Effect of Antiviral Treatment on the Outcome of Secondary Bacterial Pneumonia after Influenza

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Secondary bacterial pneumonia is an important cause of influenza-associated death. Although antibacterial therapy is standard, antiviral therapy has been ignored because viral infections usually resolve by the time bacterial pneumonia presents. In the present study, antiviral compounds were tested in a mouse model of secondary pneumococcal pneumonia after influenza. Treatment with oseltamivir improved survival in mice from 0% to 75%, even when therapy was delayed for up to 5 days after infection with influenza virus. In mice, treatment with rimantadine had no effect on survival. Treatment with ampicillin cleared infection but, in the absence of treatment with oseltamivir, did not improve survival. Pneumonia developed in only 7 of the 22 mice receiving oseltamivir, and subsequent treatment with ampicillin resulted in cure (100% survival). Treatment of the predisposing influenza-virus infection with inhibitors specific for the viral neuraminidase may improve the efficacy of antibiotics and increase survival in persons who are at high risk for complications and mortality during influenza.

The earliest suggestion that viral infections predispose to bacterial diseases has been attributed to Laennec [1], who observed that the prevalence of pneumonia increased after an epidemic of influenza in 1803. This association came into particular focus after the 1918 influenza pandemic, during which an estimated 40–50 million persons died [2], many of them from secondary bacterial pneumonia [3–5]. This catastrophic event was the genesis of clinical and epidemiologic investigations into the interactions between viruses and bacteria, investigations that continue today. In the United States, influenza and pneumonia are currently the seventh leading cause of death [6], accounting for 36,000 excess deaths/year [7]. Despite the availability of an excellent health-care system and effective antimicrobials directed against both infection with influenza virus and bacterial causes of pneumonia, a substantial number of these deaths are due to secondary bacterial pneumonia.

The high mortality exhibited in secondary bacterial pneumonia has created the perception among clinicians that antibiotics alone are not clinically effective in all cases. Before the advent of effective antimicrobials, the case-fatality rate for pneumonia caused by Streptococcus pneumoniae was 30%. After the introduction of penicillin, this rate declined to 5% overall and to 13% in cases complicated by bacteremia [8] (the remarkable consistency of the latter rate since then can be seen in recent large studies, in which the combined case-fatality rate for bacteremic pneumococcal pneumonia was 13.8% [9–12]). In contrast, the case-fatality rate for bacterial pneumonia after influenza did not change with the availability of antimicrobials. Scadding reported 7 deaths in a series of 19 patients with secondary bacterial pneumonia (a case-fatality rate of 37%) during 1936–1937 [13], a finding comparable both to those of the early antibiotic era—when, for example, the case-fatality rate in confirmed cases of influenza was 38% [1, 14–16]—and to those of the modern era, when the case-fatality rate in one study was 50% [17]. Thus, there may be a higher overall rate of death for pneumonia in the setting of combined infection, a rate that has not changed despite improvements in health care and antimicrobial efficacy.
It has been suggested that prevention or treatment of the underlying viral infection might be a better strategy for the reduction of secondary complications from influenza [18, 19]. Vaccination against influenza prevents hospitalizations for pneumonia in elderly adults [20–22], whereas vaccination with only 23-valent pneumococcal vaccine is not effective [23]. In recent years, the efficacy of neuraminidase (NA) inhibitors for the treatment of influenza has been demonstrated in large clinical trials [24, 25]; early treatment with oseltamivir reduced both the development of acute otitis media by 44% in influenza virus–infected children [26] and the occurrence of secondary complications (i.e., otitis media, sinusitis, bronchitis, and pneumonia), as well as antibiotic use, by 50% in healthy adults 18–65 years old [27], and an analysis of prospective data compiled from 10 clinical trials of oseltamivir demonstrated a reduction in both antibiotic use and hospitalization for lower respiratory tract infection [28]. However, such studies have not been powered to directly answer questions about secondary complications, and the people (such as infants, elderly adults, and those with underlying illnesses) who are most susceptible to secondary infections usually have been excluded. Similar results have not been seen with the M2 inhibitors, amantadine and rimantadine [29].

