Review

Diagnosis, management and outcomes of adults hospitalized with influenza

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Introduction

It has been estimated that 5–10% of the world’s population are affected by influenza annually, causing 3–5 million severe infections and 250,000–500,000 deaths annually [1]. Pandemics may be associated with a significant increase in the proportion of the population affected and increases in hospitalizations and deaths. In the recent 2009 A/H1N1 pandemic, infection rate up to 20–40% in some populations has been reported; in the United States, 195,000–403,000 persons were hospitalized for severe H1N1 infection, and 8,870–18,300 died by April 2010 [1–3]. Hospitalization due to influenza can occur as a result of severe respiratory tract infections, and a variety of apparently ‘non-infective’ or ‘extra-pulmonary’ complications. Because the clinical presentations in adults are diverse and often complicated, the diagnosis of influenza is frequently missed at time of admission. Optimal management strategies have not been confirmed, as few prospective, controlled studies have been performed in hospitalized patients [4–6].

Influenza is an orthomyxovirus that is typed on the basis of their surface haemagglutinins (HA; H1–16) and neuraminidases (NA; N1–9) [7]. In the past few decades, circulating ‘seasonal’ H1N1, H3N2 and influenza B strains have accounted for most of the human infections. Antigenic drift occurs when there are small changes in individual amino acids of the HA or NA that develop over time and allow these viruses to evade existing host immunity; such antigenic drift accounts for the need to update component viruses in influenza vaccines over time [7]. Alternatively, antigenic shift occurs when an entirely novel HA or NA circulates in the population; this often results in a pandemic, as the world recently experienced with the emergence of the novel A/H1N1 virus in 2009 [8,9]. Sometimes, human infections may occur as a result of zoonotic transmission of avian influenza viruses (for example, H5N1, H7N7 and H9N2) [7]. ‘Seasonal’, ‘pandemic’ and ‘zoonotic’ transmissions of influenza can all result in severe diseases; interplay between virological and host factors may determine such risks.
This article summarizes the information concerning the diagnosis, management and outcomes of adults hospitalized for influenza infections. A literature search was performed using PubMed for English articles published within the past 10 years until January 2011. The keywords input for the search included ‘influenza’, ‘H1N1’, ‘adults’, ‘hospitalization’, ‘pneumonia’, ‘complications’, ‘death’, ‘diagnosis’ and ‘antiviral treatment’. The majority of the literature on hospitalized influenza was focused on patients with influenza A infections; data were more scarce for hospitalized patients with influenza B or C.

**Epidemiology and risk factors for hospitalization**

Hospitalization for influenza typically occurs during the influenza season, although it may occur all-year round, particularly in tropical and subtropical climates, during influenza pandemics or following zoonotic infections [1,10]. In the United States, seasonal influenza is associated with an average of 226,054 (range 157,911–430,960) excess hospitalizations, and 23,670 (range 3,349–48,614) deaths per year [3,11]. Data from tropical and subtropical regions have revealed similar or even greater disease burden [10,12,13]. Established risk factors for hospitalization as the result of seasonal influenza include extremes of age (for example, >65 years), underlying medical and immunocompromised conditions, and pregnancy [1,3,4,11,14]. Although the incidence of infection is highest among children, risks for serious complication, hospitalization and death from seasonal influenza are highest among the elderly [1,3,11,14,15]. In North America, the overall attributable mortality of influenza is estimated to be 13.8/100,000 person-years but is significantly higher among older individuals (132.5/100,000 person-years in those aged >65 years; the risk of influenza-related death is 16–32× higher in persons aged >85 years compared with those aged 65–69 years) [3,15,16]. Among pregnant women, the risk of hospitalization increases from the first to the third trimester (from 2.4–16.3 to 7.4–44.9 hospitalizations per 10,000 woman-months, respectively), and is especially high (6–22×) in those with underlying lung disease, such as asthma [4,17,18]. In addition to host factors, virus type and subtype appears to affect severity of illness, with influenza A/H3N2 virus associated with higher rates of hospitalizations and deaths among the circulating seasonal strains (by 2.7×) [3,11,15,16].

Influenza infection by novel strains may affect the risk factors for hospitalization. The pandemic caused by the 2009 A/H1N1 virus was associated with increased hospitalization and mortality not only in patients with the usual risk factors but also in those with morbid obesity; certain indigenous ethnic groups were also at risk [2,19–22]. Compared with seasonal influenza, the median age of hospitalized adults was significantly younger (38–46 years) and one-quarter to one-half of patients had no reported coexisting medical conditions; many of these same individuals experienced serious or fatal infections [2,19,23–27]. Furthermore, 2009 A/H1N1 infection was associated with a higher than expected rates of hospitalization and clinical deterioration among pregnant woman, who have accounted for 7–10% of hospitalized patients, 6–9% of ICU patients and 6–10% of fatalities [2,23–26,28–31].

H5N1 avian influenza virus continues to pose serious threats in many parts of the world and causes the most severe form of influenza disease in humans with high fatality (>500 cases reported to the WHO since 2003; over 15 countries were affected, including Indonesia, Egypt, Vietnam, China and Thailand to name a few) [32]. H5N1 infections typically occur in children and younger, healthy adults (median age approximately 18–20 years) [33–36]. In most cases, a history of exposure to sick poultry can be identified [33,35,36]. To conclude, clinicians need to be aware that adults in any age group, with or without classical risk factors, may be hospitalized for severe influenza infection.

