Recognizing H1N1 Flu: An In-Depth Look at Its Clinical Characteristics

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The ability to recognize cases of the new H1N1 flu and distinguish these from seasonal influenza and other respiratory illnesses is perhaps the overriding concern of primary care practitioners. Prompt and accurate identification of this entity is the key to both effective management of individual illness and effective public health measures. Here I present pertinent and up-to-date information on the clinical characteristics of H1N1 influenza to help clinicians achieve this goal.

Background. After the large initial outbreak of novel H1N1 influenza in Mexico in March and April 2009, the virus quickly spread to the United States, Canada, and many other countries. The rapid spread—via occult human-to-human transmission between unsuspecting persons—was in part facilitated by air travel, although there were also de novo non–travel-associated cases. Since last spring, the United States has experienced an unprecedented amount of influenza activity, which is largely attributable to the circulation of the H1N1 virus. A recently published document found that the pattern in the United States is similar to patterns seen in selected comparator Southern Hemisphere countries (Argentina, Australia, Chile, New Zealand, and Uruguay) with regard to virological data (including antigenic characteristics), types of at-risk affected populations, socioeconomic impact, and community interventions used.

To better understand the clinical and epidemiological presentation of the illness caused by the new H1N1 virus, it is helpful to place the current outbreak in the context of past outbreaks of "swine flu" or H1N1 infections seen in the 20th century. The H1N1 virus that is causing the current influenza pandemic is a quadruple reassortment influenza A virus that is considered by many experts to be a "fourth-generation descendant of the 1918 virus." An important 2007 analysis of all previous human cases of swine-origin influenza (from 1958 to 2005) described 37 civilian cases; 22 (61%) involved exposure to pigs, and human-to-human transmission was considered possible in 5.

An analysis of 11 cases of sporadic reassortment swine H1N1 or H1N2 influenza reported to the CDC during a more recent period (2005 to 2009) revealed that in only 7 cases had the patients reported exposure to pigs before becoming ill. Although there were no associated fatalities, all patients had cough, 9 patients (82%) had fever, 6 (55%) had headache, and about one-third had diarrhea.

Recent reports indicate that persons older than 50 years appear to be relatively less affected by the current H1N1 virus. This may be because they have some immunity as a result of having been exposed to a similar strain that circulated before 1957, the year of the H2N2 influenza pandemic.

Presentation. H1N1 influenza appears to have an incubation period of 1 to 4 days, with an overall range of 1 to 7 days, although the exact duration is not known and likely variable. The period of viral shedding, during which viral particles may be released, making the patient potentially contagious, extends from 1 day before symptoms develop to about a week after illness onset. Children may shed for even longer periods.

The most common presentation of patients with H1N1 influenza includes the cardinal symptom of fever (temperature usually about 38°C [100.5°F] or higher), along with cough and/or sore throat and/or myalgias. In fact, the syndrome of influenza-like illness (ILI) is defined as "fever with cough [continued]"
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or sore throat." Overall, the signs and symptoms of H1N1 infection and seasonal influenza are similar.\textsuperscript{10} Although it may vary according to many factors, acute onset of cough plus fever has an overall predictive value for laboratory-confirmed influenza of 79\% to 88\%, especially during peak periods of influenza virus circulation.\textsuperscript{11} Bear in mind, however, that clinicians are likely to see a range of scenarios, including patients with afebrile influenza (seasonal or H1N1)—especially in children and the elderly—and, conversely, patients infected with other viral pathogens who present with mild to moderate fever. A wide spectrum of illness may occur, including respiratory arrest and neurological illness (including seizures). Secondary bacterial pneumonia (caused by \textit{Streptococcus pneumoniae} and \textit{Staphylococcus aureus} [both susceptible and methicillin-resistant strains]) with respiratory collapse has been recently reported, especially in children. A high index of suspicion is required to diagnose and treat such bacterial complications of influenza virus infection.\textsuperscript{12,13}

Other symptoms that may be seen in H1N1 influenza include chills, headache, fatigue, and GI symptoms (such as nausea, vomiting, and diarrhea). The presence of GI symptoms is a distinctive feature of H1N1 influenza (as compared with seasonal influenza) and may be seen in elderly patients, infants, and immunocompromised persons. Presenting symptoms such as conjunctivitis would be uncommon for H1N1 or seasonal influenza.

