cause a tickling sensation.
c. Remove the swab from its protective package
d. Remove the cap from the tube of transport medium. Place the tube in a container so that it doesn't fall over.
e. Ask the patient to look slightly upward
f. Steady the patient's head with one hand under their chin if necessary
g. Have the patient remove their mask.
h. Holding the swab horizontally, insert it into the base of the nare and pass it straight backward, rotating the swab as it passes into the nasopharynx. During the entire collection process the swab should remain parallel to the hard palate.
i. Remove the swab from the nasopharynx. Offer the patient a tissue in case he or she is going to sneeze or cough.

j. Ask the patient to place their mask on again
k. Place the swab into the tube of viral transport medium. Break off or cut the swab and replace the cap on the tube.
l. Label the tube with the patient's identifying information.
m. Place the tube and requisition into the specimen bag for transport to the lab.
n. Remove your protective equipment
o. Perform hand hygiene.
p. Place the specimen and any requisition into the specimen bag and send to the laboratory.
q. Remove personal protective equipment and clean hands.

Treatment of Novel Influenza A/H1N1

- The viral dynamics of seasonal influenza have been well studied among hematopoietic stem cell transplant recipients and prolonged viral replication, even in the setting of active antiviral therapy has been shown.[15] Similar studies have not been conducted in solid organ transplant recipients.

- Lymphocyte depletion as well as enhanced immune suppression, particularly high doses of steroids, are likely to prolong viral replication.[16] Further, viral replication secondary to the novel influenza A/H1N1 is predicted to be prolonged in transplant recipients.

- As such, the optimal duration of therapy for influenza has not been well established but courses longer than the currently approved 5 days may be needed. Some experts recommend continuing antiviral therapy until viral replication (as documented by PCR or culture) has ceased. Duration of therapy should be guided based on current CDC treatment recommendations and individualized patient assessments. Lung transplant patients with impaired lung function may need longer treatment than other organ transplant recipients.

- As recommendations on therapy may change over time, please always consult the CDC antiviral therapy page prior to selecting antiviral therapy (http://www.cdc.gov/h1n1flu/recommendations.htm [17].

- In healthy individuals use of antiviral agents has not been found to be beneficial if symptoms have been present for more than 48 hours. Contrary to this, there is likely to be benefit in treating symptomatic SOT recipients with evidence of viral replication (positive culture, rapid antigen, or PCR-based testing), even if symptoms have extended beyond 48 hours. Current CDC guidance recommends treatment of all transplant patients, regardless of the duration of symptoms [17].

- Empiric antiviral therapy can be considered in SOT recipients in whom a diagnostic test is not available but symptoms are highly suggestive of novel influenza A/H1N1 (also see Diagnosis section). All attempts must be made to confirm a diagnosis, however.

- Prolonged shedding has been noted in SOT recipients with novel influenza A/H1N1. Therefore, repeated positive tests should be interpreted with caution and should be an alert for possible resistance (see Antiviral Resistance section).

- Data on treating the recipient who is asymptomatic at the time of diagnosis are not available. Clinical judgment should be used.

- Currently, wild-type novel H1N1 is resistant to both M2 inhibitors (amantadine and rimantadine) and this class should not be used as monotherapy. All wild-type

novel H1N1 are susceptible to all approved (oseltamivir and zanamivir) and investigational (peramivir) neuraminidase inhibitors. A number of novel H1N1 viruses have been described to have developed resistance to oseltamivir secondary to a mutation, typically at position 275, over the course of therapy [18]. These strains have typically continued to be susceptible to zanamivir (see Antiviral Resistance section). If co-circulation of neuraminidase-inhibitor resistant influenza occurs, combination therapy with both a M2 inhibitor and oseltamivir or zanamivir monotherapy may be indicated.

- Intravenous antiviral therapy may be considered in those individuals who are severely ill and have progressed despite oral therapy or in whom there is concern about the absorption of oral therapies. Alternatively, some experts recommend that the dose of oseltamivir may be doubled (e.g. increased to 150mg bid) in critically ill adult patients. In patients with significant disease, a reduction in immunosuppression is recommended.

- Currently, there are two investigational IV anti-influenza antivirals: peramivir and zanamivir. An Emergency Use Authorization has recently be issued for peramivir (see website for details: http://www.cdc.gov/h1n1flu/eua/peramivir.htm) which facilitates access to this antiviral. IV zanamivir is available via compassionate use request and required the site to file an eIND with the FDA (see below for contact details).