**Clinical presentations, complications and outcomes**

Although influenza primarily causes a respiratory tract infection, its clinical presentation is diverse and non-specific, and the diagnosis is frequently masked by the non-pulmonary indications for admission [4,5,23,24,37–44]. Cardinal symptoms, such as fever, may be absent, which can be related to medication use (that is, paracetamol, non-steroidal anti-inflammatory drugs and corticosteroids), immune compromise, debilitation or advanced age [26,38,42]. In contrast to outpatients, upper respiratory symptoms, such as rhinorrhea and sore throat, are reported in less than one-third of hospitalized adults [2,23,24,40,43–45]. Frequently, there is a delay in presentation to the hospital for evaluation (Table 1). In one representative study, only 59% of patients with seasonal influenza presented within 48 h of symptom onset [39]; among patients with severe 2009 A/H1N1 infection, the median delay to hospitalization was about 3 days (range 0–31 days) [2,23,24,26,27,43,45]. Late presentation poses extra challenges for both diagnosis and management (see **Timing of antiviral therapy**).

Influenza-related pulmonary and extra-pulmonary complications

Influenza-related pneumonia can be ‘primary viral’, ‘secondary bacterial’ or ‘mixed viral–bacterial’.
Influenza in hospitalized adults

Table 1. Clinical characteristics, complications and outcomes of adults hospitalized for seasonal or pandemic H1N1 influenza

<table>
<thead>
<tr>
<th></th>
<th>McGeer et al. [39] (n=327)</th>
<th>Murata et al. [40] (n=193)</th>
<th>Babcock et al. [37] (n=754)</th>
<th>Lee et al. [41] (n=207)</th>
<th>Louie et al. [24] (n=744)</th>
<th>Jain et al. [23] (n=150)</th>
<th>Denholm et al. [44] (n=112)</th>
<th>Viasus et al. [43] (n=583)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Influenza virus (%)</strong></td>
<td>A (81), B (19)</td>
<td>A (100), B (10)</td>
<td>A (72), B (28)</td>
<td></td>
<td>pH1N1</td>
<td>pH1N1</td>
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<tr>
<td><strong>Age, years</strong></td>
<td>77 (16–99)</td>
<td>75 ±14</td>
<td>60 (15–99)</td>
<td>70 ±18</td>
<td>38–46</td>
<td>41 (18–86)</td>
<td>42 (15–79)</td>
<td>39 (16–87)</td>
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<td><strong>Comorbidity</strong></td>
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<td><strong>Amy, %</strong></td>
<td>75</td>
<td>&gt;90</td>
<td>81</td>
<td>61–70</td>
<td>72</td>
<td>83</td>
<td>79</td>
<td>54</td>
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<tr>
<td><strong>Cardiovascular, %</strong></td>
<td>42</td>
<td>55</td>
<td>17</td>
<td>30</td>
<td>19</td>
<td>20</td>
<td>–</td>
<td>–</td>
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<tr>
<td><strong>Pulmonary, %</strong></td>
<td>34</td>
<td>52</td>
<td>22</td>
<td>22</td>
<td>37</td>
<td>42</td>
<td>37</td>
<td>29</td>
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<tr>
<td><strong>Onset-to-presentation, days</strong></td>
<td>1.5 (1.0–2.6)</td>
<td>4.4 ±6.7</td>
<td>2.2 ±1.6</td>
<td>(0–31)</td>
<td>(0–18)</td>
<td>(0–21)</td>
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<td><strong>Seasonal influenza</strong></td>
<td>71</td>
<td>76</td>
<td>–</td>
<td>21</td>
<td>–</td>
<td>44</td>
<td>–</td>
<td>12.5</td>
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<td><strong>Methods for diagnosis and case recognition</strong></td>
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<td><strong>Pneumonia, %</strong></td>
<td>22</td>
<td>17</td>
<td>27</td>
<td>35</td>
<td>67</td>
<td>39</td>
<td>45</td>
<td>43</td>
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<td><strong>Secondary bacterial infection, %</strong></td>
<td>9</td>
<td>9</td>
<td>9–13</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>–</td>
<td>8</td>
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<td><strong>Intensive care with or without ventilation, %</strong></td>
<td>16</td>
<td>15</td>
<td>17</td>
<td>5</td>
<td>34</td>
<td>29</td>
<td>27</td>
<td>12</td>
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<tr>
<td><strong>Length of hospitalization, days</strong></td>
<td>6 (1–103)</td>
<td>8.6 ±5.1</td>
<td>–</td>
<td>5 (3–10); 9.0 ±9.8</td>
<td>–</td>
<td>4 (1–43)</td>
<td>4 (3–8)</td>
<td>5 (1–98)</td>
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<tr>
<td><strong>Mortality, %</strong></td>
<td>8.3</td>
<td>5.7</td>
<td>3.4</td>
<td>5.2</td>
<td>14.8</td>
<td>9.3</td>
<td>–</td>
<td>2.2</td>
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<tr>
<td><strong>Antiviral use (%)</strong></td>
<td>NAI (31); M2 (1), none (68)</td>
<td>NAI (8), M2 (27), none (65)</td>
<td>NAI (10), M2 (2), none (88)</td>
<td>NAI (52); M2 (0), none (48)</td>
<td>NAI (81), NAI (79); none (19)</td>
<td>NAI (83); none (21); none (17)</td>
<td>NAI (83); none (7)</td>
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*Published studies with subject numbers >100 are included for presentation. Only patients >17 years old are described. The prospective cohort studies listed are McGeer et al. [39], Lee et al. [37], Louie et al. [24], Jain et al. [23], Denholm et al. [44] and Viasus et al. [43]. The cohort and retrospective studies listed are Murata et al. [40] and Babcock et al. [41], respectively. The percentage of patients with pulmonary infiltrates are 44%, 43%, 46% and 50% in Murata et al. [24], Babcock et al. [23], Jain et al. [37], Lee et al. [37] and babcock et al. [41], respectively. The cohort and retrospective studies listed are Babcock et al. [41] and Denholm et al. [44], respectively. Values are listed either as median (range) or mean ±SD according to data reported in the individual study. Reported outcomes related to antiviral use. EIA, enzyme immunoassay; IF, direct or indirect immunofluorescent antibody staining; M2 inhibitors (adamantanes), amantadine or rimantadine; NAI, neuraminidase inhibitors including oseltamivir and zanamivir; NP, nasopharyngeal; NPA, nasopharyngeal aspirate; N+OP, nasal plus oropharyngeal swabs; RAI, rapid influenza (antigen) tests.

