Complications of seasonal and pandemic influenza

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Influenza is a seasonal viral infection associated with significant morbidity and mortality. In 2009, a novel H1N1 influenza A virus emerged and has been classified as a pandemic. In contrast to seasonal influenza, severe disease from pandemic H1N1 seems concentrated in older children and young adults, with almost no cases reported in patients older than 60 yrs. Although patients with underlying cardiopulmonary disease remain at risk, most complications have occurred among previously healthy individuals, with obesity and respiratory disease as the strongest risk factors. Pulmonary complications are common. Primary influenza pneumonia occurs most commonly in adults and may progress rapidly to acute lung injury requiring mechanical ventilation. Secondary bacterial infection is more common in children. *Staphylococcus aureus*, including methicillin-resistant strains, is an important cause of secondary bacterial pneumonia with a high mortality rate. Treatment of pneumonia should include empirical coverage for this pathogen. Neuromuscular and cardiac complications are unusual but may occur. (Crit Care Med 2010; 38[Suppl.]:S000–S000)

KEY WORDS: influenza; complications; pneumonia; pandemic; H1N1

Influenza occurs in seasonal epidemics. Uncomplicated influenza typically presents with the abrupt onset of fever, malaise, myalgia, headache, and dry cough. Respiratory tract manifestations can include tracheitis, bronchitis, and pneumonia (1). Historically, complications are generally limited to patients at the extremes of age (<6 mos or >65 yrs) and those with comorbid medical illness. Influenza is estimated to cause 36,000 deaths and >200,000 hospitalizations annually in the US (2, 3), mostly from secondary pulmonary and cardiovascular disease. In recent years, most severe disease and 80% of influenza deaths have been attributable to H3N2 strains of influenza A (3).

In the spring of 2009, a novel H1N1 influenza A virus appeared in Mexico. This virus, a descendant of the 1918 pandemic strain (4), is sufficiently different from previously circulating viruses to qualify as an antigenic shift, and its resultant spread around the globe has been classified as a pandemic. In contrast to seasonal H1N1 viruses, the 2009 pandemic H1N1 (also called pH1N1, novel H1N1, S-OIV, or swine flu) disproportionately affects children and young adults, and the presentation is often severe. Critical illness has been rare among patients older than 60 yrs, and hospitalized patients often do not have predisposing chronic illness. To date there have been 300,000 confirmed cases and 3917 deaths, or a case-fatality rate of 1.3% (5). If undiagnosed cases were included, the overall case-fatality rate would probably be much lower, perhaps as low as 0.1% (6). By comparison, the 1918 pandemic is estimated to have had a case-fatality rate of >2.5%. This review focuses on the complications of pH1N1 infection as they have been described to date. Because pandemic viruses have potential to evolve with widespread infection, we review complications from seasonal influenza, as well as past pandemics.

MATERIALS AND METHODS

Epidemiology

In both seasonal and pH1N1 influenza, complications are not evenly distributed across the population. During seasonal epidemics, patients at the extremes of age are at highest risk for hospitalization and mortality. Patients with chronic medical conditions, such as heart disease, lung disease, diabetes, renal disease, rheumatologic disease, dementia, and stroke, are also at high risk for influenza complications, regardless of age (7, 8). Older patients with multiple comorbidities are particularly vulnerable (9).

The epidemiology of pH1N1 varies from seasonal influenza in two ways. First, the age distribution for complications is weighted toward older children and young adults, with few cases among the elderly. Second, severe cases among children are mostly attributable to secondary bacterial infections, predominantly in children with comorbidities, whereas adults seem to have primary viral pneumonia and ARDS, often without preexisting illness. The most common risk factor in adults appears to be obesity.

As of August 8, 2009, 36 pediatric deaths from pH1N1 had been reported, only seven of which occurred in children younger than 5 yrs (10). Compared to previous influenza seasons, children hospitalized with H1N1 were more likely to have underlying medical conditions (67% vs. 35% to 55% in past years), primarily neurodevelopmental. Almost half the children had laboratory-confirmed bacterial coinfections, including all those older than age 5 yrs without any high-risk conditions.