My colleagues and I have previously developed and characterized a mouse model of secondary bacterial pneumonia after influenza [30]. In this model, treatment with oseltamivir reduces mortality due to pneumococcal pneumonia [19]. In the present study, I have examined the efficacy of antiviral and antibacterial compounds in this mouse model of lethal synergism. I hypothesized that combination therapy with both an antiviral and an antibiotic would be an effective treatment strategy for secondary bacterial pneumonia. The resultant data from the present study may aid in understanding the limited efficacy of antibiotics against combined viral-bacterial infections.

MATERIALS AND METHODS

Infectious agents. The Mount Sinai strain of mouse-adapted influenza virus A/Puerto Rico/8/34 (H1N1), hereafter referred to as “PR8”; a mouse-adapted strain of influenza virus A/Fort Monmouth/1/47 (H1N1); and A/Sydney/5/97 (H3N2) were grown in Madin-Darby canine kidney cells from stock from the influenza-virus repository at St. Jude Children’s Research Hospital (Memphis, TN). The delNA mutant of influenza virus A/Charlottesville/31/95 [31] was a gift from Larisa Gubareva (University of Virginia, Charlottesville); respiratory syncytial virus type A (strain Long) was a gift from John Devincenzo (LeBonheur Children’s Medical Center; Memphis, TN); S. pneumoniae D39, an encapsulated type 2 strain, and its unencapsulated derivative, R6T, were gifts from Elaine Tuomanen (St. Jude Children’s Research Hospital).

Mice. Eight-week-old female BALB/cByJ mice (Jackson Laboratory) were used in the present study. All experimental procedures were performed with the mice under general anesthesia, with inhaled isoflurane 2.5% (Baxter Healthcare). Mice used in the present study were cared for in accordance with the guidelines of the Committee on Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, National Research Council), under an approved protocol from the Animal Care and Use Committee of St. Jude Children’s Research Hospital. All work with mice was performed in biosafety level–2 facilities.

Adherence assays. Adherence assays were performed as described elsewhere [20]. In brief, washed A549 cells were overlaid with a suspension (250 μL/well) containing 5 × 10^5 infectious units (TCID50 or pfu) of virus. After a 30-min incubation period at 37°C, monolayers were washed, were overlaid with a suspension (200 μL/well) containing 2 × 10^6 cfu of R6T, and were incubated for 2 h at room temperature. Then monolayers were washed, were detached by use of 0.05% trypsin–EDTA (Life Technologies), and were lysed by use of 0.025% triton X-100 (Sigma Chemicals). Serial dilutions in sterile PBS were plated on tryptic soy agar that had been supplemented with 3% vol/vol sheep erythrocytes, to quantitate the numbers of bacterial cells that were adherent to the monolayers. Controls were treated identically, but without the addition of virus. For experiments with oseltamivir, the prodrug Ro 64-0796 (Roche Products) was added to the virus suspension at a concentration of 10 μmol/L 30 min before incubation with monolayers (the concentration of the active metabolite, oseltamivir carboxylate, was not determined).

Infectious model. Infectious agents were diluted in sterile PBS and were administered intranasally, in a volume of 100 μL (50 μL/nostril), to anesthetized mice held in an upright position. Groups of 6–10 mice were weighed and were monitored, at least daily, for illness and mortality; mice found to be moribund were killed and were considered to have died on that day. Influenza virus was given at a dose of 50 TCID50/mouse, followed, 7 days later, by pneumococcal challenge at a dose of 100 cfu/mouse. For experiments with antiviral compounds, either oseltamivir phosphate oral suspension (Roche Products) or rimantadine hydrochloride (Sigma-Aldrich) was administered, by oral gavage diluted in sterile water, at a dosage of 10 mg/kg/day, divided into 2 daily doses. Ampicillin sodium (Sigma-Aldrich) was administered intraperitoneally in sterile water, at a dosage of 200 mg/kg/day, divided into 2 daily doses. In prophylaxis experiments, drugs were initially administered 4 h before viral infection, and administration continued for 5 days. In delayed-treatment experiments, drugs were initially administered ≥48 h after viral infection, and administration continued for 5 days. To insure that all mice received equal anesthesia during drug-treatment studies that had a staggered drug-administration schedule, all mice were put under anesthesia twice...
daily every day; if no drug dose was due, mice were mock-treated with sterile water.