Influenza is increasingly recognized as an important cause of community-acquired pneumonia (CAP) in hospitalized adults worldwide and is linked to >9–22% of all CAP admissions, particularly during seasonal peaks or pandemics [46–48]. Patients who develop primary viral pneumonia more commonly have pre-existing cardiopulmonary diseases or are immunocompromised, and usually present at 3–5 days of symptom onset with fever, dry cough and dyspnea [2,23–25,40,43,45,49]. Upper respiratory symptoms are frequently absent. Chest radiographs may show multifocal patchy or diffuse ground-glass infiltrates or consolidations; sometimes the features can mimic pulmonary oedema (Figure 1) [23,40,45,50]. Depending on a combination of ‘host’ (for example, level of immunosuppression and pre-existing immunity to the infecting strain) and ‘virus’ factors (for example, genetic constellation, virulence and inoculum size), the clinical course can become rapidly progressive, resulting in refractory hypoxaemia and the requirement of intubation and mechanical ventilation [25,26,45,49]. In many cases of H5N1 infection, less frequently in pandemic 2009 H1N1 influenza, and rarely with seasonal influenza strains, acute respiratory distress syndrome (ARDS) and multi-organ failure develop, resulting in high fatality [2,23,25,26,33,35,40,49,51]. Barotrauma may further complicate ARDS and a low tidal volume ventilation strategy is generally advisable [25,26,28,33,40]. The pathogenesis of fulminant disease may involve persistent, uncontrolled viral replication in the lungs (contributed by inefficient adaptive immunity) and activation of proinflammatory cytokine/chemokine responses, which result in excessive inflammation and tissue destruction via multiple direct and indirect mechanisms, as reviewed elsewhere [2,23,33,51–56].

In seasonal and pandemic H1N1 influenza, secondary bacterial infection is evident in approximately 9–13% and 5–15% of all hospitalized cases, respectively (but up to 25–30% in ICU patients) [40,44,45]. The percentage of patients with secondary bacterial infection was 8.3%, 8.6%, 3.4%, 5.2%, 14.8%, 9.3%, 3.4%, 2.2% and 9.3% in McGeer et al. [39], Babcock et al. [41], Lee et al. [37], Jain et al. [23], Denholm et al. [44] and Viasus et al. [43], respectively.
Figure 1. Chest radiographs of patients with pandemic H1N1 and seasonal influenza infections