Initial reports of pH1N1 in adults from Mexico, US, Canada, Spain, and Australia all are similar. Complications are rare among adults aged older than 60 yrs who appear to have immunity from influenza strains that circulated before 1950. Tests of stored serum reveal that high titers of cross-reactive neutralizing antibodies against pH1N1 are common among patients born before 1930 but almost never appear in patients born after 1980 (11). More than 80% of the 100 deaths in Mexico occurred in patients between the ages of 15 and 59 yrs (12).

The other striking feature is the severity of respiratory illness in previously healthy, relatively young individuals. Several large case series have been reported from the US, Spain, Canada, Mexico, and Australia (Table 1) (13–17). Of 1047 patients admitted to intensive care, 186 (18%) died. Only one-third had any

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Table 1. Demographic characteristics of 1047 patients admitted to intensive care for 2009 pandemic H1N1 infections in five countries

Country	US	Spain	Canada	Mexico	Australia/ New Zealand	Total	%
Number admitted to ICU	67	32	168	58	722	1047	
Age, mean	29	40	32	42	40	38	
Female, %	NR	27	67	55	52		50
Obesity BMI >30*	NR	10	56	21	172	259/859	30
Morbid obesity BMI >40	NR	4	NR	8	NR	12/90	13
Comorbid illness							
Asthma/COPD	19	9	54	4	231	317/1032	31
Renal insufficiency	NR	1	11	4	NR	16/258	6
Diabetes	NR	1	35	10	112	158/958	16
Pregnancy	6	2	13	1	66	88/1047	8
Immune suppression	12	NR	33	2		47/293	16
Congestive heart failure	NR	1	12	1	74	88/961	9
Neurologic disease	12	1	26	1	NR	40/325	12
No major comorbid conditions	22	15	117	37	495	664/1012	66

NR, not reported; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; BMI, body mass index.

major comorbid conditions. The most commonly reported comorbidities were obesity (30%), asthma/chronic obstructive pulmonary disease (COPD) (31%), and pregnancy (8%). Among patients who died, however, more than three-quarters had a comorbid illness (16).

Other groups at risk for influenza complications include those who are pregnant or immunosuppressed. Changes in immune function or cardiovascular and pulmonary physiology attributable to pregnancy pose a special risk for complicated influenza infection (18), especially in the third trimester (19). As a result, pregnant women have been four-times more likely to be admitted to hospital and had higher-than-expected rates of death attributable to pH1N1. Of the first 34 pregnant patients reported to the Centers for Disease Control and Prevention, 11 were hospitalized (three to intensive care) and one died (20). In addition, six of the first 45 deaths in the US were pregnant women, with four in their third trimester. Most were previously healthy and all had primary viral pneumonia followed by ARDS, without evidence of bacterial superinfection.

Immunocompromised patients, including those who had undergone solid organ transplantation (particularly lung), bone marrow transplantation, and who had cancer, are at higher risk for complicated seasonal influenza and death (21). Organ transplant recipients face the highest risk from influenza, with two-thirds demonstrating either viral pneumonia or secondary bacterial pneumonia, with a related 50% mortality rate (22). In addition, influenza frequently triggers allograft rejection (23). Among adults and children infected with human immunodeficiency virus, the rate and duration of hospitalization appear to be increased, as is mortality (24–28). No reports of complicated pH1N1 infection among transplant recipients or human immunodeficiency virus-infected patients have been published to date.

Pulmonary Complications

The most frequent serious complications of influenza are pulmonary and include primary viral pneumonia, secondary bacterial pneumonia, pneumonia attributable to unusual pathogens, and exacerbations of chronic underlying pulmonary diseases such as COPD and asthma.

