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 world3 (Figure 1). The virologic characteristics of the 2009 H1N1 strain and events that led to its emergence have been described elsewhere.5 Pandemic 2009 H1N1 infection rates have been highest among persons younger than 25 years, but death rates have been highest among persons aged 25 to 49 years (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 persons7-9 Although older populations may be less likely to acquire 2009 H1N1, the higher prevalence of comorbidities 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 women10 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.11-14 These limited reports suggest that cancer patients are at a high risk for acquisition of influenza in both the community and health care 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 population that has received a hematopoietic cell transplant (HCT), in whom this has been studied prospectively,15 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 to 2 weeks in immunocompromised patients, although viral shedding may be prolonged.16 Asymptomatic viral shedding of influenza is uncommon in this setting but can occur with both seasonal and 2009 H1N1 influenza (M.B., unpublished observation, December 2009).

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.17,18 Progression from upper to lower tract disease occurs after a median of 1 week in patients with hematologic malignancies,16 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.17 Influenza pneumonia may be complicated by bacterial or fungal coinfection.16 Therefore, we advocate aggressive diagnostic workup 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.16,18,19 The impacts of corticosteroids on influenza severity and outcome are conflicting, with no randomized trials assessing these effects. Although high-dose steroids seemed to prolong viral shedding in HCT recipients with upper respiratory infection16 and one study in pediatric cancer patients showed a higher rate of progression to lower tract disease,20 another study in HCT recipients suggests that progression to lower respiratory tract disease may be reduced.16 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.

How I treat influenza in patients with hematologic malignancies

Corey Casper,1,5 Janet Englund,6 and Michael Boeckh1,3

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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. (Blood. 2010; 115:1331-1342)
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.21 Ferret models of 2009 H1N1 influenza have not demonstrated viral dissemination into the blood or other organs,22 in contrast to H1N5 avian influenza studies showing RNA detection in blood.23 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.16,19,24-26 One large cohort study demonstrated that seasonal influenza lower respiratory tract disease is independently associated with mortality after hematopoietic cell (HC) transplantation (adjusted hazard ratio, 2.60; 95% confidence interval, 1.40-4.86).26 Influenza-associated death can be caused either directly by influenza viral infection or by infection with secondary concomitant pathogens.16 Whether patients with influenza virus infection also have long-term sequelae, such as restrictive or obstructive airway disease as seen after infection with parainfluenza and respiratory syncytial viruses,27 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.28,29 An initial report in cancer patients suggests that fever and cough occurs in more than 90% of patients infected with 2009 H1N1 influenza, and lower respiratory tract involvement was seen in 27% of patients.30 In immunocompetent patients, gastrointestinal and neurologic symptoms appear to be more prevalent with 2009 H1N1 infection, especially in small children.31 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,32 with polymerase chain reaction (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 cocirculate, as during the 2008/2009 season when different H1N1 strains (oseltamivir-resistant seasonal and oseltamivir-susceptible 2009 H1N1 influenza) were cocirculating.33 Upper respiratory samples are obtained by nasal wash or by a nasopharyngeal swab, with nasal wash being the most sensitive method.34 A BAL is typically performed to evaluate lower respiratory disease in highly immunosuppressed patients as it allows for concurrent testing for concomitant pathogens. All patients with confirmed influenza upper respiratory tract illness 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 after myeloablative conditioning with in vivo or 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 pre-existing conditions, although a recent meta-analysis found an average case fatality rate of 17%, with a range of 0% to 33% among patients infected with seasonal influenza with hematologic malignancies and who received a HCT. Neuraminidase inhibitor therapy appears to be effective when instituted early after onset of symptoms. A preliminary report in patients with hematologic and solid cancers by Redelman-Sidi et al 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 days) and 1 person required intensive care unit care without mechanical ventilation. No deaths were reported in this series of 45 patients, most of whom received oseltamivir (n = 43). 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 had lower respiratory tract influenza disease caused by 2009 H1N1, with 4 patients experiencing respiratory failure and 1 death (C.C., unpublished data, December 2009).

Choice of antiviral

Anti-influenza antiviral agents have not been studied in randomized trials specifically in patients undergoing chemotherapy or after HC transplantation. Antiviral susceptibilities of circulating influenza strains must be continually evaluated, with information available on websites at the US Centers for Disease Control and Prevention (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 (Table 1). Presently, 2 neuraminidase inhibitors (ie, zanamivir and oseltamivir) are licensed for the treatment of influenza. These compounds are licensed for inhaled (zanamivir) and oral (oseltamivir) use, 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 US Centers for Disease Control and Prevention (CDC).

