How we treat influenza in patients with hematologic malignancies

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ABSTRACT

The 2009 H1N1 influenza pandemic has heightened the interest of clinicians for options in the prevention and management of influenza virus infection in immunocompromised patients. Even before the emergence of the novel 2009 H1N1 strain, influenza disease was a serious complication in patients with hematologic malignancies receiving chemotherapy or undergoing hematopoietic cell transplantation. Here we review the clinical manifestations of seasonal and 2009 H1N1 influenza and discuss current diagnosis, antiviral treatment, and prophylaxis options. We also summarize infection control and vaccination strategies for patients, family members, and caregivers.
EPIDEMIOLOGY

In March 2009, a series of severe influenza cases were described among otherwise healthy Mexican young adults\(^1\), followed by similar cases in the United States\(^2\), and within weeks, thousands of late-season influenza cases were reported throughout the world\(^3\) (Figure 1). The virologic characteristics of the 2009 H1N1 strain and events that led to its emergence have been described elsewhere\(^4\). Pandemic 2009 H1N1 infection rates have been highest among persons less than 25 years of age, but death rates have been highest among persons 25-49 (Figure 2). One potential explanation for these trends is that exposure to strains of influenza circulating after 1957 may confer some protective immunity, resulting in neutralizing antibody titers against 2009 H1N1 likely to be protective in older individuals\(^5\)\(^6\)\(^7\). While older populations may be less likely to acquire 2009 H1N1, the higher prevalence of co-morbidities in these populations may lead to higher morbidity and mortality rates among persons who do become infected. Studies also show that obese persons and pregnant women\(^8\) have higher mortality associated with 2009 H1N1 infection.

Patients with hematologic malignancies are likely to be at an increased risk for infection with influenza. A few small series have documented seasonal influenza outbreaks among such patients, demonstrating the susceptibility of immunocompromised populations\(^9\)\(^10\)\(^11\)\(^12\). These limited reports suggest that cancer patients are at a high risk for acquisition of influenza in both the community and healthcare settings.
NATURAL HISTORY OF INFLUENZA IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES

Upper Respiratory Infection

Similar to immunocompetent patients, most patients with influenza infection and hematologic malignancies present with symptomatic upper respiratory symptoms, consisting of sore throat, nasal symptoms, malaise, and/or headache. Notably, systemic symptoms such as fever, myalgia and fatigue may be reduced or completely absent. In the HCT population, where this has been studied prospectively, most patients were afebrile and lacked systemic symptoms. We speculate that the cytokine response associated with acute influenza infection may be decreased in these patients; use of corticosteroids may play an additional role. The symptomatic phase typically lasts for 1-2 weeks in immunocompromised patients, although viral shedding may be prolonged. Asymptomatic viral shedding of influenza is uncommon in this setting but can occur with both seasonal and 2009 H1N1 influenza (unpublished observation).

Progression to Lower Respiratory Disease and Mortality

A devastating complication of influenza infection is lower respiratory tract disease and pneumonia, frequently leading to acute lung injury and death. Progression from upper to lower tract disease occurs after a median of 1 week in patients with hematologic malignancies, presenting clinically and radiographically as viral pneumonia. The radiographic appearance can range from typical diffuse ground-glass infiltrates to areas of consolidation resembling fungal or bacterial disease. Influenza pneumonia may be complicated by bacterial or fungal coinfection. Therefore, we advocate aggressive diagnostic work-up with bronchoalveolar lavage (BAL) and testing for a broad range of opportunistic pathogens. The most significant risk factor for progression to lower tract disease is profound lymphopenia. The impact of corticosteroids on influenza severity and outcome are conflicting, with no randomized trials assessing these effects. While high-dose steroids seemed to prolong viral
shedding in HCT recipients with upper respiratory infection \(^{14}\) and one study in pediatric cancer patients showed a higher rate of progression to lower tract disease \(^{18}\), another study in HCT recipients suggests that progression to lower respiratory tract disease may be reduced \(^{14}\). Possibly, steroids prolong viral shedding but paradoxically reduce the inflammatory cytokine response. Risk factors among hematologic malignancy patients for 2009 H1N1 influenza disease progression to lower respiratory tract disease are not known.

The dissemination of 2009 H1N1 influenza virus infection to distant organs has not been studied in humans. One report described RNA detection in the plasma in patients with lower respiratory tract disease \(^{19}\). Ferret models of 2009 H1N1 influenza have not demonstrated viral dissemination into the blood or other organs \(^{20}\) in contrast to H1N5 avian influenza studies showing RNA detection in blood \(^{21}\). Further studies are needed.

Influenza infection may lead to acute lung injury, respiratory failure and death. Mortality rates of influenza vary widely among HCT recipients and patients with hematologic malignancies, ranging from approximately 25% for lower tract disease in some HCT recipients to 0% in other series \(^{14,17,22-24}\). One large cohort study demonstrated that seasonal influenza lower respiratory tract disease is independently associated with mortality after HCT (adjusted hazard ratio 2.60, 95% confidence interval 1.40–4.86) \(^{14}\). Influenza-associated death can be caused either directly by influenza viral infection or by infection with secondary concomitant pathogens \(^{14}\). Whether patients with influenza virus infection also have long-term sequelae, such as restrictive or obstructive airway disease as seen following infection with parainfluenza and respiratory syncytial viruses \(^{25}\), is under investigation.