Primary Influenza Pneumonia

The influenza pandemic of 1918 predated the isolation of influenza A virus. Thus, controversy existed as to whether pneumonia could result solely from primary viral infection or if it was always attributable to bacterial superinfection. During that pandemic, two clinical syndromes emerged: (1) an acute bronchopneumonia, characterized by necrosis, hemorrhage, edema, and vasculitis, associated with heavy growth of bacteria on sputum samples and autopsied lung tissue; (2) ARDS (29) associated with the rapid onset of cyanosis, delirium, incontinence, and lungs filled with frothy blood-tinged sputum, likely attributable to primary viral pneumonia (30). Confirmation of primary viral pneumonia came in 1958 to 1959, when patients who died of viral pneumonia exhibited pathologic features identical to descriptions of patients who died of the ARDS-like syndrome associated with influenza pneumonia in 1918 (31). Findings included necrotizing bronchitis, hyaline membranes, intra-alveolar hemorrhage and edema, and interstitial inflammation (32).

Thus far, among patients who have complicated pH1N1, both syndromes are again present. Adults appear to manifest severe primary viral pneumonia, often requiring advanced ventilatory strategies; children have higher rates of bacterial coinfection.

Early reports of American cases of pH1N1 indicated that most patients had relatively mild disease. Among those with severe disease, the manifestations were predominantly respiratory failure with ARDS-like features and a prolonged course (33). The sickest patients described to date were those referred to a Michigan hospital that specializes in advanced ventilatory strategies and extracorporeal membrane oxygenation for severe ARDS (34). Among these 10 patients, all had primary viral pneumonia with no evidence of bacterial coinfection, manifested by extensive bilateral multilobar infiltrates suggestive of ARDS. All cases had not responded to conventional ventilation and required high-frequency oscillation or bilevel ventilation, and two cases were treated with venovenous extracorporeal membrane oxygenation. Nine had multi-organ failure and shock requiring use of vasopressors. Pulmonary embolism complicated half the patients' courses, six had acute renal failure requiring continuous renal replacement, and three patients died. Pathologic specimens from two revealed hemorrhagic viral pneumonitis, diffuse alveolar damage, interstitial inflammation, and pulmonary emboli.

Four other studies describing critically ill patients with H1N1 have been published and describe the experiences in Mexico, Spain, Canada, and Australia (13–16); all show similar findings and are summarized in Table 2.

Fewer data are available describing children with complicated pH1N1 infections. However, it appears from small case series that children admitted with complicated pH1N1 have higher rates of bacterial coinfection than adults, including otitis media, respiratory tract infections, appendicitis, and cellulitis (35). Compared to children with seasonal influenza, critically ill children with pH1N1 have had a higher rate of shock and a more fulminant course (36).

Studies of one pH1N1 strain (CA-04) *in vitro* and *in vivo* offer insight into the virus virulence (37). Although sequence analyses do not reveal any of the markers associated with high pathogenicity in avian or mammalian species, and titers of virus grown in primary human airway epithelial cells with CA-04 are similar to those for contemporary H1N1 viruses, the 50% lethal dose in mice is much lower for the pandemic strain. In addition, CA-04 viral antigen can still be detected in the lungs at day 6, whereas other influenza strains are rarely detected that late. CA-04 induces a strong proinflammatory response with increased production of IL-10, interferon-γ, and IL-4. Ferrets and macaques infected with CA-04 demonstrate severe bronchopneumonia with inflammatory alveolar infiltrates and presence of viral antigen. Interestingly, CA-04, which appears to be of swine origin, causes asymptomatic infection in pigs.