\textbf{Physical examination findings.} Although of limited benefit in the diagnosis of influenza, a physical examination may guide the clinician in determining the following:

- Which relevant organ systems are involved in the clinical illness.
- Whether there are other active underlying or concurrent diseases.
- The general severity of the illness and degree of structural or functional impairment.

All of this information can assist the clinician with triage decisions, such as whether to hospitalize a patient or manage his or her illness on an outpatient basis.

It is important to carefully assess the vital signs and to use such findings as tachypnea, tachycardia, fever, hypothermia, or hypotension to determine the acuteness of the patient's illness. In addition, carefully note the patient's appearance (healthy, chronically ill, or "toxic"); significant respiratory findings (eg, pharyngeal injection/exudate, nasal discharge, evidence of head and neck syndromes [eg, otitis, sinusitis], rales, consolidation, rhonchi, pleural rubs); lymphadenopathy; abdominal findings; and any neurological abnormalities (eg, altered mental status). Signs of disease severity in children can include apnea, cyanosis, lethargy, or irritability.

\textbf{Differential diagnosis.} Because H1N1 disease resembles mild seasonal influenza, the differential diagnosis of H1N1 influenza is similar to that of seasonal influenza. Consider illnesses that are caused by other respiratory pathogens but that have a similar presentation. These include disease caused by:

- Respiratory viruses (influenza viruses, parainfluenza viruses, respiratory syncytial virus, rhinovirus, adenoviruses, human metapneumovirus, non-SARS [severe acute respiratory syndrome] coronaviruses, bocaviruses).
- Atypical bacteria (\textit{Legionella}, \textit{Mycoplasma}, \textit{Chlamydia} species).
- Community-acquired bacteria (\textit{S pneumoniae}, \textit{Haemophilus influenzae}, \textit{Bordetella} pertussis).\textsuperscript{14}

Rarer infections that may also present as ILI include anthrax, SARS, and possibly \textit{A(H5N1)} influenza and \textit{Pneumocystis jiroveci} pneumonia (especially in patients who are immunocompromised).

Further evaluation and management is based on the presence of clinical findings that suggest entities listed in the differential diagnosis.

\textbf{Triage.} Consider for further evaluation those patients who present with elevated temperature (at least 38°C [100.5°F]) and cough or sore throat or even nasal symptoms (coryza, nasal congestion, rhinorrhea) or nonspecific pneumonia and/or sepsis. Many patients who present with an ILI, who report mild symptoms, and who do not have conditions that predispose them to complications may
be monitored—preferably at home—without their coming to a health care facility for evaluation (to reduce the risk of transmission of the infection).

 Patients who have any of the conditions that place them at higher risk for severe disease (Table) but who are clinically stable and so situated that good follow-up is feasible may be empirically treated with antiviral medications—especially if they present within 48 hours of symptom onset.

The most common reasons for admitting patients with H1N1 influenza have been lower respiratory tract infection and dehydration. Vulnerable groups—such as infants, children, pregnant women, the elderly, and immunocompromised persons—may have a lower threshold for being cared for in the hospital setting. However, with patients such as these, one might argue that efforts should be made to keep them in an outpatient setting, where they may be less likely to be exposed to drug-resistant organisms or to experience iatrogenic complications.
Disease progression. Uncomplicated influenza may result in general lethargy or lassitude for weeks after the initial infection; this is often seen in the elderly and has no known pathophysiological mechanisms, although pulmonary function abnormalities may occur for a prolonged duration and could be a factor.\(^\text{16}\)

The novel H1N1 pandemic does appear to have had a disproportionate impact on younger populations. In a recent study that focused on the outbreak in Mexico, almost 87% of deaths and 71% of cases of severe pneumonia occurred in patients between the ages of 5 and 59 years\(^\text{17}\) (in previous influenza epidemics, the respective average rates in this age group were 17% and 32%). Although current recommendations suggest that, for the most part, the groups considered to be at higher risk for H1N1-related complications are comparable to the groups who usually manifest complications related to seasonal influenza, the data suggest that older persons have a lower incidence of H1N1 disease and of associated complications.