*Differences in presentation between immunocompromised and immunocompetent patients*

No comprehensive data describe whether clinical manifestations during the initial phase of 2009 H1N1 influenza infection are different from those reported with seasonal influenza infection, however,
recent series have included both immunocompetent and immunocompromised patients\textsuperscript{26, 27}. An initial report in cancer patients suggests that fever and cough occurs in >90% of patients infected with 2009 H1N1 influenza, and lower respiratory tract involvement was seen in 27% of patients\textsuperscript{28}. In immunocompetent patients, gastrointestinal and neurological symptoms appear to be more prevalent with 2009 H1N1 infection, especially in small children\textsuperscript{29}. Therefore, we suggest a low index of suspicion during outbreak situations and favor enhanced testing for influenza.

**MANAGEMENT OF INFLUENZA**

*Indications for testing and treatment*

Any patient with new onset of upper or lower respiratory symptoms during sustained influenza activity in the community should be evaluated for influenza. The present 2009 H1N1 strain is not reliably detected with commercial rapid tests or direct fluorescent antibody testing\textsuperscript{30}, with PCR testing recommended for optimal sensitivity. PCR methods also can differentiate influenza strains and susceptibility patterns. This is important when strains with different susceptibility patterns co-circulate, as during the 2008/2009 season when different H1N1 strains (oseltamivir-resistant seasonal and oseltamivir-susceptible 2009 H1N1 influenza) were co-circulating\textsuperscript{31}. Upper respiratory samples are obtained by nasal wash or by a nasopharyngeal swab, with nasal wash being the most sensitive method\textsuperscript{32}. A BAL is typically done to evaluate lower respiratory disease in highly immunosuppressed patients as it allows for concurrent testing for concomitant pathogens. All patients with confirmed influenza URI should have both clinical and radiographic assessments to rule out lower tract involvement.
A wide spectrum of immunosuppression exists among patients with hematologic malignancies, ranging from chemotherapy to allogeneic transplantation following myeloablative conditioning with \textit{in vivo} or \textit{ex vivo} T cell depletion or refractory graft versus host disease. Underlying conditions that complicate influenza disease in otherwise immunocompetent persons may be present, including diabetes, obesity, and pulmonary or cardiac disease. Few studies have evaluated the outcome of influenza disease relative to the underlying immunosuppression and preexisting conditions, although a recent metaanalysis found an average case fatality rate of 17\% with a range of 0-33\% among patients with hematologic malignancies and HCT infected with seasonal influenza\textsuperscript{33}. Neuraminidase inhibitor therapy appears to be effective when instituted early after onset of symptoms\textsuperscript{14}. A preliminary report in patients with hematologic and solid cancers by Redelman-Sidi et al.\textsuperscript{28} suggests that lower respiratory tract disease occurs in 27\% of 45 patients; 37\% of patients were hospitalized for an average of 7 days (range 3-15) and one person required ICU care without mechanical ventilation. No deaths were reported in this series of 45 patients, most of whom received oseltamivir (N=43)\textsuperscript{28}. The 2009 H1N1 influenza may be more serious than typical seasonal influenza: as of mid-November at the Seattle Cancer Care Alliance, 21 patients had upper and 6 lower respiratory tract influenza disease caused by 2009 H1N1 with 4 patients experiencing respiratory failure and one death (unpublished data).

\textit{Choice of antiviral}

Anti-influenza antiviral agents have not been studied in randomized trials specifically in patients undergoing chemotherapy or following HCT. Antiviral susceptibilities of circulating influenza strains must be continually evaluated\textsuperscript{31}, with information available on websites at the CDC. Due to resistance against the M2-inhibitors in 2009 H1N1 strains, amantidine and rimantidine should not be used as single agents to treat or prevent influenza A (\textit{Table 1}). Presently, two neuraminidase inhibitors, i.e. zanamivir and oseltamivir, are licensed for the treatment of influenza. These compounds are licensed for inhaled
(zanamivir) and oral use (oseltamivir), with intravenous agents now available under special circumstances. Investigational agents including intravenous peramivir, zanamivir, and oseltamivir are under study and some are available under Emergency Use Authorization through the United States Centers for Disease Control and Prevention (CDC).

**Management of upper and lower respiratory infection.**

Non-randomized studies suggest that preemptive therapy with oral or inhaled neuraminidase inhibitors (i.e., oseltamivir, zanamivir) is effective in preventing progression to lower tract disease. Monotherapy appears to be effective in these non-randomized studies. For lower respiratory tract disease, a more aggressive approach with intravenous drug administration, high-dose oral regimens, and/or combination therapy approaches in the case of respiratory failure can be considered (Table 2).

1. Choice of Neuraminidase inhibitors.

If the susceptibility pattern of the circulating strain is not available, an antiviral effective against all influenza strains, i.e., zanamivir, or a drug combination should be used until this information is available. For instance, most seasonal H1N1 influenza viruses circulating during 2008-2009 were resistant to oseltamivir, and empiric treatment consisting of zanamivir or oseltamivir plus rimantidine was recommended by the CDC. As of mid early December 2009, the predominant circulating strain in the United States is the 2009 H1N1 strain, which to date is almost universally susceptible to oseltamivir, and always susceptible to zanamivir.
2. Dose and duration of treatment

One issue causing considerable debate among physicians caring for highly immunocompromised patients with influenza is that of appropriate dosing and duration of antiviral therapy. Oseltamivir has been studied at doses of 75 mg or 150 mg twice daily in immunocompetent subjects with seasonal influenza, in which no advantage of the higher dose was demonstrated but a somewhat higher rate of adverse effects noted. The relevance of these studies for highly immunosuppressed patients or with highly virulent strains is questionable. Complicating factors include higher viral load in immunocompromised patients, prolonged shedding, uncertain drug absorption especially in patients with chemotherapy-associated gastrointestinal malabsorption or gastrointestinal GvHD in HCT recipients, and the propensity to antiviral drug resistance in a setting of viral replication and low-level drug pressure. With 2009 H1N1 influenza, the issue of prolonged viral shedding may be even more pressing. Taken together, these factors may favor using a higher dose in immunosuppressed patients, especially when absorption is uncertain. We have adopted this strategy (Table 1) for patients with influenza (both seasonal and 2009 H1N1) and lower respiratory tract disease. We also advocate consideration of the higher dose in patients with upper respiratory tract infection due to 2009 H1N1 in a setting of HCT and profound lymphopenia. Whether a high-dose strategy is necessary or beneficial in other immunocompromised patients is unknown.