Pandemic H1N1 influenza (A–D): (A) Viral pneumonia: a healthy 53-year-old male presented with fever, shortness of breath and hemoptysis. His chest radiograph (CXR) at presentation showed bilateral pulmonary infiltrates. (B) Viral pneumonia: a healthy 29-year-old male presented with fever and shortness of breath. His CXR showed a predominant lobar involvement. (C) Viral pneumonia: a healthy 56-year-old female presented with fever and cough. Her CXR showed patchy infiltrates (right upper and lower zones). (D) Mixed bacterial and viral pneumonia: a 57-year-old female who had rheumatoid arthritis presented with fever, cough and bilateral pulmonary infiltrates. She had superimposed infection with Streptococcus pneumoniae. Seasonal influenza (E–I): (E) Viral pneumonia: a healthy 24-year-old male presented with community-acquired pneumonia and was confirmed to have seasonal influenza A infection. His CXR showed right upper and lower lobes infiltrates; no bacterial pathogens were identified. His white cell, lymphocyte and platelet counts were 7.2, 0.6 and 110×10^9 cells/l, respectively. (F) Viral pneumonia: a 70-year-old male who had history of hypertension and stroke presented with community-acquired pneumonia and was confirmed to have influenza A/H3N2 infection. His white cell, lymphocyte and platelet counts were 3.7, 0.5 and 102×10^9 cells/l, respectively. He deteriorated rapidly and died. (G) Viral pneumonia: a 57-year-old female who had rheumatoid arthritis presented with fever, cough and bilateral pulmonary infiltrates. She had superimposed infection with Streptococcus pneumoniae. Seasonal influenza (E–I): (E) Viral pneumonia: a healthy 24-year-old male presented with community-acquired pneumonia and was confirmed to have seasonal influenza A infection. His CXR showed right upper and lower lobes infiltrates; no bacterial pathogens were identified. His white cell, lymphocyte and platelet counts were 7.2, 0.6 and 110×10^9 cells/l, respectively. (F) Viral pneumonia: a 70-year-old male who had history of hypertension and stroke presented with community-acquired pneumonia and was confirmed to have influenza A/H3N2 infection. His white cell, lymphocyte and platelet counts were 3.7, 0.5 and 102×10^9 cells/l, respectively. He deteriorated rapidly and died. (G) Viral pneumonia: a 67-year-old male with underlying lymphoma presented with pneumonia and was confirmed to have influenza B. (H) Viral pneumonia: CXR of the same patient as (G), taken 2 days later showing rapid progression of pneumonia. He deteriorated further and died within a few days. (I) Acute pulmonary oedema: a 47-year-old male who had diabetes, coronary artery disease and renal impairment presented with shortness of breath and was confirmed to have influenza B. His condition was complicated by acute pulmonary oedema and required mechanical ventilation support. His white cell, lymphocyte and platelet counts were 5.3, 0.3 and 107×10^9 cells/l, respectively.
It should be noted that because most of these studies have used databases that did not discriminate among influenza types/subtypes, the degree of risk for these extra-pulmonary complications associated with each virus type/subtypes may warrant further investigation. During influenza infection, endothelial dysfunction, inflammatory cell infiltration, fibrin deposition within atherosclerotic plaques and the production of a proinflammatory, procoagulant state (for example, high interleukin-6, C-reactive protein and platelet reactivity) may lead to thrombosis and plaque rupture [68,70]. Studies have shown that influenza vaccination may reduce risk of cardio- and cerebrovascular events and deaths in the high-risk patients [68,70–73]. Recently, antiviral treatment has been associated with reduced risk of cardiovascular (8.5% versus 21.2%) as well as cerebrovascular events following influenza infection [74,75].

Influenza infection is known to cause neurological complications, such as encephalopathy, encephalitis, seizures, transverse myelitis and Guillain–Barre syndrome (GBS), in addition to increased risks of cerebrovascular events [76,77]. Delirium or altered mental status may occur in up to 3–4% of hospitalized elderly patients. Such influenza encephalopathy is believed to be metabolic or cytokine-mediated, as evidence for viral neuroinvasion is usually lacking; however overt encephalitis has occasionally been reported in young children [38,76]. Influenza infection (not the vaccine) may explain up to 20% of GBS that occur during seasonal peaks [78]. Neurological complications have been reported for pandemic 2009 A/H1N1 and H5N1 infections, but their true incidence requires further study [2,33,77].

Other influenza-associated complications that occur among hospitalized patients include myocarditis, myositis, dehydration, rhabdomyolysis, acute renal failure, coagulopathy, uncontrolled diabetes, syncope and falls, and have been described elsewhere [23,25,26,37,39,49,51].

Mortality, ICU admission and duration of hospitalization

Reports on clinical outcomes of adults hospitalized for seasonal influenza have consistently shown high morbidity and mortality, although older adults with comorbidities are predominantly involved and few received antiviral treatment (Table 1). The rate of ICU admissions has ranged from 5% to 17%, whereas mortality has ranged from 3.4% to 8.3% (>10–12% if untreated) [37,39–42,79]. Available data on influenza B have shown comparable severity and outcomes among hospitalized patients [37,39,64]. Mortality further increases in those with compromised immunity. Among haematopoietic stem cell transplant recipients, for example, mortality may be 25% overall.
and 40% in those with severe pneumonia who did not receive effective antiviral therapy [80,81]. Duration of hospitalization averages 4–8 days (range 1–103 days), tends to increase with patient’s age, and depends on the nature and severity of complications [11,37–41]. Those patients who receive ventilation support may require prolonged periods of hospitalization and rehabilitation [37,39,40,79].

Severe pneumonia and critical illnesses have been common among adults hospitalized with pandemic 2009 A/H1N1 infection, despite their younger age (Table 1). Overall mortality has ranged from 2% to 15%; approximately 9–34% had required ICU-level care and ventilation support and 14–46% of such patients died [2,19,23–28,43–45,49,82–85]. Delayed presentation or treatment (5.5% increase mortality per day delay), increased age, pregnancy, indigenous ethnicity, presence of underlying medical conditions including obesity and corticosteroid use have been associated with critical illnesses and adverse outcomes [19,21,23–27,31,82–86]. For the survivors, prolonged periods of hospitalization and rehabilitation are often required [2,25,26,43,82–84].

Influenza A/H5N1 infection has been associated with the highest rate of ICU admission and mortality [33–36]. Data from a global patient registry suggests that the overall mortality exceeds 56.5%; survival among patients aged >16–34 and ≥35 years is only about 10% and 20%, respectively, in those who did not receive oseltamivir treatment [34].