Table 1: CDC-recommended doses of oseltamivir and zanamivir:

Drug	Treatment Dose*	Dose Adjustment	
		CrCl (mL/min)	Dose
Zanamivir**	2 puffs (10mg) twice daily	No dose adjustment needed	
Oseltamivir	75 mg twice daily	CrCl < 30[§]	75mg once daily

CrCl Creatinine clearance

*Dose recommended in normal renal function. Some experts recommend consideration of higher doses of these agents (typically twice the approved dose) as registration studies demonstrated a trend toward increased antiviral activity with similar toxicity profiles [19].

[§]No treatment or prophylaxis dosing recommendations are available for patients undergoing renal dialysis.

** There are limited data on the safety and tolerability of zanamavir in lung transplant recipients. Also, there is limited systemic exposure of the drug. The clinical significance of this is unknown.

Ongoing Studies
Currently, there are a number of antivirals and antiviral combinations that are currently undergoing investigation and/or are available for compassionate use. These are listed below:

(i)Compassionate Use:
IV Zanamivir – contact Annie Cameron (annie.m.cameron@gsk.com) and/or Vinnie Lopez (vinnie.a.lopez@gsk.com) at GlaxoSmithKline.

(ii)Studies Open to All or Selected Transplant patients:
IV Peramivir – BioCryst
http://www.clinicaltrials.gov/ct2/show/NCT00957996?term=peramivir&rank=5
http://www.clinicaltrials.gov/ct2/show/NCT00958776?term=peramivir&rank=1
Triple Combination Antiviral Drug (TCAD) – Adamas
http://www.clinicaltrials.gov/ct2/show/NCT00867139?term=zanamivir&rank=6

Antiviral Resistance

- Most novel influenza A/H1N1 is susceptible to oseltamivir (IC_{50} range 0.34-1.41 nM), zanamivir (IC_{50} range 0.30-1.34 nM) and peramivir (IC_{50} range 0.07-0.26 nM) [20]. However, a number of viruses have been isolated that contain the H275Y (histidine-to-tyrosine at position 275 of the N1 neuraminidase) mutation that confers resistance to oseltamivir and increases in IC_{50} to peramivir; viruses with the H275Y mutation retain sensitivity to zanamivir.

- The frequency and characteristics of these viruses are catalogued by the World Health Organization (http://www.who.int/csr/disease/swineflu/frequently_asked_questions/swineflu_faq_antivirals/en/index1.html) and the Centers for Disease Control (http://www.cdc.gov/H1N1flu/recommendations.htm), as well as other reference laboratories.

- Resistance typically has emerged in the setting of prophylaxis failure with breakthrough infections (typically in immunocompetent patients) [21] and following treatment (typically in immunocompromised patients with prolonged shedding) [22]. Although not always indicative of resistance, clinically, antiviral resistance should be considered in the following settings :

    - Documented influenza in a patient receiving antiviral prophylaxis
    - Patient with documented influenza who has failed to improve after 5 days of antiviral therapy
    - Patient with documented influenza who has persistent shedding despite antiviral therapy for >7-10 days

- If resistance is considered, a nasopharyngeal swab should be collected and submitted for testing. Bronchoalveolar lavage (BAL) fluid may be sent if a BAL is otherwise clinically indicated. There are several reference laboratories that can do resistance testing; optimally testing should include screening for more than just the presence of the H275Y mutation. In the United States, specimens may be submitted to the Centers for Disease Control for testing. To have testing done at the CDC, you must contact the CDC EOC Laboratory (eoclaboratory@cdc.gov) and completed the appropriate forms.

- It is important to remember that the H275Y mutation has emerged after exposure to oseltamivir; mutations at other locations may occur if patients are treated with other neuraminidase inhibitors (such as zanamivir or peramivir). As such, if the patient has received other antiviral therapies, tests that only screen for the H275Y mutation are inadequate for detecting resistance.

- Although the optimal management of oseltamivir-resistant influenza has not been established. The IC_{50}s of all H275Y mutants are increased for peramivir; susceptibility is retained for zanamivir. Some groups have used zanamivir while others have used combinations of zanamivir plus ribavirin for the management of oseltamivir-resistant influenza. Consultation with an Infectious Diseases expert should be considered when managing patients with oseltamivir-resistant influenza.