Original studies of oseltamivir were conducted in healthy patients symptomatic for < 48 hours, and there is minimal data concerning treatment of immunosuppressed patients who have had a longer duration of symptoms prior to treatment. We believe that symptomatic immunocompromised patients with influenza require antiviral therapy regardless of the duration of symptoms prior to diagnosis. The rationale for this is that these patients have ongoing viral replication, clinical symptoms can be
deceivingly mild at presentation and disease onset is often uncertain,\textsuperscript{13} and progression to lower tract disease may occur even after one week of symptoms\textsuperscript{14}.

Little guidance exists regarding the duration of treatment in immunocompromised patients. The recommended duration of treatment of influenza in immunocompetent patients is 5 days, based on clinical studies in previously healthy persons\textsuperscript{37}. However, longer treatment could be considered in immunosuppressed patients. The median time from diagnosis of URI to lower tract disease is 7 days in HCT recipients\textsuperscript{14}. Thus, a 5-day course may be too short to prevent cases of late progression. Importantly, prolonged shedding frequently occurs in immunosuppressed patients\textsuperscript{40}, which may serve as a source of progression of influenza illness and healthcare-associated disease transmission. We therefore advocate an initial course of 10 days with prolonged treatment for pneumonia and if patient remains symptomatic or if viral shedding is still ongoing (Table 1). We recognize that prolonged treatment may cause extended drug pressure and thus predispose to resistance, especially if the drug levels are low. This needs to be balanced against the potential of recurrence and infection control issues. Therefore, we recommend treatment at higher doses until cessation of shedding. To date, we have not seen an emergence of resistance with this approach but more prospective study of this issue is needed.

3. Single vs. combination therapy

To date, no data from adequately powered randomized trials are available to demonstrate a benefit from combination antiviral influenza therapy, however, a trend towards less resistance was seen in one relatively small comparative trial\textsuperscript{41}. Recommendations to use combination therapy in 2008-2009 were based on the uncertainty of antiviral susceptibility. This recommendation was not based on synergy but rather on the premise that at least one active agent should be given. However, \textit{in vitro} and animal synergy data have been used to support the hypothesis that combination therapy may be beneficial\textsuperscript{42-45}. 
A triple combination of oseltamivir, ribavirin and amantidine has been shown to inhibit seasonal, oseltamivir-resistant, and 2009 H1N1 influenza strains more efficiently than single drugs or the combination of two drugs in vitro\textsuperscript{46}. Randomized trials are ongoing in both immunosuppressed and immunocompetent patients with severe infection to test these hypotheses. If patients have severe lower respiratory tract disease, we advocate considering combination therapy when possible, given the poor outcome in immunocompromised patients and the potential for the development of resistance, acknowledging that supporting data from randomized trials are still lacking (Table 2). Combination therapy is also recommended when multiple strains with different sensitivities are circulating.

No evidence exists from randomized trials that pooled intravenous immunoglobulin (IVIG) is beneficial as adjunctive treatment. However, IVIG may be beneficial due to preexisting neutralizing antibodies in approximately one third of donors\textsuperscript{5,6} and the potential role of IgG2 subclass deficiencies\textsuperscript{47}. We reserve IVIG for critically ill patients with lower respiratory tract disease and acute lung injury.

4. Route of administration

Oseltamivir is commercially available for oral administration, and zanamivir as an inhalation powder. Intravenous administration may be preferable for critically ill patients and those with uncertain absorption or other conditions preventing oral administration (e.g. nausea, altered mental status).

Peramivir, a novel neuraminidase inhibitor available for intravenous administration, has received an Emergency Use Authorization (EUA) by the FDA for patients with laboratory confirmed or untypable but suspected 2009 H1N1 virus infection\textsuperscript{48}. Specifically, intravenous peramivir is authorized for patients not responding to either oral or inhaled antiviral therapy, or when drug delivery by a route other than IV (e.g. enteral oseltamivir or inhaled zanamivir) is dependable or feasible, or if the clinician judges IV therapy is appropriate. Pediatric patients for whom an IV agent is clinically appropriate for similar
reasons may also receive this drug under EUA, although pharmacokinetics in this age group is not yet known. An intravenous form of zanamivir is undergoing phase II evaluation in both immunocompetent and immunosuppressed patients. This drug is available through an emergency use program administered by GlaxoSmithKine.

5. Supportive care

Bacterial infections are a common complication of seasonal and 2009 H1N1 influenza infection. No evidence exists on the prophylactic use of antibiotics in immunocompromised patients infected in influenza. We routinely evaluate patients with lower respiratory tract disease with BAL and blood cultures for the presence of co-pathogens. Our threshold to start antibiotics is generally low, especially in critically ill patients, although data from randomized trials are lacking.

The role of steroids is controversial and no data from randomized trials exist. We have no consistent approach with regard to steroids but some clinicians try to reduce immunosuppression if possible. High doses of steroids (≥ 2 mg/kg) prolong viral shedding but there also seems to be an anti-inflammatory effect with moderate doses (up to 1 mg/kg of prednisone) that may be beneficial in patients with acute lung injury or ARDS. Clearly, more data are needed to make firm recommendations.