Table 2. Experiences with critically ill patients in five countries

Study Site	Michigan	Spain	Canada	Mexico	Australia	Combined N/D	% or Weighted Average
Total patients	10	32	168	58	722	990	
APACHE II	NR	13.8	19.7	20.1	NR		18.3
SOFA	NR	7.1	6.8	9	NR		7.1
Death	3	8	29	24	103	167/876	19%
Vasopressors	9	20	55	34	176	294/766	38%
Renal replacement therapy	6	7	NR	NR	27	40/764	5%
VAP	0	3	41	4		48/268	18%
Ventilator	10	24	136	54	456	680/974	70%
Prone	NR	8	5	4		17/258	7%
Nitrous oxide	NR	NR	23	0		23/226	10%
Oscillator	10	NR	20	1		31/236	13%
ECMO	2	0	7	0	53	62/974	6%
Pulmonary embolism	5	1	1	NR	NR	7/210	3%

VAP, ventilator-associated pneumonia; ECMO, extracorporeal membrane oxygenation; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment.

Secondary Bacterial Pneumonia

Bacterial pneumonia complicating influenza infection was reported during the 1918 pandemic, and during multiple subsequent epidemic and interepidemic periods (29, 32, 38, 39). Utilizing review of epidemiologic data, physician accounts, autopsy reports, and examination of re-cut existing pathologic specimens from the 1918 pandemic, several recent reports argue that bacterial superinfection was the etiology of the distinct and fulminant clinical course resulting in the majority of deaths (40, 41).

The clinical presentation of bacterial pneumonia after seasonal influenza mimics community-acquired pneumonia. Patients typically have a history of influenza infection with near resolution of symptoms, followed-up 4 to 14 days later by a recurrence of fever, dyspnea, productive cough, and consolidation on chest radiographs (42). Leukocytosis with a left shift, prolonged duration of fever, and elevated erythrocyte sedimentation rate are more likely in patients with bacterial superinfection (43). Isolates from sputum samples commonly include *Streptococcus pneumoniae, S. aureus*, *Haemophilus influenzae*, and other Gram-negative rods (44).

Secondary bacterial pneumonia caused by *S. aureus* was first described during the 1918 pandemic. The striking features were a particularly fulminant clinical course, an unusual cyanosis described as "cherry-red indigo-blue," dirty salmon–pink purulent sputum, leukopenia, multiple microabscesses on autopsy, and a near-universal fatality in an era before antibiotics (45). Subsequent reports have confirmed an increased incidence of *S. aureus* pneumonia during the Hong Kong epidemic of 1968 to 1969 (44). *S. aureus* toxic shock syndrome arising from the respiratory tract during influenza infection has also been described (46). In recent flu seasons (47, 48), severe secondary pneumonia caused by methicillin-resistant *S. aureus* has emerged, with 85% of isolates carrying genes for Panton-Valentine leukocidin and an associated mortality of 33%.

Available data from pH1N1 cases indicates that adults and children have different rates of bacterial coinfection. Among adults, clinically evident bacterial coinfections have been rare; however, histologic specimens of lung tissue from 74 patients who died of pH1N1 revealed bacterial coinfections in 22 (29%) (49). The most common pathogen was *S. pneumoniae* (10 cases), followed by *S. aureus* (seven cases), *Streptococcus pyogenes* (six cases), *Streptococcus mitis* (two cases), and *H. influenzae* (one case). In two small case series of critically ill patients from Mexico and Spain (14, 50), a single patient was determined to have coinfection with *S. pneumoniae* at presentation, although 9% to 20% of cases were complicated by ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*, *Acinetobacter baumannii,* methicillin-resistant *S. aureus, Achromobacter xylosoxidans*, and *Escherichia coli*. Among pediatric deaths from pH1N1 in the US, culture-confirmed bacterial coinfection was found in 43% of children. Bacterial coinfections were caused by *S. aureus*, with more than half caused by methicillin-resistant strains, as well as *S. pneumoniae, S. pyogenes*, and *Streptococcus constellatus* (*S. milleri* group) (10).