Management of upper and lower respiratory infection

Nonrandomized studies suggest that preemptive therapy with oral or inhaled neuraminidase inhibitors (ie, oseltamivir, zanamivir) is
### Table 1. Antiviral options for treatment of influenza

<table>
<thead>
<tr>
<th>Antiviral agent</th>
<th>2009 H1N1</th>
<th>2008/9 seasonal H1N1</th>
<th>2008/9 seasonal H3N2</th>
<th>Influenza B or C</th>
<th>Susceptibility</th>
<th>Recommended dosing and duration in patients with hematologic malignancies</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>Yes</td>
<td>Treatment: 150 mg PO twice daily for treatment; 75 mg PO once daily for prophylaxis.</td>
<td>Gastrointestinal: greatly reduced if oral drug taken with food; Neurologic (children)</td>
<td>Yes (investigational, phase 1)</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Treatment: 10 mg twice daily (by inhaler); after exposure: 10 mg twice daily (by inhaler); prophylaxis: 10 mg twice daily (by inhaler)</td>
<td>Bronchospasm</td>
<td>Yes (investigational, phase 2)</td>
</tr>
<tr>
<td>Rimantidine (amantidine)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Treatment: 100 mg PO twice daily</td>
<td>Neurologic Gastrointestinal</td>
<td>No</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Not recommended as monotherapy</td>
<td>Not recommended as monotherapy</td>
<td>Not recommended as monotherapy</td>
<td>Not recommended as monotherapy</td>
<td>Treatment: 200-400 mg PO 3× 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>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Treatment: 600 mg IV once daily</td>
<td>Gastrointestinal; Neutropenia</td>
<td>Yes (EUA in the US)</td>
</tr>
</tbody>
</table>

All doses stated are for patients with normal renal function. Dose reductions may be necessary in patients with reduced renal clearance.

PO indicates by mouth; IV, intravenous; and EUA, emergency use authorization (granted by US Food and Drug Administration).

*Authors' recommendation; see “Management of upper and lower respiratory infection” for rationale.

†Dose estimated from published case series.38-40
effective in preventing progression to lower tract disease.\textsuperscript{16,18,20,41-43} Monotherapy appears to be effective in these nonrandomized 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).

**Choice of neuraminidase inhibitors.** If the susceptibility pattern of the circulating strain is not available, an antiviral effective against all influenza strains (ie, zanamivir) or a drug combination should be used until this information is available. For instance, most seasonal H1N1 influenza viruses circulating during 2008 to 2009 were resistant to oseltamivir, and empiric treatment consisting of zanamivir or oseltamivir plus rimantadine was recommended by the CDC. As of mid-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.

**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.\textsuperscript{44,45} The relevance of these studies for highly immunosuppressed patients or with highly virulent strains\textsuperscript{46} 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 graft-versus-host disease 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.\textsuperscript{22} Taken together, these factors may favor using a higher dose in immunosuppressed patients, especially when absorption is uncertain.\textsuperscript{43} 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 fewer than 48 hours,\textsuperscript{44} and there is minimal data concerning treatment of immunosuppressed patients who have had a longer duration of symptoms before treatment. We believe that symptomatic immunocompromised patients with influenza require antiviral therapy regardless of the duration of symptoms before 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{15} and progression to lower tract disease may occur even after 1 week of symptoms.\textsuperscript{16} 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{44} However, longer treatment could be considered in immunosuppressed patients. The median time from diagnosis of upper respiratory tract to lower tract disease is 7 days in HCT recipients.\textsuperscript{16} Thus, a 5-day course may be too short to prevent cases of late progression. Importantly, prolonged shedding frequently occurs in immunosuppressed patients,\textsuperscript{47} and may serve as a source of progression of influenza illness and health care-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.