6. Delay of Transplantation or Chemotherapy.

In HCT candidates with active influenza infection, we administer antiviral therapy (Table 1, 2) and delay myeloablative HCT until resolution of symptoms and cessation of shedding, an approach consistent with recent international guidelines. Delay of chemotherapy or non-myeloablative conditioning regimens is recommended whenever feasible, although supportive data are not available. One study has suggested that progression to lower respiratory tract disease is uncommon after non-
myeloablative conditioning\textsuperscript{52}. If transplantation or chemotherapy cannot be delayed because of progressive underlying disease, our experience supports that high-dose antiviral therapy, and possibly even combination antiviral therapy should be given. A less aggressive conditioning regimen should be considered if HCT must proceed.

7. Pipeline

The need for innovative approaches could not be more urgent. Evidence suggests that antiviral therapy is associated with reduced morbidity and mortality attributable to influenza in patients receiving chemotherapy or undergoing HCT\textsuperscript{40,53}. However, emergence of drug resistance continues to be a problem\textsuperscript{40} and novel influenza strains with unknown virulence continue to emerge. Novel drugs and treatment strategies are critically needed due to resistance issues, limited routes of administration, and to improve effectiveness. A novel neuraminidase inhibitor, peramivir, is presently in advanced clinical development (\textbf{Table 3}). Intravenous zanamivir is being studied in a phase II clinical trial. An emergency use program exists for both IV peramivir and zanamivir\textsuperscript{54}. An intravenous form of oseltamivir is in early clinical evaluation. Other neuraminidase inhibitors\textsuperscript{55} as well as compounds targeting the viral polymerase\textsuperscript{56} and hemaglutinin\textsuperscript{57} are under investigation (\textbf{Table 3}).

Due to emergence of resistance, a general plea for combination therapy for influenza disease has been made, and in vitro and animal data support this approach\textsuperscript{42,45,46,58}. Clinical trials evaluating this are underway. The combination of two different neuraminidase inhibitors is also being studied to examine potential drug-drug interactions and possible additive effects.

Treatment approaches for influenza have been directed almost exclusively at viral targets. A novel approach is to target the host respiratory epithelial cell. The compound DAS181 is a novel inhaled blocker of sialic acid receptors in the airway epithelium that prevents viral entry, thereby accelerating
viral clearance and preventing progression of viral-induced lung disease. DAS181 has activity against influenza viruses, parainfluenza viruses and human metapneumovirus. It has been shown to be active even against highly resistant strains of influenza (including the presently circulating 2009 H1N1 strain and avian H5N1) in vitro and in animal models.

**PREVENTION OF INFLUENZA**

Three principle strategies exist to prevent the acquisition of influenza: infection control practices, vaccination, and chemoprophylaxis (Table 4). Each strategy is discussed in detail below.

*Infection Control*

**Personal Infection Control Practices**

Two basic tenets of infection control have been strict attention to hand hygiene and social distancing. A small body of evidence supports the efficacy of hand hygiene (defined as either the use of soap and water or alcohol-based hand sanitizer to cleanse the hands) in reducing influenza virus acquisition. A recent meta-analysis found that the frequent performance of hand hygiene was associated with a 55% reduction in the risk of acquiring respiratory virus infections.

Evidence supporting benefits of social distancing is more challenging to find in the medical literature. Typical social distancing measures include reminding patients to keep at least 6 feet from individuals who are sick, isolating or cohorting patients with respiratory symptoms in clinical areas, and strictly enforcing a “no-sick-at-work” policy for healthcare workers.
Infection Control for Influenza in Healthcare Settings

The prevention of influenza in health-care settings relies on the early detection of individuals with suspected or confirmed illness, and assuring that these patients do not infect susceptible patients and medical staff. The Infection Control Program at the Seattle Cancer Care Alliance has been highly successful in preventing respiratory virus infections among its highly vulnerable cancer patients by adapting CDC infection control recommendations. As seen in Figure 3, despite a nearly 100-fold increase in influenza cases in the Seattle area during spring, 2009, no corresponding increase in influenza cases among SCCA patients was seen. The components of our plan are outlined below.

1. Elimination of Potential Exposures. Early identification of individuals with potential influenza infection is a cornerstone of institutional infection control. All persons entering the outpatient clinic or inpatient wards are met with hand hygiene stations, replete with alcohol-based hand sanitizer, tissues, and information about respiratory infections and respiratory etiquette. Between October 1st and April 30th at SCCA, an eleven point symptom survey is administered by LPNs or volunteers to all who enter clinical areas. A sticker color-coded for the day of the week documents the completion of the survey. No individual without a sticker is admitted to these areas, and all employees are empowered to enforce this policy. Attempts are made to reschedule patients with respiratory symptoms; those who cannot are given a mask and placed in either an isolation area or private rooms until they can be assessed by their clinical care team. Isolation lists are maintained electronically as part of each patient’s medical record. Staff with any symptoms of respiratory infection are furloughed until completely asymptomatic. Respiratory virus testing by multiplex PCR is offered for staff who have minimal residual symptoms but feel well enough to work after an absence of more than four days; a negative test is sufficient for return to work.
2. Engineering controls. Patients with suspected or confirmed respiratory infections in the outpatient clinic are placed in single rooms as soon as possible or in isolation zones in the waiting area when a room is not immediately available. The inpatient facilities allow for placement of patients with suspected or proven influenza into single rooms, and patients in respiratory isolation follow special protocols when needing to leave their room for procedures, tests, etc.