**Imaging of live mice.** Mice were infected with a strain of pneumococcus D39 that had been transformed with the lux operon (Kevin Francis and Jun Yu; Xenogen) but that otherwise was isogenic to the strain used for other experiments reported here. The mice were then imaged, by use of an IVIS CCD camera (Xenogen), for 20 s twice daily, beginning 4 h after pneumococcal challenge. Total photon emission from selected and defined areas of the images of each mouse was quantified by use of the LivingImage software package (version 2.20T; Xenogen), as described elsewhere [32], and was expressed as relative light units.

**Statistical analysis.** The survival of groups of mice were compared by the Mantel-Cox \( \chi^2 \) test on Kaplan-Meier survival data. Both the relative light units and the time to development of pneumonia of paired groups were compared by Student’s \( t \) test. The numbers of bacteria adherent to monolayers in the groups of infected mice were compared with that in the control group by repeated-measures analysis of variance; \( P < .05 \) was considered to be statistically significant.

**RESULTS**

**Reversal of influenza virus–mediated adherence of pneumococci to A549 cells by inhibition of viral NA.** Influenza virus increases the adherence of bacteria to epithelial cells in vitro [19, 33, 34], in animal models [35–37], and in humans [38, 39]. To examine the effect that antivirals have on this enhancement of adherence, either oseltamivir (an inhibitor specific for influenza-virus NA) or rimantadine (an inhibitor of the ion-channel activity of the M2 protein) was added to virus suspensions during the preincubation step of the adherence assays. Oseltamivir completely reversed the influenza virus–mediated increase in adherence of *S. pneumoniae* to A549 cells, whereas rimantadine had no effect (figure 1). The increases in adherence observed with both influenza virus alone and influenza virus plus rimantadine were statistically significant (\( P < .05 \)), compared with that observed in the control group. The experiments with rimantadine were repeated with A/Sydney/5/97 as the preincubating virus, and similar results were observed. Because oseltamivir has no effect on pneumococci [19] and because an incubation time of 30 min is short for mechanisms involving the replication of influenza virus, it is likely that this inhibition of adherence is due to the enzymatic activity of viral NA. To test this hypothesis, the experiment was repeated with either NA-deficient influenza virus [31] or respiratory syncytial virus, a paramyxovirus that has a similar tropism for the respiratory tract and that naturally lacks NA activity. Neither virus affected pneumococcal adherence (figure 1); therefore, the enhancement of adherence observed in this assay is due to viral NA–specific activity and the decline in adherence observed when oseltamivir is used is specific to the inhibition of this activity. In this assay, inhibition by rimantadine of viral uncoating during fusion has no effect on subsequent bacterial adherence.

**Prevention of the development of secondary bacterial pneumonia by inhibition of viral NA.** In a previous experiment that used a mouse model of viral-bacterial synergism, oseltamivir, an inhibitor specific for influenza-virus NA, reduced mortality due to secondary pneumococcal pneumonia [19]. In the present study, treatment with oseltamivir was compared with treatment with rimantadine, by use of both prophylaxis and delayed-treatment experiments. In the delayed-treatment experiment, none of the control mice (infected with pneumococcus alone) developed pneumonia, and all of them survived (figure 2). On the other hand, all of the mice that were infected with influenza virus and then pneumococcus and that were mock-treated with water (placebo) developed pneumonia (5 of the 6 <72 h after initial challenge), and all of them died (5 of the 6 <96 h after initial challenge). Moreover, only 1 mouse of the 6 that received delayed treatment with oseltamivir developed pneumonia; this mouse died on the sixth day, 36 h after developing pneumonia. In the group that received delayed treatment with rimantadine, however, pneumonia developed in all 6 mice <72 h after initial challenge, and all mice were dead <96 h after initial challenge. There was a statistically significant difference between survival in the groups of mice receiving oseltamivir and that in the groups of mice receiving either placebo or rimantadine (\( P < .05 \)). Rimantadine-delayed treatment had no effect on survival, compared with the placebo group (\( P > .10 \)).