**Single versus 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 toward less resistance was seen in one relatively small comparative trial.\textsuperscript{48} Recommendations to use combination therapy in 2008 to 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, in vitro and animal synergy data have been used to support the hypothesis that combination therapy may be beneficial.\textsuperscript{49,52} A triple combination of oseltamivir, ribavirin, and amantadine has been shown to inhibit seasonal, oseltamivir-resistant, and 2009 H1N1 influenza strains more efficiently than single drugs or the combination of 2 drugs in vitro.\textsuperscript{53} 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

### Table 2. Treatment strategies for influenza disease at the Seattle Cancer Care Alliance

<table>
<thead>
<tr>
<th>Asymptomatic shedding</th>
<th>First-line treatment</th>
<th>Second-line treatment</th>
<th>Research protocols</th>
</tr>
</thead>
<tbody>
<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 2)</td>
</tr>
<tr>
<td>Lower respiratory tract disease (no respiratory failure)</td>
<td>Oseltamivir (high dose) Consider IV peramivir. Consider combination therapy</td>
<td>Consider IVIG</td>
<td>IV zanamivir (phase 2)</td>
</tr>
<tr>
<td>Lower respiratory tract disease (respiratory failure, mechanical ventilation)</td>
<td>IV peramivir/zanamivir combination therapy</td>
<td>IVIG</td>
<td>None</td>
</tr>
</tbody>
</table>

**Institutions comprising the Seattle Cancer Care Alliance are Fred Hutchinson Cancer Research Center, University of Washington, and Seattle Children’s Hospital. IVIG indicates intravenous immune globulin.**
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 pre-existing neutralizing antibodies in approximately one third of donors and the potential role of immunoglobulin G2 subclass deficiencies. We reserve IVIG for critically ill patients with lower respiratory tract disease and acute lung injury.

**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 (eg, nausea, altered mental status). Peramivir, a novel neuraminidase inhibitor available for intravenous administration, has received an Emergency Use Authorization by the Food and Drug Administration for patients with laboratory-confirmed or untypable but suspected 2009 H1N1 virus infection. Specifically, intravenous peramivir is authorized for patients not responding to either oral or intravenous antiviral therapy, or when drug delivery by a route other than intravenous (eg, enteral oseltamivir or inhaled zanamivir) is dependable or feasible, or if the clinician judges intravenous therapy is appropriate. Pediatric patients for whom an intravenous agent is clinically appropriate for similar reasons may also receive this drug under Emergency Use Authorization, although pharmacokinetics in this age group is not yet known. An intravenous form of zanamivir is undergoing phase 2 evaluation in both immunocompetent and immunosuppressed patients. This drug is available through an emergency use program administered by GlaxoSmithKline.

**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 copathogens. 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 acute respiratory distress syndrome. Clearly, more data are needed to make firm recommendations.

**Delay of transplantation or chemotherapy.** In HC transplantation candidates with active influenza infection, we administer antiviral therapy (Tables 1-2) and delay myeloablative HC transplantation until resolution of symptoms and cessation of shedding, an approach consistent with recent international guidelines. Delay of chemotherapy or nonmyeloablative 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 nonmyeloablative conditioning. 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 HC transplantation must proceed.

**Prevention of influenza**

Three principle strategies exist to prevent the acquisition of influenza: infection control practices, vaccination, and chemoprophylaxis (Table 4).

**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 persons who are sick, isolating or cohorting patients with respiratory symptoms in clinical areas, and strictly enforcing a “no-sick-at-work” policy for health care workers.

**Infection control for influenza in health care settings.** The prevention of influenza in health care settings relies on the early detection of persons 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
part of each patient’s medical record. Staff with any symptoms of clinical care team. Isolation lists are maintained electronically as an isolation area or private rooms until they can be assessed by their symptoms; those who cannot are given a mask and placed in either policy. Attempts are made to reschedule patients with respiratory infections and respiratory etiquette. Between October 1 and April 30 at SCCA, an 11-point symptom survey is administered with alcohol-based hand sanitizer, tissues, and information about clinic or inpatient wards are met with hand hygiene stations, replete institutional infection control. All persons entering the outpatient institution are screened by licensed practical nurses 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 person without a sticker is admitted to areas. Elimination of potential exposures. Early identification of persons 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 1 and April 30 at SCCA, an 11-point symptom survey is administered by licensed practical nurses 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 person 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 4 days; a negative test is sufficient for return to work.