3. Administrative Controls. A comprehensive isolation plan has been developed and widely distributed for both inpatient and outpatient facilities. Didactic sessions to familiarize staff with policies are conducted on an ongoing basis. The infection control program regularly monitors adherence to hand hygiene and compliance with isolation guidelines, and provides monthly feedback to staff. An electronic surveillance system allows for real-time quantification of the numbers of patients and staff who are infected with influenza, which is scrutinized daily by the infection control team. Other measures include a sick-leave policy which is tolerant of absences for respiratory illnesses, the design of redundant work plans for staff at all levels should absences be required, the requirement to either receive annual influenza vaccination or sign a written declination waiver (see below), an institutional commitment to both educate patients, families and caregivers about influenza but also to assist with identifying resources for furloughing ill caregivers, and a plan for post-exposure prophylaxis of exposed patients and staff (see below).

4. Personal Protective Equipment. For standard seasonal influenza, most organizations agree with the CDC recommendations for droplet precautions for healthcare personnel (donning of gloves, gowns and surgical masks when working in close contact with patients with suspected or proven influenza and adding goggles or face shields when appropriate). However, some agencies are recommending N95 masks or respirators either for some or all close contact with patients with 2009 H1N1 influenza (Table 5). These recommendations seem inconsistent to us, as no research to date would support a different mode of transmission / acquisition for 2009 H1N1 influenza when compared
with seasonal influenza. A recent trial randomized nurses caring for patients with acute febrile respiratory illnesses in the 2008-2009 season to either fit-tested N95 respirators or surgical masks, and found no significant difference in the proportion in each group who developed laboratory-confirmed influenza\textsuperscript{66}. This same study also found no difference in the incidence of other laboratory-confirmed respiratory viruses between nurses randomized to either arm, and found a non-significant trend towards more influenza-like illness in the nurses with surgical masks (9 vs. 1 in the N95 group, p=0.06). Taken together, we currently advocate the use of standard surgical masks for all standard exposures (Table 5). We note that these recommendations may change as more information becomes available or United States Occupational Safety & Health Administration (OSHA) rulings become clearer.

5. Vaccination. Two seasonal influenza vaccines are available: trivalent inactivated virus (TIV, injectable) and live attenuated trivalent influenza virus (LAIV, nasal spray). Both are designed to protect against two strains of influenza A and one strain of influenza B. This year, monovalent inactivated and live-attenuated preparations for prevention against 2009 H1N1 influenza have been introduced. These vaccines rely on the growth of a laboratory strain of virus in fertilized chicken eggs. Manufacturing and distribution of seasonal influenza vaccine generally takes over six months. Because the current 2009 H1N1 strain was not recognized until April 2009, this year’s seasonal influenza vaccine does not contain the 2009 H1N1 strain, and immunization against both seasonal and influenza are recommended. Antibody responses to the 2009 H1N1 vaccine in healthy adults indicate excellent immunogenicity from several different manufacturers\textsuperscript{6,7}.

\textit{Vaccination of Patients with Hematologic Malignancies.} The ability of patients with hematologic malignancies to generate a protective response following immunization depends both on the patient’s underlying disease and its therapy. In general, patients treated with high doses of systemic corticosteroids or recent HCT are least likely to develop protective antibodies after vaccination. Two
reviews summarize the existing data on vaccine efficacy in hematologic malignancy patients, with immune responses ranging from a low of 19% in adults with multiple myeloma to nearly 100% of general hematology-oncology patients. Patients immediately preceding or in the 6 months following myeloablative conditioning for HCT, or those who are within seven days after receipt of conventional chemotherapy, are unlikely mount a protective response and should have vaccination deferred, but all others are recommended to receive both seasonal and 2009 H1N1 vaccines. Importantly, contacts of these patients and particularly children in close contact with these patients need appropriate immunization to prevent spread of influenza within the family setting. Patients with hematologic malignancies and their close household contacts should preferentially receive inactivated influenza vaccines due to the theoretical risk for mutation, dissemination and morbidity from LAIV. In select cases where the inactivated vaccine is unavailable, the risk of complications from acquiring influenza should be weighed against the theoretical risks from the LAIV and its use could be considered.

**Vaccination of Healthcare Workers.** Vaccination of healthcare workers is an essential component of protecting vulnerable patients with impaired immunity to influenza. Comprehensive vaccination of healthcare workers reduces the all-cause mortality of the elderly patients by approximately 40%. One report of an influenza outbreak on a bone marrow transplant ward suggested that increased rates of vaccination of healthcare workers in the subsequent year was associated with markedly reduced number of nosocomial cases of influenza. Accordingly, healthcare institutions caring for immunocompromised patients should make 100% staff compliance with influenza vaccination a goal in the control of influenza. Mandatory vaccination of healthcare workers has been upheld in courts of law and promoted as an ethical imperative. Alternatively, a mandatory influenza vaccination declination form, acknowledging the risk posed to vulnerable patients by declining vaccination, can be utilized. The combination of increased influenza educational sessions, easier
access to vaccination clinics, and vaccine declination forms has resulted in a greater than 2-fold increase in the uptake of staff receiving influenza vaccine in our institution (Table 4, 6).

**Use of the Live Attenuated Vaccine (LAIV) in Hematologic Malignancy Patients and Staff.** LAIV contains strains of influenza which are both cold-adapted (therefore unable to replicate in the lower airways) and have reduced pathogenicity. While illness after receipt of LAIV is very unusual, rare cases of transmission of LAIV but without symptomatic disease to close contacts have been documented. Transmission of LAIV is very rare, with an estimated rate of 0.58% in a daycare setting where young influenza-naïve children received either vaccine or placebo, and secretions were liberally shared. Healthcare workers administering the vaccine have also been infected. Recent studies find the LAIV to be more effective than TIV in producing protection among children under 6 but may be less effective than TIV in adults perhaps due to incomplete preexisting immunity in adults which neutralizes the vaccine strain. Shedding of vaccine strain in healthy children and adults generally lasts 3-7 days. This vaccine is not recommended for immunocompromised patients, although safety data in HIV-infected individuals and children on maintenance chemotherapy have demonstrated safety.