Similar results were observed in the prophylaxis experiment. All of the mice in the control and oseltamivir groups survived, whereas none of the mice in the placebo or rimantadine groups survived. Mice were protected from weight loss by oseltamivir prophylaxis, losing, on average, only 5% of their weight at the time of pneumococcal challenge (hereafter, “starting weight”), compared with an average loss of 25% of starting weight for...
mice receiving placebo. The mice treated with rimantadine experienced less morbidity than did the mice receiving placebo and lost 16.5% of their starting weight. However, all 6 of the rimantadine-treated mice developed pneumonia \(=48\) h after pneumococcal challenge, and all 6 died \(=72\) h after pneumococcal challenge. Because some strains of PR8 possess an S31N mutation in the M2 ion-channel protein that, in a mouse model, confers an intermediate degree of resistance to amantadine (and to rimantadine) [40, 41], both the prophylaxis and delayed-treatment experiments were repeated with mouse-adapted influenza virus A/FM/1/47. This virus does not have mutations in M2 that would predict resistance to rimantadine. The results were identical to those of the experiments with PR8; despite prophylaxis with rimantadine, all of the mice developed pneumonia \(=48\) h after pneumococcal challenge and died \(=96\) h after pneumococcal challenge. Combined antiviral therapy with oseltamivir and rimantadine resulted in less weight loss but did not affect the development of pneumonia or mortality, compared with single treatment with oseltamivir (data not shown).

**Prevention of the development of secondary pneumonia, despite significant delays in therapy with oseltamivir.** In humans, oseltamivir must be administered \(\leq 2\) days after the onset of influenza symptoms to effectively reduce clinical symptoms [42]. Previous experiments in mice that received oseltamivir beginning \(48\) h after infection with influenza virus demonstrated protection from secondary bacterial pneumonia [19] (figure 2) but not from influenza morbidity. To determine the effect of a longer delay in administration, mice were given treatment with oseltamivir for \(5\) days beginning either 2, 3, 5, or 7 days after infection with influenza virus and then were challenged with pneumococcus on day 7. Five of the 6 control mice (which were infected only with pneumococcus) survived, and only 1 of the control mice developed pneumonia (figure 3). All 6 of the mice that received placebo for dual infection developed pneumonia, and none survived. Delayed therapy with oseltamivir when given beginning 2, 3, or 5 days after influenza infection significantly improved survival, compared with the

![Figure 2](https://academic.oup.com/jid/article-abstract/190/3/519/938816)

Figure 2. Effect of antivirals on secondary bacterial pneumonia. Groups of 6 mice were infected sequentially, first with influenza virus and then with a *Streptococcus pneumoniae* strain expressing luciferase, and were imaged twice daily. Survival (expressed as the no. of mice alive 21 days after the second infection/the total no. in the group) is shown in the column at right, for the control group (mice infected only with pneumococcus) and for groups of mice that were infected with both influenza virus and pneumococcus and that then either received placebo or were treated with oseltamivir or rimantadine. Results from the delayed-treatment group are presented. Images of a representative mouse from each group at various time points are displayed. A downward arrow indicates death.