- There have been case reports of transmission of influenza containing H275Y mutation in hospitalized immunocompromised patients [23]. Strict adherence to infection control practices should be practiced (also refer to Infection Control section).

Routine Chemoprophylaxis and Post-exposure Prophylaxis

- Based on concerns about drug resistance, chemoprophylaxis with oseltamivir for the duration of the pandemic is not routinely recommended but can be considered for select patients. Prophylaxis may be considered for recent transplant recipients, those who have recently received lymphocyte depleting antibodies, and those in whom immunization is contraindicated.

- A SOT recipient who has had known exposure to novel Influenza A/H1N1 should be counseled to watch for early signs and symptoms of influenza. A prescription can be given (with treatment doses of antivirals) and treatment initiated with early signs and symptoms.

- Alternatively, the transplant patient who has been exposed can receive chemoprophylaxis to complete 10 days from the day of last known exposure. (see doses for children in pediatric section). However, cases of oseltamivir resistance have occurred in the setting of patients receiving prophylaxis.

Prevention of Novel Influenza A/H1N1 in SOT Candidates, Recipients, and Contacts: Practical Strategies and Immunization Recommendations

Recipients of solid organ transplantation are at higher risk for serious disease from influenza and presumably also from the novel H1N1 virus. For this reason we advise SOT candidates, recipients, and their household contacts, especially pregnant women or those with chronic pulmonary disease, to avoid contact with known ill individuals. Below are guidelines for prevention of infection for these individuals:

Recommendations for individual patients and family

- Avoid contact with individuals who are known to have been diagnosed with influenza.
- Strict hand washing or hand hygiene (use of alcohol-based hand gels), particularly after coughing or sneezing, should be performed as this is the most effective way to decrease the risk of contracting H1N1.
- Avoid touching eyes, nose or mouth as germs are spread this way.
- Practice cough etiquette; cover the nose and mouth with a tissue when coughing or sneezing, and throw the tissue in the trash after use. If no tissue is available the person should cough or sneeze into their sleeve to avoid contaminating their hands
- Visits for routine well health checks and diagnostic tests to a health care facility should be limited during epidemic periods.
- Vaccinations should be obtained when available from your healthcare provider or health department for both seasonal influenza and for novel H1N1.
- There are no general restrictions for SOT patients with regards to travel.
- Transplant programs should communicate with SOT candidates and recipients outlining precautions with regards to H1N1. Principles of infection control should be reinforced at clinic visits, including use of masks for those with respiratory symptoms and hand hygiene. Any patients with suspected active H1N1 infection should be separated from other transplant patients, i.e. in waiting rooms, clinic rooms, and inpatient rooms (also see Infection Control recommendations).

Recommendations for health care providers

- Health care workers should remain off work and not have contact with patients if they have symptoms of influenza-like illness.

Immunization

- Immunization with an inactivated vaccine is recommended for all children ages 6 months to 24 years and for adults with chronic disease that puts them at high risk of complications. Therefore, transplant patients and candidates should also receive at least one dose of H1N1 vaccine. Whether more than one dose is required to achieve immunogenicity will depend on the type of vaccine [17].

- Transplant recipients, candidates and household contacts should also receive the annual trivalent inactivated influenza vaccine in addition to H1N1 vaccine. If a transplant recipient has already received vaccine pre-transplant, there is no need to give a repeat dose post-transplant. Children under the age of 9 years who are receiving seasonal influenza vaccine for the first time will require 2 shots, one month apart.

- For transplant candidates and recipients, the injectable seasonal and pandemic vaccines can be administered simultaneously in opposite arms.

- The seasonal influenza vaccine is generally recommended to be given starting 3-6 months after transplant (see AST guidelines). Given the rapid spread of virus, transplant recipients can begin to receive H1N1 vaccine as soon as one month post-transplant. However, the immune response of early vaccination may only be partially protective.

- Although the risk of adverse effects (local and systemic reactions) with H1N1 vaccine is largely unknown, there is no reason to believe that adverse effects will be greater than those seen with the seasonal annual influenza vaccine.

- If only adjuvanted vaccine is available, this should be given to SOT recipients. Adjuvants act locally to attract greater number of antigen presenting cells to the site of vaccination and reduce the amount of antigen necessary for an effective vaccine response. There is no evidence that adjuvants increase the risk of allograft rejection.