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, and so forth. 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 that is tolerant of

Table 3. Drugs and drug combinations with activity against influenza virus in clinical development or evaluation

<table>
<thead>
<tr>
<th>Drug</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>Biocryst Pharmaceuticals</td>
<td>IV, IM</td>
<td>Phase 3</td>
<td>EUA</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>GlaxoSmithKline</td>
<td>IV</td>
<td>Phase 2</td>
<td>Emergency use program</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>Roche Pharmaceuticals</td>
<td>IV</td>
<td>Phase 1</td>
<td>No</td>
</tr>
<tr>
<td>T-705 (Favipiravir)</td>
<td>Toyama Chemical</td>
<td>Oral</td>
<td>Phase 2 (US),</td>
<td>No</td>
</tr>
<tr>
<td>CS-8958 (R-118958)</td>
<td>Daiichi Sankyo Co, Ltd</td>
<td>Inhaled</td>
<td>Phase 3</td>
<td>No</td>
</tr>
<tr>
<td>Dasabivir</td>
<td>Nexbio Inc</td>
<td>Inhaled</td>
<td>Phase 2</td>
<td>No</td>
</tr>
<tr>
<td>Neuraminidase inhibitor +</td>
<td>Adamas Pharmaceuticals</td>
<td>Oral</td>
<td>Phases 2-3</td>
<td>Licensed drugs (no indication for combination)</td>
</tr>
<tr>
<td>amantidine + ribavirin</td>
<td>In vitro synergistic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>combination targeting viral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>neuraminidase, M2 and depletion of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>intracellular phosphate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>of influenza</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oseltamivir + zanamivir</td>
<td>GlaxoSmithKline Roche</td>
<td>Oral and inhaled</td>
<td>Phases 3-4</td>
<td>Licensed drugs (no indication for combination)</td>
</tr>
<tr>
<td></td>
<td>Pharmaceuticals</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EUA indicates emergency use authorization granted by US Food and Drug Administration; and IM, intramuscular.

Care Alliance has been highly successful in preventing respiratory virus infections among its highly vulnerable cancer patients by adapting the CDC infection control recommendations. As seen in Figure 3, despite a nearly 100-fold increase in influenza cases in the Seattle area during spring of 2009, no corresponding increase in influenza cases among Seattle Cancer Care Alliance (SCCA) patients was seen. The components of our plan include:

Elimination of potential exposures. Early identification of persons 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 1 and April 30 at SCCA, an 11-point symptom survey is administered by licensed practical nurses 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 person 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 4 days; a negative test is sufficient for return to work.

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, and so forth.

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 that is tolerant of

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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hand hygiene</td>
</tr>
<tr>
<td>Patients</td>
<td>++</td>
</tr>
<tr>
<td>Caregivers or family members</td>
<td>++</td>
</tr>
<tr>
<td>Medical staff</td>
<td>++</td>
</tr>
<tr>
<td>Other institutional staff</td>
<td>++</td>
</tr>
</tbody>
</table>

+++ indicates highly likely to be effective (data from randomized trials or high quality cohort data); +++, likely to be effective; +++, possibly effective; and +, unlikely to be effective.
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, an institutional commitment both to educate patients, families, and caregivers about influenza but also to assist with identifying resources for furloughing ill caregivers, and a plan for postexposure prophylaxis of exposed patients and staff.

**Personal protective equipment.** For standard seasonal influenza, most organizations agree with the CDC recommendations for droplet precautions for health care 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 for either 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.

**Vaccination.** Two seasonal influenza vaccines are available: trivalent inactivated virus (TIV; injectable) and live attenuated influenza virus (LAIV; nasal spray). Both are designed to protect against 2 strains of influenza A and 1 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 take more than 6 months. Because the

### Table 5. Summary of recommendations on mask use in caring for patients with 2009 H1N1 influenza

<table>
<thead>
<tr>
<th>Device</th>
<th>CDC73</th>
<th>WHO79/Canada Public Health79/IOM80</th>
<th>SHEA/IDSA/APIC/ACOEM81</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>N95 or PAPR</td>
<td>All health care 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 Canadian Public Health Service)</td>
<td>For bronchoscopy, open suctioning of airway secretions, resuscitation involving emergency intubation or cardiac pulmonary resuscitation, and endotracheal intubation</td>
</tr>
</tbody>
</table>

**CDC indicates Centers for Disease Control and Prevention; WHO, World Health Organization; IOM, Institute of Medicine; SHEA, Society of Healthcare Epidemiologists of America; IDSA, Infectious Diseases Society of America; APIC, Association of Professionals in Infection Control and Epidemiology; and ACOEM, American College of Occupational and Environmental Medicine.**