![Figure 3](https://academic.oup.com/jid/article-abstract/190/3/519/938816)

Figure 3. Effect that delayed treatment with oseltamivir has on secondary bacterial pneumonia. Groups of 6 mice were infected with influenza virus and, 7 days later, with *Streptococcus pneumoniae*, whereas control mice were infected only with pneumococcus. Each group of mice either received placebo (water) or was treated with oseltamivir beginning 2, 3, 5, or 7 days after viral infection. *P < .05*, on Kaplan-Meier survival data (Mantel-Cox \(\chi^2\) test).
Ampicillin improves survival from secondary bacterial pneumonia only when oseltamivir also is administered. *A*, Eight mice were sequentially infected, first with influenza virus and then with a *Streptococcus pneumoniae* strain expressing luciferase, and were imaged twice daily. All 8 mice developed pneumonia and died; 6 of the 8 mice visually cleared the pneumonia prior to death. Images of 4 representative mice from this group are shown. *B*, Twenty-two mice were sequentially infected, first with influenza virus and then with an *S. pneumoniae* strain expressing luciferase, and were imaged twice daily. These mice were treated with oseltamivir twice daily for 5 days, beginning 48 h after virus infection. Of the 22 mice, 7 developed pneumonia, and all 7 visually cleared the pneumonia and survived. Images of 4 representative mice from this group are shown. A downward arrow indicates death.

Administration of placebo (*P* < .05). All of the mice that developed pneumonia died, and the mean number of days between development of pneumonia and death was 1.1 for mice receiving placebo but was 2.2, 1.7, and 1.4 for mice treated with oseltamivir beginning 2, 3, or 5 days after influenza infection, respectively. In addition, the time between pneumococcal challenge and development of pneumonia was longer in oseltamivir-treated mice: 2.6 days for mice receiving placebo versus 4.0 days for oseltamivir-treated mice. Thus, delayed treatment with oseltamivir prevents pneumonia, improves survival, slows the development of pneumonia, and slows the progression from pneumonia to death.

No improvement in survival from secondary bacterial pneumonia with antibiotic therapy. To determine whether antibiotics can effectively treat secondary bacterial pneumonia after influenza in this model, 8 mice were infected with influenza virus and, 7 days later, with pneumococcus. As soon as pneumonia was detected, treatment with ampicillin was begun. Despite antibiotic therapy, all 8 mice developed pneumonia and died. Pneumonia cleared from the lungs before death in 6 of the 8 mice; the remaining 2 mice died ≤24 h after detection of pneumonia (figure 4A). Therefore, antibiotic therapy can kill the bacteria causing pneumonia but does not alter survival from secondary bacterial pneumonia after influenza.

Effective treatment of secondary bacterial pneumonia with combined therapy. The central hypothesis of the present study is that combined therapy with both an NA inhibitor and an antibiotic would be effective for the treatment of secondary bacterial pneumonia. To test this hypothesis, 22 mice were challenged, received delayed treatment with oseltamivir, and, as
soon as pneumonia was detected, began receiving ampicillin twice daily. Of the 22 mice, 7 (32%) developed bacterial pneumonia during treatment with oseltamivir. The average peak output of relative light units from the thorax (which, in this model, correlates well with lung bacteria load [19]) was 7.6 \times 10^2 for the group of mice that developed pneumonia during treatment with oseltamivir and was 3.5 \times 10^1 for the group of mice receiving placebo \((P > .10)\) (not statistically significant). All 7 of the mice that developed pneumonia during treatment with oseltamivir visually cleared the pneumonia and recovered, resulting in 100% survival (figure 4A). In oseltamivir-treated mice, pneumonia developed, on average, 5.4 days after pneumococcal challenge, compared with only 1.8 days, on average, in mice receiving placebo \((P < .05)\). Therefore, in a mouse model, combined therapy with both an NA inhibitor and an antibiotic effectively treats secondary bacterial pneumonia.