- Pregnant SOT recipients are a priority group for vaccination.

- Seasonal influenza vaccine is approved for infants and children greater than 6 months of age. Pediatric solid organ transplant recipients 6-12 months of age should be a priority group for vaccination, given the paucity of data on the use of antiviral agents in infants < 12 months of age. Pediatric transplant recipients do respond to influenza vaccines although their cellular responses may not be as vigorous as that found in healthy children [24].

- Pneumococcal vaccine should also be updated given the risk of pneumococcal super- infection in those infected with influenza.

- Healthcare workers in contact with SOT candidates and recipients should also be immunized with both seasonal and novel H1N1 vaccines. Both vaccines can be administered simultaneously in opposite arms.

- If a SOT candidate or recipient has had prior documented H1N1, he or she does not need to be immunized with H1N1 vaccine. However, vaccine can only be deferred if the H1N1 illness was documented by a positive diagnostic test. In the case where vaccine is administered to such a patient, no increase in adverse effects is expected.

Specific considerations for Live Attenuated Influenza Vaccine:

- **Intranasal influenza vaccine is a live attenuated virus vaccine and should not be given to solid organ transplant recipients.**

- There may be a theoretical and undefined risk of transmission of vaccine strain virus to transplant recipients from close contacts who receive intranasal influenza vaccine.

- For **healthcare workers** in contact with transplant recipients, if both inactivated and live vaccines are available, then inactivated vaccine is preferred. However, if only live vaccine is available, those caring for transplant recipients should be vaccinated. All healthcare workers should be reminded to observe strict hand hygiene which is especially critical for those that have received live vaccine. The use of masks may be considered as well.

- For **household contacts**, if both inactivated and live vaccines are available, then inactivated vaccine is preferred. However, if only live vaccine is available, vaccination should still be given. In this circumstance, the importance of good hand hygiene practices and minimizing contact with secretions (e.g., sharing food/drink, direct saliva contact) should be emphasized to the patient and their household contacts.

- Organs from a donor who has received the LAIV can be utilized. Vaccine virus has not been shown to replicate in lung tissue. See package insert for LAIV: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm123743.pdf

Special Issues of Novel Influenza A/H1N1 for Pediatric Solid Organ Transplant (SOT) Recipients

The general principles relating to the management of novel influenza H1N1 (swine flu) among adult and pediatric patients are similar and readers should review individual general sections as well. This notwithstanding, there are some special pediatric issues that should be highlighted, insofar as they may identify the need for modifications to management and resource planning.

- *Clinical Presentation:* Influenza illness is more likely to present in a non-specific manner in young infants compared to older children and adults. Young infants, for example, may present with a sepsis-like picture. In addition, diarrhea may be seen in younger children. When influenza illness is present in young children, the likelihood of illness among adult family members is high. Thus, when a child presents with influenza illness to a health care setting, the accompanying family member might also have influenza illness.

- *Infection Control:* Compliance with infection control measures is difficult in young children. The use of masks poses practical challenges in very young infants. In addition, young children are not likely to be compliant with accepted respiratory etiquette. Viral shedding may be more prolonged and copious in young children compared to adults. Thus, the young SOT patient is expected to shed virus for an even more prolonged period, and be more likely than adults to spread the virus to close contacts and to the environment. Family members should use frequent hand hygiene for themselves and their children.

- *Immunizations:* Seasonal influenza vaccine is approved for infants and children greater than 6 months of age. All household and close contacts of pediatric SOT recipients should also be vaccinated. Pediatric SOT recipients 6-12 months of age should be a priority group for vaccination, given the paucity of data on the use of antiviral agents in infants < 12 months of age. Pediatric transplant recipients do respond to influenza vaccines although their cellular responses may not be as vigorous as that found in healthy children [24].

- *Antiviral agents:* The approach to the use of antiviral agents in the treatment and prophylaxis of novel H1N1 influenza in children is similar to adults and has been adapted from existing CDC and other guidelines. The recommended dosing is shown in Tables 2 and 3. There are age-related issues that should be highlighted as follows:

(i)There was initial concern regarding the safety of oseltamivir in infants less than 1 year of age. This was based on animal data using drug exposures that were several fold greater than what would be experienced in infants. While data are emerging, the collective body of evidence relating to the safety of oseltamivir in infants less than 1 year of age is increasing. As such, at this point in time, current consensus favors the use of oseltamivir in infants less than 1 year of age.