More concern about the administration of LAIV to health care workers has emerged recently with the availability of 2009 H1N1 live vaccine and a simultaneous shortage of 2009 H1N1 monovalent inactivated vaccine. This concern is based on theoretical concerns of lack of control of replication in immunocompromised hosts, potential for recombination with wild type virus during prolonged periods of shedding, and documentation of rare cases of secondary transmission post-vaccination. The CDC recommends that LAIV may be given to individuals, including HCW, who are not involved in the care of patients requiring protective isolation. Until recently, our institution has restricted the use of LAIV to persons without direct patient contact for a period of at least seven days. However,
we have recently modified our approach due to the shortage of the TIV, the high risk of transmission of wild-type strain (10-37% transmission rate \textsuperscript{81}; Englund J personal Communication), and the overall low risk of transmission with LAIV (0.58-2.4%), and permitted use of LAIV in HCW in outpatient settings and family members of patients > 100 days post transplant (Table 6).

6. Chemoprophylaxis. Vaccination is our primary prophylaxis modality. However, persons with significant exposure (i.e. close face-to-face contact for more than just a few seconds or direct contact with direct secretion) to confirmed cases of influenza who have not been vaccinated (or who received the vaccination less than 3 weeks prior to the time of exposure) should be considered for prophylactic antiviral therapy with either oseltamivir or zanamivir based on the susceptibility of the circulating strain. CDC has also endorsed “preemptive” therapy as an option for persons exposed to influenza, where antiviral use is deferred until the exposed individual manifests symptoms. We do not endorse the “preemptive” approach for hematologic malignancy and HCT patients, but have considered it to be a useful alternative, for example, in certain healthcare workers with limited patient contact. Post-exposure therapy should not be delayed until influenza testing is returned on exposed individuals.

Antiviral prophylaxis given to all patients at risk during a community or institutional outbreak is another option\textsuperscript{82}. Initial results from a randomized trial in mildly to moderately immunosuppressed (mainly solid organ) transplant recipients has been presented\textsuperscript{83} and suggests a beneficial effect for laboratory-confirmed seasonal influenza with little drug resistance. Whether such approach is effective without increased emergence of resistance in severely immunocompromised patients with the current pandemic strain is unknown, although resistance has been described even in normal hosts receiving prophylaxis\textsuperscript{54}. We would consider this option if a nosocomial outbreak were to occur. Such a strategy has been successfully utilized in a seasonal influenza outbreak at an
outpatient living facility. The 2008 global HCT infection prevention guidelines endorse the use of antiviral prophylaxis during community outbreaks that lead to nosocomial transmission.

CONCLUSIONS AND FUTURE DIRECTIONS

The initial experience with 2009 H1N1 influenza suggests that this virus can cause serious disease in immunosuppressed patients. Clinical findings include respiratory failure, treatment failures due to drug resistance, and death (and unpublished data). Published data are currently unavailable but based on the course of the pandemic at our center and elsewhere several concepts appear to emerge. First, rapid diagnosis using PCR is critical for identifying infected patients, initiating antiviral treatment, and implementing appropriate infection controls. Second, effective antiviral treatment should be started early. In critically ill patients with compatible symptoms and influenza circulating at high levels in the community, empiric treatment while awaiting test results seems justified. We also favor a higher dose of oseltamivir in analogy to recommendations for H5N1 avian influenza and the questionable absorption in patients with chemotherapy- or GvHD-associated malabsorption. Third, our experience shows that aggressive infection controls procedures can minimize transmission within the immunocompromised patient population and also reduce acquisition from sources outside the system.

Future work should focus on conducting randomized trials in immunocompromised patients, the development and evaluation of drugs with new mechanisms of action (Table 3), and the evaluation of combination therapies and adjunctive anti-inflammatory agents. To fully understand the impact of the 2009 H1N1 and seasonal influenza, studies of the epidemiology, risk factors and factors associated with outcome should be initiated using existing networks to increase sample size and allow for multivariable analyses. Initial observations suggest a wide spectrum of disease severity and that patients with hematologic malignancies are not a homogeneous group. Therefore, pathogenesis studies are needed to
define the role of the underlying immunosuppression, viral load, cytokine responses, and to evaluate RNA detection in blood and other biomarkers that may correlate with disease severity.

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AUTHORSHIP

Drs. Casper, Englund and Boeckh researched the topic and wrote the manuscript.

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FIGURES

**Figure 1.** Number of Cases of Influenza-Like Illness Presenting to Sentinel Providers and Reported to the Centers for Disease Control and Prevention.

[Graph showing the number of visits of Influenza-like Illness (ILI) reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet) National Summary 2008-2009, by Age.]

Figure 2. Pandemic Influenza Infection Rates and Mortality, By Age (Mainly Immunocompetent)

Panel A: Infection Rates

Panel B: Mortality

Source: http://www.cdc.gov/H1N1FLU/surveillanceqa.htm
Figure 3. Aggressive Implementation of a Novel Infection Control Program at the Seattle Cancer Care Alliance Assisted in Controlling Influenza During the 2009 H1N1 Pandemic of Spring 2009.
Table 1. Antiviral Options for Treatment of Influenza (all doses for normal renal function; dose reductions may be necessary in patients with reduced renal clearance).