From a practical perspective, however, this may be a moot point. The illness and death that will inevitably result from the current H1N1 pandemic in the fall will overlap with illness associated with the 2009-2010 regular influenza season, with its usual morbidity and mortality patterns, in which populations at the extremes of age are disproportionately affected.

Significant complications seen after influenza infection (seasonal or H1N1) include:

- Primary viral pneumonia or mixed viral/bacterial pneumonia.
- Other secondary respiratory tract complications, including head and neck syndromes (sinusitis, otitis media, croup); bronchiolitis; asthma exacerbations; bacterial pneumonia (with secondary causative organisms, such as \textit{S pneumoniae} or group A -hemolytic streptococci); infection with \textit{S aureus} (either susceptible or resistant organisms) or \textit{H influenzae} (generally, clinicians treating community-acquired pneumonia syndromes associated with IILI, regardless of care setting, should consider including anti-influenza viral treatment [neuraminidase inhibitors] in their empiric management strategies [see \textit{H1N1 Influenza: Prevention and Treatment—How and for Whom}]).
- Sepsis, toxic shock syndromes.
- Carditis (either myocarditis or pericarditis).
- Neurological conditions (Guillain-Barr syndrome [GBS], aseptic meningitis, postinfectious encephalopathy, seizures, status epilepticus, myelitis).
- Myositis, rhabdomyolysis.
- Reye syndrome (especially in children who are given aspirin).\(^\text{18}\)

A recent limited case series implied that novel H1N1 infection alone can lead to a primary severe pneumonia.\(^\text{19}\) The authors suggested that clinicians who care for patients with suspected H1N1 influenza in hospital and ICU settings should carefully monitor patients for evidence of rapidly progressive respiratory failure and related complications, including acute respiratory distress syndrome, pulmonary emboli, and circulatory collapse.

Possible future complications to keep in mind. An especially important influenza virulence gene, \textit{PB1-F2}, codes for a protein that results in decreases in viral clearance from the lungs and increased susceptibility to secondary bacterial infections.\(^\text{20}\) To date, this gene has not been found in the H1N1 virus associated with the current outbreak. However, it is important for clinicians to remain vigilant for any future data that indicate that circulating and/or novel influenza strains (such as H1N1) have acquired this \textit{PB1-F2} gene or other virulence factors through mutations and/or viral reassortments. Such a development would be especially significant because of the increased prevalence of drug-resistant bacteria (including drug-resistant \textit{S pneumoniae} and \textit{S aureus}) in the United States and worldwide. Some virologists believe that the increased mortality seen in the 1918 pandemic was caused by the presence of the \textit{PB1-F2} gene in that H1N1 virus, which led to secondary bacterial complications.

Although controversy surrounds the association of the 1976 swine flu vaccine with GBS, recent findings suggest that the risk of GBS in cases of natural influenza is actually fairly high—and may, in fact, be reduced by the use of seasonal influenza vaccine. To extrapolate, this might mean that the vaccine developed to combat the current outbreak could even reduce the risk of GBS—or at least...
Future vaccine development will assuredly incorporate a focus on safety assessment and prevention of vaccine-induced adverse effects, including GBS. In fact, as part of ongoing surveillance efforts, the American Academy of Neurology and the CDC have requested that clinicians—especially neurologists—report new cases of GBS subsequent to H1N1 vaccination, using the Vaccine Adverse Event Reporting System (VAERS).22

Another important concern is that postinfluenza encephalitis and Parkinson disease might develop after even mild infection with the H1N1 virus. Such was the case in the decades following the 1918 pandemic.23 Actually, encephalopathy may occur concurrently with primary H1N1 or seasonal influenza as well as in the few weeks after recovery in the post-infectious period. Post-infectious encephalopathy is thought to be caused by demyelination and vasculopathy related to an autoimmune reaction.24

**Conclusion.** Although H1N1 and seasonal influenza virus infections are similar in presentation and complications, in other ways they are different—particularly in age distribution (H1N1 is more common in children and younger adults) and incidence of symptomatic infections (higher primarily with H1N1).

**References:** REFERENCES:


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