(ii) The dosing of infants less than 1 year of age remains problematic, as data are limited on appropriate dose of oseltamivir in this age group, notably neonates and those with lower body weights. For these infants, most experts now prefer dosing based on body weights where such weights are available. In all situations, an infectious diseases expert must be consulted when antiviral agents are being considered in this age group.

Table 2: Dose Recommendations for Children 12 Months of Age or Greater†

Age	**Treatment (Duration = 5 days)**	**Chemoprophylaxis (Duration = 10 days)**
	Oseltamivir	
Children ≤ 15 kg	30 mg twice daily	30 mg once daily
Children 15-23 kg	45 mg twice daily	45 mg once daily
Children 24-40 kg	60 mg twice daily	60 mg once daily
Children > 40 kg	75 mg twice daily	75 mg once daily
	Zanamivir‡	
Children	Two 5-mg inhalations (10 mg total) twice daily [age, 7 years or older]	Two 5-mg inhalations (10 mg total) once daily [age, 7 years or older]

‡ Zanamivir use is impractical below 7 years of age

Table 3: Dose Recommendations for Children Less than 12 Months of Age*†(weight-based dosing preferred; see footnote)

Age	**Treatment with Oseltamivir (Duration = 5 days)**	**Chemoprophylaxis with Oseltamivir (Duration = 10 days)**
< 3 months	3 mg/kg/dose twice daily	Not recommended unless situation judged critical due to limited data on use in this age group
≥ 3 months	3 mg/kg/dose twice daily	3 mg/kg/dose once daily

† Dose adjustments are recommended for patients with creatinine clearance between 10-30 mL/min. For these patients, the treatment dose is reduced to a once daily dose. Similarly, the prophylaxis dosing regimen is altered, with the dose being given every other day.

† Weight-based dosing is preferred, but, if weights are not known, dosing by age for purposes of prophylaxis in full-term infants less than 1 year of age may be necessary. In such situations, the recommendations are as follows: 3-5 months = 20 mg once daily; 6-11 months = 25 mg once daily.

† No firm recommendations can be made for premature infants.

† Health care providers should be aware of the lack of data on safety and dosing of oseltamivir in seriously ill young infants with confirmed 2009 H1N1 infection or following exposure to a confirmed 2009 H1N1 influenza case. Infants should be carefully monitored for adverse events when oseltamivir is used. A pediatric infectious disease consult is advised. Additional information on oseltamivir for this age group can be found at:*http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM153547.pdf 

Infection Control Recommendations for Novel Influenza A/H1N1

- Influenza is a respiratory infection transmitted from person-to-person through large respiratory droplets that are produced when infected patients cough or sneeze. These infectious droplets can be directly deposited on the mucosal surfaces of people who are within 3 to 6 feet of the infected patient.

- Aerosolized respiratory secretions may also contaminate nearby surfaces leading to infection spread when susceptible individuals touch the contaminated areas and then touch mucosal surfaces on their face, including their eyes, nose, and mouth.

- Influenza A remains viable on hard nonporous surfaces like countertops for 24-48 hours, while it may persist less than 8-12 hours on porous materials such as cloth or paper. Viruses can survive much longer on wet surfaces, though dry virus particles may live for 3 hours on human hands [25]. Infection control measures are aimed at preventing the production of viral aerosols as well as their inhalation or mucosal self-application by susceptible persons.

- SOT candidates and recipients who present at health care facilities including physician offices seeking care should be encouraged by signs and personal inquiry to identify themselves immediately if they have symptoms of influenza-like illness. Cough etiquette should be encouraged, and tissues and hand sanitizer should be provided. Masks should be provided to patients who are actively coughing and sneezing until they can be placed in a private room.

- A system for separating possible influenza cases from other patients is strongly recommended; but sometimes cannot distinguish one respiratory viral infection from another.

- If an SOT recipient requires admission to the hospital for influenza-like illness, isolation using Standard and Droplet Precautions should be implemented. This requires that healthcare personnel wear a surgical or procedure mask and nonsterile gloves, when examining patients who are being evaluated for influenza-like illnesses. Nonsterile gowns should be worn if there is a risk that the healthcare worker's clothing will be exposed to the patient's respiratory secretions [26].