The mechanisms by which bacteria act synergistically with influenza virus include increased binding and invasion of bacteria, increased viral replication, and modification of the host inflammatory response. Certain *S. aureus* strains have been shown to produce a protease that directly activates influenza virus hemagglutinin, whereas other bacteria activate plasminogen that promotes the replication of the virus. Increased proteases in inflamed host tissues lead to increased activation of influenza, although cleavage of hemagglutinin (51). In turn, influenza virus causes damage to the epithelial layer of the upper and lower airways, leading to increased exposure of the binding sites necessary for adherence of pneumococcus (52).

Pulmonary Superinfection With Unusual Pathogens

During inter-pandemic years, superinfection with atypical and fungal organisms also occurs among patients with documented influenza. Infection with *Chlamydia pneumoniae* was found to be the third most common isolate after pneumococcus and *H. influenzae* in a small Japanese study (53). Simultaneous infection with *Legionella pneumophila* occurred at a low level in one small retrospective study, whereas *Mycoplasma pneumoniae* coinfection appears to be uncommon, suggesting a possible antagonistic effect of these two organisms (54). Secondary invasive *Aspergillus* has been reported and carries a very high mortality rate (55, 56). Noninfectious mimics incited by influenza also have been reported, including bronchiolitis obliterans with organizing pneumonia (57) and usual interstitial pneumonia (58).

Exacerbations of Chronic Lung Diseases

Viral infections are a major precipitant of exacerbations of asthma and COPD. In studies of asthmatic children and adults, approximately 80% of subjective asthma exacerbations were associated with an upper respiratory tract infection (59, 60). Rhinoviruses and coronaviruses accounted for the majority of pathogens, although influenza, respiratory syncytial virus, parainfluenza, and *Chlamydia* also comprised a small proportion. Among adults with COPD, respiratory viruses were isolated from 56% of those with acute exacerbations, but from only 19% of patients with stable chronic COPD (61). The mechanisms by which respiratory viruses induce exacerbations of chronic respiratory diseases are incompletely understood but are likely multifactorial and related to inflammatory mediators including interleukins, cytokines, and modifications in the ratio of T-cell subsets leading to increased sensitivity to other allergens (62, 63). Available data from pH1N1 cases reveal that asthma and COPD were two of the main comorbidities reported among patients who became critically ill (6, 14, 31, 32).

Extrapulmonary Complications

In addition to its respiratory effects, the virus can exert direct and indirect effects on other body systems. Direct cardiac complications are uncommon, but both pericarditis and myocarditis have been noted. In one pro-

spective study, 50% of adult flu patients without cardiac symptoms had abnormal electrocardiographic findings at presentation (64). Most resolved by 28 days, and no patients had muscle damage or reduced ejection fractions. Elevation of creatine phosphokinase is also common, but this appears to be primarily of skeletal muscle origin, because elevated troponin is rare (65). No cardiac complications have been reported in patients with H1N1, although we have seen one case of a previously healthy 24-yr-old woman who presented with myopericarditis in the setting of H1N1 infection.

The indirect effects of influenza on underlying cardiac problems, such as congestive heart failure and ischemic heart disease, appear to play a more important role in cardiac morbidity. Strong observational data support the link between influenza infection and acute myocardial infarction and death (66). Although the mechanism is not definitely elucidated, influenza is a potent inducer of proinflammatory cytokines (e.g., tumor necrosis factor-α and IL-6), (67), and inflammation is now considered an important component of atherosclerotic disease (68).

Myositis and rhabdomyolysis rarely have been reported with seasonal influenza A and B (69). In one study, >50% of patients hospitalized with influenza A were noted to have elevations of creatine phosphokinase. Clinical severity varies but can include renal failure and problems with ambulation involving proximal leg muscles. Symptoms generally resolve in 4 to 6 wks. Elevations of creatine phosphokinase also have been common among patients hospitalized with H1N1. Of those in the intensive ICU, two-thirds had abnormal creatine phosphokinase, with a median level of 999 (range, 51–6572) (34). Acute renal failure, probably unrelated to the elevated creatine phosphokinase, has also been common among patients requiring intensive care, with seven of 20 requiring continuous renal replacement therapy (6, 33, 34).