<table>
<thead>
<tr>
<th>Antiviral Agent</th>
<th>Susceptibility of 2009 H1N1</th>
<th>Susceptibility of 2008/9 seasonal H1N1</th>
<th>Susceptibility of 2008/9 seasonal H3N2</th>
<th>Susceptibility of Influenza B or C</th>
<th>Recommended Dosing and Duration in Patients with Hematologic Malignancies: Adults</th>
<th>Recommended Dosing and Duration in Patients with Hematologic Malignancies: Children</th>
<th>Key Toxicities</th>
<th>Parenteral Formulation Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Treatment: 150 mg PO twice daily x 10 days*</td>
<td>Dosing guidelines: see CDC guidelines: <a href="http://www.cdc.gov/HPN1flu/recommendations.htm">http://www.cdc.gov/HPN1flu/recommendations.htm</a></td>
<td>Gastrointestinal - greatly reduced if oral drug taken with food</td>
<td>Yes (Investigational, phase I)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Post-exposure Prophylaxis: 75mg PO once or twice daily x 10 days*</td>
<td>Care to be taken for dosing in children &lt; 1 year, with dose of 3-3.5 mg/kg/dose recommended</td>
<td>Neurologic (children)</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
<td>Seasonal Prophylaxis: 75 mg PO once daily</td>
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<td></td>
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</tr>
<tr>
<td>Zanamivir</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Treatment: 10 mg twice daily (by inhaler)</td>
<td>Not available for children &lt; 7 years</td>
<td>Bronchospasm</td>
<td>Yes (Investigational, phase II)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Post-exposure: 10 mg twice daily (by inhaler)</td>
<td>For Children &gt; 7 years: use adult doses</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prophylaxis: 10 mg twice daily (by inhaler)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rimantidine</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Treatment: 100 mg PO</td>
<td>Age 1-10 yrs:</td>
<td>Neurologic</td>
<td>No</td>
</tr>
</tbody>
</table>

For personal use only.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Monotherapy Recommendation</th>
<th>Treatment</th>
<th>Dosing Guidelines</th>
<th>Side Effects</th>
<th>Dose Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Amantidine)</td>
<td></td>
<td>twice daily</td>
<td>5 mg/kg/day PO, 1-2 divided doses, max 150 mg/day</td>
<td>Gastrointestinal</td>
<td>Age ≥10 yrs: 100 mg PO twice daily</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Not recommended as monotherapy</td>
<td>Treatment: 200-400 mg PO three times daily</td>
<td>No dosing guidelines available</td>
<td>Hematologic Gastrointestinal</td>
<td>Yes (investigational in the US)</td>
</tr>
<tr>
<td>Peramivir</td>
<td>Yes</td>
<td>Treatment: 600 mg IV once daily</td>
<td>Birth-day 30: 6 mg/kg, Day 31-90: 8 mg/kg, Day 91-180: 10 mg/kg, Day 181-5 yr: 12 mg/kg, 6 yr-17 yr: 10 mg/kg (max 600 mg/day)</td>
<td>Gastrointestinal Neutropenia</td>
<td>Yes (EUA in the US)</td>
</tr>
</tbody>
</table>

* Authors’ recommendation; see text for rationale.

* Dose estimated from published case series.85-87
Table 2. Treatment strategies for influenza disease at the Seattle Cancer Care Alliance (FHCRC, University of Washington and Seattle Children’s Hospital)

<table>
<thead>
<tr>
<th>Category</th>
<th>First line treatment</th>
<th>Second line treatment</th>
<th>Research protocols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic shedding</td>
<td>Consider neuraminidase inhibitors (monotherapy)</td>
<td>No treatment, isolation, observe for development of symptoms</td>
<td>None</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>Oral/inhaled neuraminidase inhibitors (monotherapy) – dependent on circulating strain susceptibility</td>
<td>Oral/inhaled neuraminidase inhibitors (monotherapy) – alternative agent</td>
<td>Triple combination therapy vs. monotherapy (Phase II)</td>
</tr>
<tr>
<td>Lower respiratory tract disease</td>
<td>Oseltamivir (high-dose)</td>
<td>Consider IVIG</td>
<td>IV zanamivir (Phase II)</td>
</tr>
<tr>
<td>(no respiratory failure)</td>
<td>Consider IV peramivir</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider combination therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower respiratory tract disease</td>
<td>IV peramivir/zanamivir</td>
<td>IVIG</td>
<td>None</td>
</tr>
<tr>
<td>(respiratory failure, mechanical ventilation)</td>
<td>Combination therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Drugs and drug combinations with activity against influenza virus in clinical development or evaluation.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug target</th>
<th>Manufacturer/Sponsor</th>
<th>Route of administration</th>
<th>Clinical Development Stage</th>
<th>Emergency use mechanism available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peramivir</td>
<td>Viral Neuraminidase</td>
<td>Biocryst Pharmaceuticals</td>
<td>IV, IM</td>
<td>Phase III</td>
<td>EUA*</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Viral neuraminidase</td>
<td>GlaxoSmithKline</td>
<td>IV</td>
<td>Phase II</td>
<td>Emergency use program</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>Viral neuraminidase</td>
<td>Roche Pharmaceuticals</td>
<td>IV</td>
<td>Phase I</td>
<td>No</td>
</tr>
<tr>
<td>T-705 (Favipiravir)</td>
<td>Viral polymerase</td>
<td>Toyama Chemical</td>
<td>Oral</td>
<td>Phase II (US)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase III (Japan)</td>
<td></td>
</tr>
<tr>
<td>CS-8958 (R-118958)</td>
<td>Viral neuraminidase</td>
<td>Daiichi Sankyo Co., Ltd.</td>
<td>Inhaled</td>
<td>Phase III</td>
<td>No</td>
</tr>
<tr>
<td>DAS181</td>
<td>Sialic acid receptor of the respiratory</td>
<td>Nexbio Inc.</td>
<td>Inhaled</td>
<td>Phase II</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>epithelial cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>Viral hemaglutinin</td>
<td>Romark Laboratories</td>
<td>Oral</td>
<td>In vitro, no animal or human data</td>
<td>Licensed for treatment of cryptosporidiosis (no indication for influenza treatment)</td>
</tr>
<tr>
<td>Neuraminidase inhibitor +</td>
<td>In vitro synergistic combination targeting</td>
<td>Adamas Pharmaceuticals</td>
<td>Oral</td>
<td>Phase II, III</td>
<td>Licensed drugs (no indication for combination)</td>
</tr>
<tr>
<td>amantidine + ribavirin</td>
<td>viral neuraminidase, M2 and depletion of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>intracellular phosphate of influenza</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oseltamivir + zanamivir</td>
<td>Viral neuraminidase</td>
<td>GlaxoSmithKline</td>
<td>Oral and inhaled</td>
<td>Phase III, IV</td>
<td>Licensed drugs (no indication for combination)</td>
</tr>
</tbody>
</table>