- Patients should be placed in private rooms with the doors kept closed. Consideration should be given to rooming patients in wards away from the "traditional transplant ward". Further infection control strategies may be necessary as new information on antiviral resistance emerges.

- Isolation precautions should continue until hospital discharge, or until the signs and symptoms of influenza have resolved and the patient has been afebrile for at least 24 hours. Immunocompromised patients are known to have more prolonged viral shedding and may not manifest the usual symptoms of ongoing infection; therefore it is reasonable to maintain Droplet Precautions until hospital discharge if possible, or documentation of a negative test for H1N1 [27].

- Hospital visitors with respiratory symptoms should be discouraged. Healthy visitors should be required to wear appropriate personal protective equipment when visiting infected patients, including a surgical mask and gloves [28]. Household contacts of the influenza patient, who may themselves be experiencing early symptoms of influenza, should be screened closely for symptoms and encouraged to stay home if appropriate. Unimmunized household contacts may be candidates for antiviral prophylaxis.

- Patients with influenza are contagious to others one day before symptoms develop. Adults remain infectious for approximately five days after symptom onset, although immunosuppressed individuals and children may be contagious for 10 or more days.

Donor Derived Novel Influenza A/H1N1: Prevention, Identification, and Management

Prevention of Donor-Derived Influenza

- During an influenza pandemic, all donors and recipients should be screened for clinical symptoms and signs of recent flu-like symptoms. Every potential organ donor and recipient must be evaluated individually, with specific guidance if needed from infectious disease specialists or clinical microbiologists. Even with other causes of death, potential for influenza illness and/or carriage should be considered. Nosocomial transmission has occurred, thus a prolonged hospital stay does not preclude novel H1N1 infection. In general, centers should have a low threshold to test potential donors and recipients.

- Many of the rapid tests are poorly sensitive [12] and thus more sensitive testing should be used, optimally with a sensitivity of over 90%. The relatively short duration of positive assays (often five to seven days or less from the onset of symptoms) should be taken into consideration when screening donors and recipients with recent flu-like symptoms.

- Potential organ donors who have been diagnosed as recently having influenza (e.g. within the previous two weeks) should likely be deferred from lung and small bowel donation; those donors with influenza who have received appropriate anti-viral therapy could be considered as potential non-lung or small bowel organ donors, after obtaining input from the organ procurement organization's medical director and local infectious disease experts. (see also UNOS website (http://www.unos.org/news/newsDetail.asp?id=1292).

- There are currently no data on the duration of therapy required for the donor before organs can be safely used. Accordingly, until more data are available many would recommend a five to 10 day course of therapy for the recipient if the donor did not complete a course of treatment.

- Since only a very small number of cases of peri-transplant novel H1N1 infection have occurred, organ procurement in the presence of suspected infection should be carefully evaluated. If the potential living donor is found to have novel H1N1 then transplantation should be deferred if possible until the donor has received a course of treatment and is clinically well.

Identification of Donor-Derived Influenza

- When transmission of influenza is suspected, attempts should be made to fully diagnose disease in both the donor (when possible) and recipient. Transplant centers may wish to bank blood specimens and nasal washes or nasopharyngeal swab samples for further diagnostics. When influenza is diagnosed and felt to be donor-derived in origin, other centers with recipients from the same donor should be notified through local organ procurement organization.

Management of Donor-Derived Influenza

- Donor-derived influenza in solid organ transplant recipients should be treated with oseltamivir and/or zanamivir, depending on the individual patient and local resistance patterns at the time of transplant, similar to the recommendations by the WHO, CDC, and others (see section on Treatment). With emerging resistance, optimal treatment recommendations may evolve over time.

- Since recent solid organ transplant recipients are often in their deepest period of immunosuppression, clinicians caring for such patients may elect to increase the duration of treatment medications and continue antiviral therapy until viral replication has been documented to be eradicated.

- Recipients should be monitored closely for allograft rejection, and for co-infection or super-infection with *S. pneumoniae*, *S. aureus*, CMV, *Pneumocystis jiroveci* pneumonia (PCP), or other infections. In addition, clinicians should consider minimizing immunosuppression if possible although the risk of rejection in the early transplant period must be weighed against the risk of influenza on an individual basis.

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