**DISCUSSION**

Secondary bacterial pneumonia after influenza is a leading cause of mortality worldwide. Antibiotic therapy alone may not be the most efficacious therapy for this dual infection. In the present study, antiviral and antibiotic therapies were tested separately and then together in a mouse model of secondary bacterial pneumonia. Data from all the mouse experiments are presented, in combined form, in Table 1. Rimantadine, an inhibitor of the ion-channel activity of the viral M2 protein, was ineffective. Despite bacteriologic success (measured by a decline in luminescence in live mice), ampicillin alone also did not improve mortality. Oseltamivir, a selective inhibitor of influenza-virus NA, demonstrated efficacy by preventing most pneumonias, delaying the development and progression of pneumonia, and improving survival. The hypothesis that combined therapy with both an antiviral and an antibiotic would be effective was tested by use of an experimental design meant to mimic the expected clinical course of a person who developed secondary bacterial pneumonia after influenza. Combined therapy with oseltamivir, begun 48 h after influenza-virus infection, and ampicillin, begun only after pneumonia was diagnosed (by imaging), achieved 100% survival. In oseltamivir-treated mice, it is likely that the delay in onset and the slowing of the progression of pneumonia altered the pathogenesis of the infection such that eradication of bacteria from the lungs resulted in clinical cure.

The failure of antibiotics to effectively treat certain bacterial pneumonias is not unique to infections that follow influenza. Austrian and Gold [43] first noted in 1964 that a subset of patients with a disease course severe enough to result in death within 5 days did not benefit from therapy. The survival curves of this group, of untreated patients from the preantibiotic era, and of serum-treated patients were indistinguishable for the first 5 days and then diverged sharply, with therapy showing a clear benefit only after the 5-day window [44]. At the time, it was speculated that the development of specific anti-capsular antibody was necessary for clinical cure, even in the setting of antibiotic treatment [43]—the appearance of antibody around day 5 allows more efficient opsonization of pneumococci by the abundant leukocytes present in the lung and begins the resolution phase of the pneumonia [45]. This concept has support in contemporary studies of pneumococcal pneumonia: in 2 studies, 63% [9] and 74% [46] of deaths occurred within the first 5 days, and, in a third study, 63% [12] of deaths occurred within the first 4 days. In studies examining outcomes of bac- teremic pneumococcal pneumonia, these early deaths were independent of concordance of antibiotic therapy for susceptible versus resistant strains [12, 46, 47].

In the present study, antibiotics were ineffective against secondary bacterial pneumonia in a mouse model, despite the clearance of bacteria from the lungs. All deaths in mice receiving antibiotics occurred \(<5\) days after pneumococcal challenge. When mice were treated with oseltamivir, pneumonia developed an average of 5.4 days after pneumococcal challenge, and no deaths occurred if ampicillin therapy was begun when pneumonia presented. This corresponds well with the “physiologic point of no return” concept proposed by Austrian and Gold.

**Table 1. Data on pneumonia and survival in mice, from combined experiments.**

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Proportion (%)</th>
<th>Mean time of survival, days&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Mean time from onset of pneumonia to death, days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mice with pneumonia</td>
<td>Mice that survived</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1/12 (8)</td>
<td>11/12 (92)</td>
<td>4.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>18/18 (100)</td>
<td>0/18 (0)</td>
<td>3.7</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>8/8 (100)</td>
<td>0/8 (0)</td>
<td>4.7</td>
</tr>
<tr>
<td>Rimantadine</td>
<td>18/18 (100)</td>
<td>0/18 (0)</td>
<td>3.3</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>4/12 (25)</td>
<td>8/12 (75)</td>
<td>6.0</td>
</tr>
<tr>
<td>Oseltamivir and ampicillin</td>
<td>7/22 (32)</td>
<td>22/22 (100)</td>
<td>NC</td>
</tr>
</tbody>
</table>

<sup>a</sup> Calculated as the mean no. of days of survival after second challenge, considering only mice that died.

NOTE. Data are pooled from several experiments. Exact treatments for individual mice within groups may vary slightly (see Materials and Methods and Results). NC, not calculated.
Antimicrobials for Secondary Infections. In studies of bacterial pneumonia after influenza, fatal cases typically succumb rapidly to infection. During the 1918 influenza pandemic, 2,624 cases of pneumonia occurred at a military base, and 941 people died—86% of them from the pneumococcus—after spending an average of 7.3 days in the hospital [3]. During the 1957 influenza pandemic, rapid progression to death was also observed; one study reported 86 of 477 deaths occurring before arrival at the hospital and two-thirds of the hospitalized dying ≤48 h after admission [48].