**Diagnostic challenges**

Clinical diagnosis of influenza in hospitalized adults is unreliable. Among hospitalized patients, the sensitivity and specificity of ‘influenza-like illness’ (ILI; fever >37.8°C or 100°F, cough and/or sore throat) was found to be 21–43% and 86–93%, respectively; its positive predictive value was 23–50% [4,41,42,87]. The diagnosis is further confounded by the underlying conditions, immunosuppression and the development of extra-pulmonary complications; thus, up to half of the cases may go unrecognized [39,41,88]. As such, clinicians should consider influenza as a potential cause or contributor to any hospitalization whenever influenza is circulating in the community (for example, seasonal peaks and pandemics). This can include patients who present with fever and acute respiratory symptoms with or without pneumonia, acute exacerbations of underlying cardio-respiratory conditions, unexplained ‘sepsis’ in the advanced age, and those involved in institutional respiratory illness outbreaks [5,88]. A history of influenza vaccination should not preclude testing in asymptomatic patients as vaccine efficacy is incomplete, especially among the elderly [5]. Furthermore, onset of illness after admission may indicate nosocomial transmission. The approach of active case finding and virological testing in hospitalized patients (for example, in medical wards and ICUs) has been shown to allow timely initiation of antivirals, reduction in antibiotics use and guide proper implementation of isolation precautions [37,46,89–91].

Laboratory diagnosis of influenza is also challenging among hospitalized patients. Commonly used diagnostic assays include rapid antigen tests (RAT), immunofluorescence detection, enzyme immunoassay (EIA), virus culture and reverse transcription PCR (RT-PCR); their respective advantages and limitations are listed in Table 2 [4,5,19,88]. Sensitivity is dependent on the site of specimen collection (that is, nasal/pharyngeal versus tracheal aspirates or bronchoalveolar lavage), collection method (that is, swab versus wash or aspirate), assay type, virus strain involved and the viral load at the time of testing (the viral load may decrease below an assay’s detection limit as time elapses in late presenters) [4,5,19,37,39,64,88]. Sensitivities of RATs are generally quite low, particularly for the 2009 A/H1N1 virus (10–51%); therefore, a negative test result cannot be used to exclude influenza infection and should be interpreted with great caution [2,4,19,24,25,45,88]. False-negative results, even with RT-PCR techniques, can occur with upper respiratory tract samples in patients with pneumonia (up to 19%). In such cases, viral RNA may remain detectable in the lower airway due to the differential viral kinetics at these sites [2,26,51,92]; therefore, sampling of the lower respiratory tract should be considered in cases of suspected influenza pneumonia. Furthermore, approximately 10% of patients with severe 2009 A/H1N1 pneumonia had initial negative test results with lower respiratory tract samples and repeated testing may be necessary [19].

Viral RNA detection using nucleic acid amplification methods (for example, RT-PCR) is currently considered the ‘gold standard’ [4,5,19,88,91]. Due to its high sensitivity, it allows virus detection in later-presenting patients and use of wider range of specimen types among hospitalized patients [4,5,19,45,64,88]. Newer multiplex PCR techniques may further allow differentiation of influenza A subtypes and simultaneous detection of multiple respiratory viruses, which may have important treatment implications (for example, H3, considered oseltamivir-susceptible and the 2007/2008 seasonal H1 strain, considered oseltamivir-resistant) and provide guidance for proper patient cohorting [4,5,88,93,94]. Other possible roles of RT-PCR may include quantitative assessment of treatment response and detection of resistance emergence [19,45,64,93–95]. Main limitations include the
lack of immediate access of these molecular diagnostics in some hospitals, and that viable viruses cannot be distinguished from non-viable viruses.

**Use of antiviral therapy**

Available antivirals that are active against influenza include neuraminidase inhibitors (NAIs; laninamivir, oseltamivir, peramivir and zanamivir), adamantanes (amantadine and rimantadine) and ribavirin [4,5,19,96]. NAIs are generally well-tolerated, but they may have pharmacological limitations relevant to hospitalized patients. Oral agents are difficult to deliver to patients who cannot swallow and in those with hypotension or gastrointestinal dysfunction. Recent studies, however, have shown reasonable absorption of oseltamivir, delivered through a nasogastric tube in critically ill patients [97,98]. Zanamivir and laninamivir are active against most influenza strains, but inhalation delivery is challenging in individuals who are unable to inspire deeply, and may induce bronchospasm in patients with underlying lung diseases (for example, COPD and asthma) [4,5,96]. Limited penetration to lung periphery and limited systemic availability are also of concern when treating severe influenza pneumonia with inhalational drugs [99,100]. Nebulization of the commercially available preparation of zanamivir can lead to ventilator dysfunction and patient death and must not be attempted [101]. Alternative delivery methods and new antivirals, particularly the parenteral agents (for example, intravenous oseltamivir, intravenous peramivir and intravenous zanamivir) are being investigated specifically for hospitalized patients, as discussed in *Parenteral antivirals* [96]. Both oseltamivir and zanamivir are pregnancy category C medications; limited clinical experiences have suggested their tolerability without evident teratogenicity [2,4,5,102,103]. Pregnancy should not be considered a contraindication to NAI treatment as available data suggest the benefit may outweigh the potential risk [2,4,31,102,103].