Neurologic complications of seasonal influenza include encephalopathy (Reye syndrome), encephalomyelitis, transverse myelitis, aseptic meningitis, focal neurologic disorders, and Guillain–Barré syndrome; these occur mostly in children (70). The pathogenesis is unclear but may include direct viral invasion and development of antigen/antibody complexes or overproduction of systemic cytokines. Diagnosis is based on clinical and laboratory findings. Lumbar puncture is often normal (71) and viral particles are rarely detected (72). The electroencephalogram is usually abnormal. Computed tomography/magnetic resonance imaging scanning should be performed in cases of focal or severe neurologic symptoms; abnormalities predict adverse outcomes (70). In 1999, an outbreak of encephalopathy/encephalitis was associated with influenza A in Japan. Presentation and outcomes were described for 147 children, 82% of whom were younger than 5 yrs, and almost none were older than 10 yrs; 85% had no underlying disease (73). All had altered levels of consciousness and 80% had seizures. Multiorgan failure was common and 41 patients died. Thrombocytopenia (<50,000) and elevated aspartate aminotransferase (>1000 U/L) were associated with mortality rates of 83% and 74%, respectively.

Neurologic complications also have been reported with H1N1 in four children aged 7 to 17 yrs in Dallas, Texas (74). All had altered mental status, three had encephalopathy, and three had seizures. Electroencephalography was abnormal in the three who were tested. Cerebrospinal fluid influenza real-time reverse-transcription polymerase chain reaction was negative in all cases. Computed tomography and magnetic resonance imaging showed only minor abnormalities or none at all. All patients received antiviral therapy and recovered fully by discharge.

Reye syndrome is an acute, noninflammatory encephalopathy characterized by cerebrospinal fluid containing <8 leukocytes/mm^3 or histologic sections of the brain demonstrating cerebral edema without perivascular or meningeal inflammation, associated with either fatty liver or a three-fold elevation of transaminases or serum ammonia (75). A correlation with influenza, usually type B, has existed for several decades, primarily in children younger than 14 yrs, although there have been confirmed adult cases. The incidence has dramatically declined along with aspirin use among children.

Psychiatric complications after influenza infection are considered controversial. In 2007, reports of abnormal behavior and suicide attempts in teenagers receiving oseltamivir prompted the Japanese government to issue a warning to not prescribe the drug to children between 10 and 19 yrs of age (76). Subsequent observational studies by the manufacturer found that neuropsychiatric events were common in influenza patients (1.75-fold the rate in the general population), but that oseltamivir was protective (77). The US Food and Drug Administration advises that persons receiving oseltamivir be monitored closely for abnormal behavior.

DISCUSSION

Management of Complications: Antiviral Medications

Antiviral medication is the mainstay of therapy for seasonal influenza and is recommended in all severe cases of pH1N1. Of the medications available in the US, the pH1N1 and the seasonal H3N2 viruses appear sensitive to oseltamivir and zanamivir, whereas the seasonal H1N1 virus is sensitive to all antivirals except oseltamivir. Influenza viruses are prone to mutate and later in the season resistance may increase, especially if they acquires the resistant neuraminidase gene through re-assortment with co-circulating seasonal H1N1 viruses (37). To date, 28 samples of pH1N1 have proved resistant to oseltamivir, although all remain sensitive to zanamivir.

In studies of healthy adults and children, antiviral medications appear to prevent complications from seasonal influenza if started within 48 hrs (78, 79). There are no randomized trials of antivirals in hospitalized patients, but a prospective observational study of 327 Canadian patients hospitalized with confirmed influenza found that treatment with antiviral therapy was associated with decreased risk of death (odds ratio, 0.21; 95% confidence interval, 0.06–0.80) (80). Those who received therapy >48 hrs into their illness still received some benefit. Other observational studies have found decreased mortality among nursing home (81) and hospitalized patients (82) receiving oseltamivir compared with those who did not.