Figure 3. Aggressive implementation of a novel Infection Control Program at the Seattle Cancer Care Alliance assisted in controlling influenza during the H1N1 pandemic of spring 2009. Influenza A detections in the Puget Sound Area and among SCCA inpatients and outpatients, November 2008 to August 2009.
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.8,9

Vaccination of patients with hematologic malignancies: The ability of patients with hematologic malignancies to generate a protective response after immunization depends on both the patient’s underlying disease and its therapy. In general, patients treated with high doses of systemic corticosteroids or recent HC transplantation are least likely to develop protective antibodies after vaccination. Two reviews summarize the existing data on vaccine efficacy in hematologic malignancy patients,35,79 with immune responses ranging from a low of 19% in adults with multiple myeloma to nearly 100% of general hematopoietic cell transplantation oncology patients. Patients, immediately preceding or in the 6 months after myeloablative conditioning for HC transplantation,80 or those who are within 7 days after receipt of conventional chemotherapy,81,82 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 theoretic 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 theoretic risks from the LAIV and its use could be considered.

Vaccination of health care workers: Vaccination of health care workers is an essential component of protecting vulnerable patients with impaired immunity to influenza. Comprehensive vaccination of health care workers reduces the all-causes mortality of the elderly patients by approximately 40%.83 One report of an influenza outbreak on a bone marrow transplant ward suggested that increased rates of vaccination of health care workers in the subsequent year was associated with markedly reduced number of nosocomial cases of influenza.14 According, health care institutions caring for immunocompromised patients should make 100% staff compliance with influenza vaccination a goal in the control of influenza. Mandatory vaccination of health care workers has been upheld in courts of law and promoted as an ethical imperative.84 Alternatively, a mandatory influenza vaccination declination form, acknowledging the risk posed to vulnerable patients by declining vaccination, can be used.85 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 (Tables 4, 6).

Use of the LAIV in hematologic malignancy patients and staff: LAIV contains strains of influenza that are both cold-adapted (therefore unable to replicate in the lower airways) and have reduced pathogenicity. Although 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-naive children received either vaccine or placebo, and secretions were liberally shared.86 Health care workers administering the vaccine have also been infected.87,88 Recent studies find the LAIV to be more effective than TIV in protecting among children younger than 6 years89 but may be less effective than TIV in adults90 perhaps due to incomplete pre-existing immunity in adults that neutralizes the vaccine strain. Shedding of vaccine strain in healthy children and adults generally lasts 3 to 7 days. This vaccine is not recommended for immunocompromised patients, although safety data in HIV-infected persons and children on maintenance chemotherapy have demonstrated safety.91

More concern about the administration of LAIV to health care workers has emerged recently with the availability of 2009 H1N1 live

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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 mo of chemotherapy‡)</td>
<td></td>
</tr>
<tr>
<td>HCT recipients</td>
<td>Yes (6 mo after transplantation)</td>
<td>No</td>
<td>During shortage of inactivated vaccine, LAIV vaccine may be considered late after hematopoietic cell transplantation &gt; 6 mo after discontinuation of all immunosuppressive agents</td>
</tr>
<tr>
<td>Health care workers</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 d</td>
</tr>
<tr>
<td>Caregivers</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 d</td>
</tr>
<tr>
<td>Visitors</td>
<td>Yes</td>
<td>Yes (second line)</td>
<td></td>
</tr>
</tbody>
</table>

*Contraindications (obtained from package insert): Persons with a history of Guillain-Barré syndrome that occurred after receiving influenza vaccine; persons who have a severe allergy to chicken eggs.
†Contraindications (obtained from package insert): persons younger than 2 or older than 50 years; 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 younger than 5 years 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.
‡Based on authors’ opinion.
Clinical findings include respiratory failure, treatment failures due to drug resistance, and death\textsuperscript{26,61} (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\textsuperscript{23,46} and the questionable absorption in patients with chemotherapy- or graft-versus-host disease-associated malabsorption. Third, our experience shows that aggressive infection control 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, and cytokine responses, and to evaluate RNA detection in blood and other biomarkers that may correlate with disease severity.

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Authorship

Contribution: C.C., J.E., and M.B. researched the topic and wrote the paper.

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Conclusions and future directions

The initial experience with 2009 H1N1 influenza suggests that this virus can cause serious disease in immunosuppressed patients.


How I treat influenza in patients with hematologic malignancies

Corey Casper, Janet Englund and Michael Boeckh

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