Clinical studies in hospitalized adults

Clinical studies on antiviral treatment of hospitalized influenza patients are limited. Registration studies of available NAIs involved predominately young, healthy individuals with mild seasonal influenza and showed modest benefits, with illness being shortened by 0.5–1.5 days when initiated within 48 h of onset [4–6]. However, because of differences in clinical

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**Table 2. Summary on available diagnostic assays for seasonal and pandemic influenza infections**

<table>
<thead>
<tr>
<th>Diagnostic assays</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>RAT</td>
<td>Results available within a few minutes</td>
<td>Unable to distinguish influenza A subtypes</td>
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<tr>
<td></td>
<td>Simple specimen collection (nasal/throat swabs)</td>
<td>Low sensitivities (&lt;40–60%); less sensitive for pandemic H1N1 infection</td>
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<td>Most test kits can differentiate influenza A versus B</td>
<td>Negative test result cannot exclude influenza</td>
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<td>Available for use at ‘point-of-care’</td>
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<tr>
<td>Immunofluorescence microscopy</td>
<td>Results available within a few hours</td>
<td>Unable to distinguish influenza A subtypes</td>
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<tr>
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<td>Higher sensitivity than RAT for seasonal ‘flu’ (70–85%)</td>
<td>Less sensitive than culture or PCR</td>
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<td></td>
<td>Able to detect other respiratory viruses simultaneously (for example, RSV, parainfluenza and adenovirus) depending on antibody pool used</td>
<td>Quality specimens containing enough epithelial cells (for example, NPA and flocked swab) affect sensitivity and laboratory expertise required</td>
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<tr>
<td>Virus culture</td>
<td>Higher sensitivity than antigen assays</td>
<td>Less sensitive than PCR (by 7–20%)</td>
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<td></td>
<td>Allows virus subtyping, strain identification and detection of phenotypic resistance to antivirals</td>
<td>Results not immediately available to assist patient care (conventional: 3–10 days; shell-vial: 2–3 days)</td>
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<tr>
<td>Reverse transcription PCR</td>
<td>‘Gold standard’ for diagnosis (highly sensitive/specific)</td>
<td>Not widely available due to cost and technical demands</td>
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<td>Results available within a few hours if done in-house</td>
<td>Unable to distinguish non-viable from viable viruses</td>
</tr>
<tr>
<td></td>
<td>Wide range of specimen types acceptable</td>
<td>‘False-negatives’ may still occur due to differential viral kinetics in the respiratory tract</td>
</tr>
<tr>
<td></td>
<td>May be able to distinguish virus subtypes</td>
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<tr>
<td></td>
<td>Able to detect other respiratory viruses simultaneously using multiplex PCR technique</td>
<td></td>
</tr>
<tr>
<td></td>
<td>May be useful for the detection of genotypic resistance</td>
<td></td>
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</tbody>
</table>

Data from [4,5,19,45,64,88,91–95]. Assays are listed in order of increasing sensitivity. Direct or indirect immunofluorescent antibody staining (IF). Data for pandemic H1N1 infection is limited; available data suggested a lower sensitivity (46–84%). Enzyme immunoassays applied to nasopharyngeal samples may have comparable (but lower) sensitivities than IF for seasonal influenza. Collection of nasopharyngeal aspirates (NPA) or washes requires training and precautions to prevent virus transmission. Nasopharyngeal flocked swabs contain brush-like nylon fibers to improve epithelial cell collection. PCR assays can provide universal detection of influenza A virus by targeting the matrix (M) gene, or subtype-specific virus detection (for example, pandemic H1N1 and seasonal H1N1, H3N2 and H5N1) by targeting the haemagglutinin (HA) gene. Newer multiplex PCR techniques may additionally detect other respiratory viruses (for example, respiratory syncytial virus [RSV] and parainfluenza) that cause influenza-like illnesses. Some reports of pandemic H1N1 pneumonia described detectable virus in the lower respiratory tract (for example, tracheal aspirates) and bronchoalveolar lavage but negative results with upper respiratory tract samples (for example, NPA), which is possibly related to the different levels of viral replication in these sites at the time of testing. Testing a lower tract sample, if available, might be helpful in cases of influenza pneumonia. RAT, rapid antigen tests.
course and viral kinetics, the ambulatory treatment data and paradigms likely do not apply in hospitalized patients [6,4,96].

At time of writing, only four prospective, randomized clinical trials have been completed among hospitalized patients, and only one is published [19,104–107]. The potential role of combination therapy (rimantadine plus investigational nebulized zanamivir versus rimantadine) [104], increased doses of oseltamivir (150 mg twice daily versus 75 mg twice daily) [107] and intravenous therapies (zanamivir or peramivir versus oral agent) [105,106] were examined. Results so far have revealed that hospitalized influenza patients have high virus burden, and that their viral shedding and course of illness are prolonged even with antiviral treatment; resistant virus strain can emerge easily with adamantane monotherapy, and different virus subtypes may show difference in response clinically (for example, influenza A versus B) towards an NAI in this patient group.