There are no clinical trials of antiinfluenza medications for either pH1N1 or avian influenza, but oseltamivir and zanamivir appear active against both strains *in vitro* and are recommended for all patients hospitalized with influenza (83). Consequently, most ICU patients have received oseltamivir, so the effect on survival could not be assessed. In Mexico, however, receipt of a neuraminidase inhibitor was associated with survival (odds ratio, 7.4; 95% confidence interval, 1.8–31) (13). Unfortunately, observational studies of avian influenza found that patients treated with oseltamivir and untreated patients have similar mortality rates (84). Based on ferret models, earlier treatment or higher dosing might improve the efficacy of oseltamivir (85). Similar data on humans are not available.

Antibiotics

Secondary bacterial pneumonia should be treated promptly with antibiotics. Because the bacteriology of secondary pneumonia does not differ substantially from those implicated in community-acquired pneumonia, the selection of antibiotic should follow established guidelines for management of community-acquired pneumonia (86), including a third-

generation cephalosporin plus a macrolide, or monotherapy with a quinolone, after sputum and blood samples have been drawn for culture. Because of recent reports of severe methicillin-resistant *S. aureus* pneumonia after influenza infection, clinicians should strongly consider empirical use of vancomycin or other antimicrobial with efficacy against methicillin-resistant *S. aureus* pneumonia, especially if Gram-negative stain, sputum culture, or blood culture results indicate the presence of a Gram-positive organism. Use of daptomycin for treatment of *S. aureus* pneumonia should be avoided because this drug is inhibited by pulmonary surfactant, leading to clinical failure (87).

Antisera

Given that avian influenza has been associated with a 71% to 100% mortality rate despite treatment with oseltamivir in the majority of cases (88), there is renewed interest in novel therapeutic approaches to treat the severe pulmonary complications of influenza. One such possibility is the administration of anti-influenza antibodies in the form of convalescent human plasma from patients recovering from influenza infection. In a meta-analysis of studies performed in the Spanish influenza era (1918–1925), a pooled absolute risk reduction in influenza mortality of 21% was shown, raising the possibility of an alternative virus-specific approach to the treatment of influenza (89).

Statins

The rapid progression of viral pneumonia to ARDS in previously healthy adults suggests that the damage of influenza might be mediated by the body's reaction to the infection, rather than by the virus itself (90). Experimental 1918-like and H5N1 influenza virus infections are associated with elevated levels of proinflammatory cytokines, sometimes referred to as a cytokine storm. Although antiviral therapy, if initiated early enough, might prevent this reaction (91), three classes of drugs with anti-inflammatory properties—statins, peroxisome proliferator-activated receptors-α agonists (fibrates), and peroxisome proliferator-activated receptors-γ agonists (glitazones)—might individually or in combination prevent influenza-associated acute lung injury (90). Observational trials suggest that statins may reduce risk of pneumonia hospitalization (92, 93) or death (94), although these results may be confounded by a "healthy user" effect (95). One small randomized trial (96) in sepsis patients was reported to have demonstrated a 51% reduction in mortality among patients randomized to receive atorvastatin; however, these results have yet to be published in a peer-reviewed journal. At least one large randomized trial of rosuvastatin for ARDS in patients with pH1N1 is scheduled to begin enrolling patients in the fall of 2009.

CONCLUSIONS

Early reports of pH1N1 influenza describe a virus that is more pathogenic than seasonal influenza and that causes severe infection and complications in relatively young, otherwise healthy individuals. Pulmonary complications are most common, including ARDS in adults and secondary bacterial pneumonia in children. Treatment is mostly supportive, although antiviral therapy and antibiotics should be administered. Better understanding of the pathogenesis of pandemic influenza may lead to more effective therapies.

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