* Emergency use authorization granted by US Food and Drug Administration
Table 4. Estimated effectiveness of prevention techniques for influenza virus acquisition in institutions caring for patients with hematologic malignancies.

<table>
<thead>
<tr>
<th>Target Population</th>
<th>Technique</th>
<th>Hand Hygiene</th>
<th>Social Distancing</th>
<th>Vaccination</th>
<th>Chemoprophylaxis (postexposure)</th>
<th>Chemoprophylaxis (long-term prophylaxis throughout the season)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
<td>++++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++/+++</td>
</tr>
<tr>
<td>Caregivers or Family Members</td>
<td></td>
<td>++++</td>
<td>+++ (if feasible)</td>
<td>+++</td>
<td>+++</td>
<td>No data</td>
</tr>
<tr>
<td>Medical Staff</td>
<td></td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>No data</td>
</tr>
<tr>
<td>Other Institutional Staff</td>
<td></td>
<td>++++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>No data</td>
</tr>
</tbody>
</table>

+++       Highly likely to be effective (data from randomized trials or high quality cohort data)
+++       likely to be effective
++        possibly effective
+         unlikely to be effective
Table 5. Summary of Recommendations on Mask Usage in Caring for Patients with 2009 H1N1 influenza.

<table>
<thead>
<tr>
<th>Device</th>
<th>CDC</th>
<th>WHO / Canada Public Health / IOM</th>
<th>SHEA / IDSA / APIC / ACOEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Surgical Masks</td>
<td>Never</td>
<td>Acceptable, except for “aerosol generating procedures”</td>
<td>Acceptable, including the following procedures: Collection of nasopharyngeal specimens, closed suctioning of airway secretions and administration of nebulized medications</td>
</tr>
<tr>
<td><strong>N95 or PAPR</strong></td>
<td>All healthcare personnel who are in close contact with patients in isolation with confirmed, suspected, or probable 2009 H1N1 influenza should wear a fit-tested disposable N95 respirator or better</td>
<td>Use for “aerosol generating procedures”, INCLUDING “obtaining specimens by nasopharyngeal aspirate, nasopharyngeal swab, throat swab or bronchial aspirate” (per WHO, not defined by CAPHS)</td>
<td>For bronchoscopy, open suctioning of airway secretions, resuscitation involving emergency intubation or cardiac pulmonary resuscitation, and endotracheal intubation.</td>
</tr>
</tbody>
</table>

Abbreviations: CDC – Centers for Disease Control; WHO – World Health Organization; IOM – Institute of Medicine; SHEA – Society of Healthcare Epidemiologists of America; IDSA – Infectious Disease Society of America; APIC – Association of Professionals in Infection Control and Epidemiology; ACOEM – American College of Occupational and Environmental Medicine.
Table 6. Influenza Vaccination Guidelines at the Seattle Cancer Care Alliance.

<table>
<thead>
<tr>
<th>Population</th>
<th>Inactivated vaccine (injection) *</th>
<th>Live-attenuated vaccine (nasal spray) **</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic malignancy patients (non HCT)</td>
<td>Yes</td>
<td>No (within 3 months of chemotherapy***)</td>
<td>During shortage of inactivated vaccine, LAIV vaccine may be considered late after HCT &gt; 6 months after discontinuation of all immunosuppressive agents</td>
</tr>
<tr>
<td>HCT recipients</td>
<td>Yes (after 6 months post-transplant)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Health care worker</td>
<td>Yes</td>
<td>Yes (second line)</td>
<td>LAIV only during shortage of inactivated vaccine, should not have direct patient contact for at least 3 days</td>
</tr>
<tr>
<td>Care giver</td>
<td>Yes</td>
<td>Yes (second line)</td>
<td>If LAIV recipients develop fever (particularly in children), nasal stuffiness or runny nose (rhinorrhea), they are at higher risk of shedding the vaccine virus, and should remain sequestered from the patient for at least 3 days</td>
</tr>
<tr>
<td>Visitors</td>
<td>Yes</td>
<td>Yes (second line)</td>
<td></td>
</tr>
</tbody>
</table>

* Contraindications: Persons with a history of Guillain–Barré Syndrome that occurred after receiving influenza vaccine; persons who have a severe allergy to chicken eggs [obtained from package insert].

** Contraindications: persons < 2 or > 50 years of age; persons with a medical condition that places them at high risk for complications from influenza, including those with chronic heart or lung disease, such as asthma or reactive airways disease; people with medical conditions such as diabetes or kidney failure; or people with illnesses that weaken the immune system, or who take medications that can weaken the immune system; children <5 years old with a history of recurrent wheezing; children or adolescents receiving aspirin; persons with a history of Guillain–Barré Syndrome that occurred after receiving influenza vaccine; pregnant women; and persons who have a severe allergy to chicken eggs or who are allergic to any of the nasal spray vaccine components [obtained from package insert].

***Based on authors’ opinion
How we treat influenza in patients with hematologic malignancies

Corey Casper, Janet Englund and Michael Boeckh