Nonetheless, results from several large observational cohort studies have suggested clinical and virological benefits in hospitalized patients who receive antiviral treatment (Table 1) [23,24,37,39,4,44]. For seasonal influenza, antivirals initiated within 1–4 days of illness have been shown to accelerate viral load reduction and shorten duration of viral shedding [64]. Reductions in hospital length-of-stay [38] and risk of death (untreated versus treated 10% versus 3.9%, OR 0.21 [0.06, 0.80] [39]; 6.1% versus 4.3%, OR 0.27 [0.13, 0.53] [37]; 5.0% versus 1.5%, OR 0.13 [0.04, 0.40] [108]) are also reported. The benefits appear greatest among severely immunocompromised patients in preventing pneumonia progression and fatality (30–38% untreated versus 0% treated in two studies) [80,81,109]. Reports concerning 2009 A/H1N1 influenza similarly suggest that timely antiviral treatment is associated with enhanced viral clearance and improved survival among hospitalized adults in general [23,25–27,43,57,65,83,85], as well as pregnant women [29,31] and the immunosuppressed [109]. Moreover, survival benefit has been reported with antiviral treatment in patients with H5N1 infection [33–36,99]. Given these potential benefits and low toxicity of antivirals/NAIs, it has been recommended that treatment be considered in all patients hospitalized for severe influenza, regardless of time from onset, as long as active viral replication are evident [2,4,5,19,64].

Timing of antiviral therapy

The timing of antiviral commencement is an important factor for efficacy and may sometimes limit the increases in viral load [64,110]. In general, treatment started within the first 48 h of illness is associated with the best clinical and virological outcomes, even among the hospitalized patients [23,29,36–38,64]. Indeed, evidence suggests that if antiviral treatment can be initiated as early as the day of illness onset, the benefits would be greatest (for example, lowest subsequent viral loads and shortest duration of illness) [64,111,112]. As such, antiviral treatment should be offered to patients hospitalized for influenza without causing further delay. Given the severity of illness and limitations of available diagnostic assays, empirical antiviral therapy should be considered (especially during seasonal peaks or pandemics when prevalence of influenza infection is high) while awaiting test results, or when reliable assays are not readily available. This approach is analogous to that in the management of bacterial CAP and deserves evaluation [4,19,48,88,89].

Many hospitalized influenza patients, however, do not present with 48 h of onset; but despite their late presentation, active, on-going viral replication (especially among those of advanced age, with medical comorbidities or those immunosuppressed) is often evident [2,4,5,31,64,65,81,82,113]. Available data suggest that antiviral therapy may provide clinical benefit in such patients. For seasonal influenza, antiviral treatment started within 96 h has been associated with improved clinical/virological outcomes compared with no treatment; other studies suggest that treatment may be beneficial even beyond 96 h if viral replication is active [37,39,64,90,109]. In hospitalized patients with 2009 A/H1N1 pneumonia, viral replication is more prolonged, and antiviral treatment initiated within 3–5 days of onset has been shown to produce clinical benefits and improve outcomes [25,31,43,57,110,114]. Likewise survival benefit with antiviral treatment started up to 1 week from onset has been reported in H5N1 infection [34]. Therefore, withholding antiviral treatment in those with severe influenza based on the time elapsed from onset is unadvisable. Well-designed clinical trials are needed to determine when antiviral therapy among hospitalized adults ceases to provide clinical benefit [6].

Dosage and duration of antivirals in hospitalized adults

The optimal dosages and duration of treatment needed in hospitalized patients is widely debated and there are currently very limited data to provide definitive guidance. Although most use the approved dosage (oseltamivir 75 mg twice daily and zanamivir 2 inhalations twice daily), higher dosages of oseltamivir (for example, 150 mg twice daily) and zanamivir have been evaluated in clinical trials and have shown to be well-tolerated [4,5,96,104]. Oseltamivir 150 mg twice daily has been used to treat H5N1 disease and severe 2009 H1N1 pneumonia to overcome the high
viral loads and to achieve higher tissue levels [2,99]. A recent study, which was conducted among predominantly hospitalized paediatric patients in Southeast Asia with severe influenza, however, found no difference in virological and clinical responses with the higher dose therapy as compared with standard dose therapy [107]. Alternatively, as the steady-state concentration of oseltamivir required for optimal viral suppression usually takes approximately 2 days to attain, loading dosing regimens have been proposed recently to rapidly achieve the target drug level within the first day of treatment [115]; whether this translates into more rapid viral clearance requires investigation. Studies on newer intravenous formulations, which immediately deliver high concentrations of active compounds to the bloodstream, may provide further insight into this issue [6,19]. Clinicians should be reminded that dosage adjustment for systemic antivirals are required in patients with renal impairment or those undergoing dialysis to avoid excess drug levels and potential toxicity [4,97]; dosage adjustment is unnecessary for inhalational laninamivir or zanamivir [4,5,96].

Prolonged duration of illness and viral shedding has been documented among hospitalized adults with seasonal influenza and those with 2009 A/H1N1 virus pneumonia, particularly in patients who are immunocompromised [2,19,43,45,51,64,65,109,113,114]. Among these patients, on-going illness despite a standard 5-day treatment course, and/or clinically manifested viral reactivation after its discontinuation have been reported [19,45,109,110,116,117]. Therefore, many experts recommend longer treatment duration, together with careful viral monitoring for response (and resistance) in such patients [2,4,45,99]. Although the most optimal duration of therapy has not been standardized, for patients with 2009 A/H1N1 pneumonia requiring ICU-level care and/or who are immunosuppressed, a minimum of 10 days of therapy has been recommended [2,4,45]. Similarly, a longer duration of treatment for at least 10 days has been recommended for H5N1 diseases [33,99].