More recently, Nicholson described bacterial pneumonia complicating influenza in Leicester, United Kingdom, during the 1989–1990 influenza season, during which 35 (45%) and 51 (65%) of 78 deaths occurred ≤4 days and ≤8 days after hospitalization, respectively [17]. It can be argued that influenza affects the pathogenesis of pneumonia such that the host is in a physiologic state in which clearance of bacteria is insufficient for cure. Data from both the present and previous studies [19, 30] suggest that the progression of pneumonia may be accelerated during influenza infection such that infection overwhelms the host prior to the development of specific defenses from the adaptive immune system. Treatment with oseltamivir alters this pathogenesis, by delaying the onset and progression of pneumonia long enough that cure accompanies clearance of bacteria by the antibiotic.

Age, underlying conditions, and multilobar involvement are interrelated factors in the pathogenesis of the influenza–pneumococcal interaction. In recent nonpandemic years, adults >65 years old have accounted for 43% of all influenza-associated hospitalizations [49] and 86% of all influenza-associated deaths [7] in the United States. Most of these deaths are attributable to the higher frequency in this age group of underlying conditions that predispose to mortality during an influenza epidemic [1, 50]. The high case-fatality rate in persons with preexisting illness may be due to a predisposition to fatal pneumococcal disease more so than to a predisposition to influenza disease [43, 51], particularly given that multilobar pneumococcal disease increases with age and with underlying complications [44, 52].

Prognosis of pneumococcal pneumonia is directly related to the number of lobes involved [9, 43, 44, 52, 53]—compared with patients with 1 lobe involved, mortality is 2-fold higher in patients with 2 lobes involved and 5-fold higher in patients with ≥3 lobes involved [43]. Treatment decreases the number of lobes involved and is associated with improved outcomes [43, 44]. Multilobar involvement is considered to be the norm in pneumococcal pneumonia after influenza, occurring in ~75% of cases [3, 13]. Previous work in the mouse model of influenza–pneumococcal synergism, used in the present report, has demonstrated massive involvement of multiple lobes of both lungs in dually infected mice [30]. In animals with pneumonia, treatment with oseltamivir restricts this involvement to fewer lobes and to less total lung at early time points (24–48 h) [19]. In light of the experiments presented here, it is clear that this early, milder lung involvement will progress to widespread consolidation if antibacterial therapy is not administered. However, administration of ampicillin was curative in mice that were also treated with oseltamivir and, thus, had delayed development of severe pneumonia.

The data reported here suggest that secondary bacterial pneumonia can be treated effectively when both the predisposing viral infection and the bacterial pathogen are targeted. The finding that an inhibitor of influenza-virus NA was efficacious but that an inhibitor of the ion-channel activity of the M2 protein was not supports the importance of viral NA in the interaction between influenza virus and bacteria [19]. It also provides a rationale for why an effect on secondary bacterial infections can be observed with NA inhibitors but not with rimantadine [29]. Prevention of influenza infections in high-risk groups via vaccination and/or prophylaxis should remain the basic approach to reducing mortality due to secondary bacterial infections. However, a strategy of combination therapy with both an NA inhibitor and an antibiotic should be considered for persons (such as elderly adults and those with chronic medical conditions) who are at risk for complications. NA inhibitors are effective against the symptoms of influenza only when administered ≤48 h after symptoms present, and the need for early evaluation and prescription of treatment is a significant barrier to the use of these drugs. On the basis of the finding that delayed therapy with an NA inhibitor reduces secondary bacterial infections independent of the effect it has on viral spread (the present study and [19]), antiviral therapy could be extended to persons who present with influenza outside of this 48-h window. If these mouse-model findings can be extended to humans, it would represent a significant advance in the treatment of a leading cause of death. Clinical studies are warranted to examine this hypothesis.

Acknowledgment

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References

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