Parenteral antivirals
In treating critically ill patients, intravenous antiviral formulations may have advantage over the oral route as high drug concentrations can be delivered immediately and reliably to the blood stream and respiratory tract [96,118]. Also this route of delivery may be useful in cases with viraemia and disseminated infection [119]. Currently, peramivir is approved for use in Japan and South Korea, and was temporarily made available through an emergency use authorization by the US Food and Drug Administration for treating severe 2009 A/H1N1 infection [118]. Clinical experience with this agent remains limited, but preliminary data from placebo-controlled or comparative trials suggest that it is generally well-tolerated and is associated with viral clearance and clinical improvements [105,119,120,121,122]. Adverse events occur at a similar rate as comparator agents in published studies [122]. Published cases reports on intravenous zanamivir have indicated benefit in some seriously ill patients with oseltamivir-resistant (H275Y; see Antiviral resistance) virus infection or as ‘rescue’ therapy [123–127]. At the time of writing, Phase III studies in hospitalized patients are ongoing to provide further safety and efficacy data of these agents [6,96,103,106]. Intravenous oseltamivir, peramivir and zanamivir may be accessible through compassionate use programmes or research studies.

Antiviral resistance
Antiviral resistance is an emerging issue among circulating influenza viruses (‘primary’; Table 3); it may also occur during the course of antiviral prophylaxis or treatment (‘secondary’) [117,128]. In general, all seasonal A/H3N2 and pandemic 2009 A/H1N1 viruses and most clade 1 avian A/H5N1 viruses are resistant to M2 inhibitors due to mutations in one of five amino acids in the M2 gene (typically an S31N mutation), which confers high-level resistance to both amantadine and rimantadine [2,5,33,96,117]. Seasonal A/H3N2, pandemic 2009 A/H1H1, H5N1 and influenza B viruses are generally susceptible to

<table>
<thead>
<tr>
<th>Virus</th>
<th>M2 resistance</th>
<th>NAI resistance</th>
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<tbody>
<tr>
<td>Seasonal A/H1N1</td>
<td>Rare</td>
<td>100% (NA mutation H275Y)*</td>
</tr>
<tr>
<td>Pandemic A/H1N1</td>
<td>99.7% (M2 mutation S31N)</td>
<td>Rare</td>
</tr>
<tr>
<td>Seasonal A/H3N2</td>
<td>~100% (M2 mutation S31N)</td>
<td>Rare</td>
</tr>
<tr>
<td>A/H5N1 clade 1</td>
<td>~100% (M2 mutation S31N)</td>
<td>Rare</td>
</tr>
<tr>
<td>A/H5N1 clade 2.1</td>
<td>80%</td>
<td>Rare</td>
</tr>
<tr>
<td>A/H5N1 clade 2.2</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>A/H5N1 clade 2.3</td>
<td>Rare</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Adapted with permission from [19]. *Resistance emerged during the 2007–2008 influenza season; resistance was previously rarely discovered [117]. NA, neuraminidase.
N Lee & MG Ison

Nosocomial transmission and infection control

Nosocomial influenza transmission and issues related to infection control have been reviewed elsewhere and are updated regularly by health authorities [5,19,67,143]. Nosocomial influenza transmission is under-recognized/reported and multiple sources might exist (for example, patients, healthcare workers and visitors); in one report, 17% of influenza infections diagnosed was believed to be hospital-acquired [90,129,135,143,144]. For influenza virus, the predominant mode of spread is via droplets and close contact; thus, use of face masks (for healthcare workers and for symptomatic patients as 'source control') and adequate hand hygiene practices (using soap and water or alcohol-based hand-rub) are likely effective measures [19,67,143,145,146]. During routine patient care, N-95 respirators seem to offer little advantage over properly worn surgical masks [67,146–148]. However, recent evidence suggests that influenza can sometimes transmit via the airborne route in the healthcare setting [66,67,143,149]. Thus during the performance of aerosol-generating procedures (for example, resuscitation, intubation, bronchoscopy, sputum suction and use of high-flow oxygen therapy and bi-level positive pressure airway pressure ventilation), most experts would recommend the use of N-95 respirators, in addition to standard precautions and patient management in single rooms with adequate ventilation [66,67,146,150]. In hospitalized patients with either seasonal or 2009 A/H1N1 influenza infection, prolonged viral shedding is common, particularly among elderly patients, the immunocompromised and in cases diagnosed with pneumonia [2,19,45,51,64,65,113,114,151]. Therefore, a longer period of isolation precaution has been recommended in such patients (for example, for a minimum of 7 days and until symptom resolution), and the total duration determined by various host factors, symptoms and use of antiviral treatment [67,146]. This is particularly important when managing immunosuppressed patients because of the higher risk of emergence of drug-resistant viruses [67,128]. Other aspects on healthcare worker protection including annual influenza vaccination have been reviewed elsewhere [4,5,19,143,152,153].

Conclusions

Adults hospitalized with seasonal or pandemic 2009 H1N1 influenza have high morbidity and mortality. Diagnosis can be challenging and a high index of suspicion is always required. Available evidence suggests better clinical and virological outcomes with antiviral treatment, thus antivirals should be considered in all hospitalized patients, including those who present beyond 48 h of onset. Controlled studies are urgently needed to address issues on efficacy, timing, dosage and duration of antiviral regimes in hospitalized patients. Antiviral resistance should be carefully monitored. Potential outcome measures for studies in this unique population remain controversial [6], but clear pathways to approval of new antivirals and combinations are needed.

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