Bacterial Coinfection in Influenza
A Grand Rounds Review

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Bacterial coinfection complicated nearly all influenza deaths in the 1918 influenza pandemic and up to 34% of 2009 pandemic influenza A(H1N1) infections managed in intensive care units worldwide. More than 65 000 deaths attributable to influenza and pneumonia occur annually in the United States. Data from 683 critically ill patients with 2009 pandemic influenza A(H1N1) infection admitted to 35 intensive care units in the United States reveal that bacterial coinfection commonly occurs within the first 6 days of influenza infection, presents similarly to influenza infection occurring alone, and is associated with an increased risk of death. Pathogens that colonize the nasopharynx, including *Staphylococcus aureus, Streptococcus pneumoniae,* and *Streptococcus pyogenes*, are most commonly isolated. Complex viral, bacterial, and host factors contribute to the pathogenesis of coinfection. Reductions in morbidity and mortality are dependent on prevention with available vaccines as well as early diagnosis and treatment.

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PATIENT PRESENTATION

The patient, a 58-year-old man, presented to a community hospital with fever, cough, myalgias, and shortness of breath that worsened over 5 days. The history was significant for past tobacco use. Temperature on presentation was 36.5°C, and physical examination revealed wheezing and rhonchi in bilateral lungs. A nasopharyngeal wash for viral testing and sputum for bacterial Gram stain and culture were obtained. Treatment for suspected community-associated pneumonia was initiated with moxifloxacin. Emergency department evaluation showed severe hypoxia, and the patient was transferred to a tertiary care center for further assessment.

On arrival at the receiving center, the patient's arterial blood gas analysis showed a pH of 7.42, P_{CO_2} of 31 mm Hg, and Pa_{O_2} of 59 mm Hg (fraction of inspired oxygen, 100%). Laboratory testing revealed findings consistent with severe sepsis: leukopenia (white blood cell count, 1.3 cells $\times 10^9$/L), thrombocytopenia (platelet count, 106×10^3 cells/μL), acute kidney injury (creatinine level, 2.04 mg/dL [180.34 μmol/L]), liver injury (aspartate aminotransferase level, 308 U/L [5.14 μkat/L]; alanine aminotransferase level, 197 U/L [3.29 μkat/L]), coagulopathy (prothrombin time, 16.3 seconds; partial thromboplastin time, 41.1 seconds; international normalized ratio, 1.3), and tissue hypoperfusion (lactate level, 3.7 mmol/L). Chest radiography showed diffuse bilateral infiltrates (FIGURE 1).

The patient was intubated and admitted to the intensive care unit for hypoxic respiratory failure and subsequent vasopressor-dependent septic shock. Refractory respiratory failure was managed with high-frequency oscillatory ventilation, and shock was managed with high-dose norepinephrine. Initial sputum Gram stain showed gram-positive cocci in clusters, and intravenous vancomycin was started. Oseltamivir (75 mg by nasogastric tube) was also started.

Respiratory failure complicated by hemoptysis and progressive shock led to cardiac arrest. Cardiopulmonary resuscitation was initiated, with temporary return of spontaneous circula-

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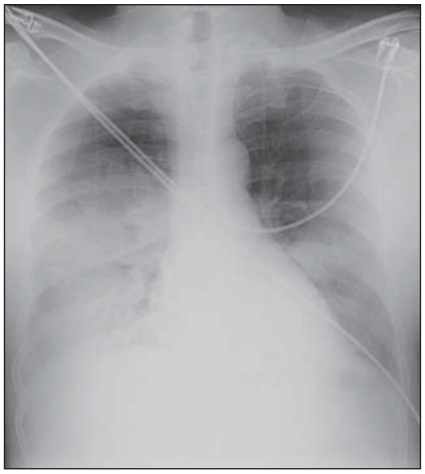
tion. A family decision for no further resuscitative efforts was made, and the patient died within 24 hours of admission. Polymerase chain reaction testing of an initial nasopharyngeal wash specimen was positive for 2009 pandemic influenza A(H1N1), and sputum and blood cultures were positive for methicillin-resistant *Staphylococcus aureus* (MRSA).

COMMENT

The 1918 influenza pandemic resulted in an estimated 50 million deaths worldwide.[1] A review of 8398 autopsies performed during that time confirmed bacterial coinfection in nearly all deaths.[2] The 2009 pandemic influenza A(H1N1) virus resulted in an estimated 284 400 deaths worldwide. Many deaths occurred in countries with limited medical services.[3] Even in countries with advanced medical services, including in the United States, Canada, Spain, Argentina, Australia, and New Zealand, bacterial coinfection complicated between 18% and 34% of 2009 pandemic influenza A(H1N1) cases managed in intensive care units (ICUs)[4-9] and up to 55% of fatal cases, based on published autopsy series.[10-12]

Figure 1. Case Patient's Chest Radiograph Showing Diffuse Bilateral Infiltrates



This article describes the epidemiology of influenza and pneumonia in the United States over the past 30 years, emphasizing the continued central role of bacterial coinfection in severe and fatal cases. The clinical course, pathogenesis, and rational clinical management of severe coinfection are discussed.

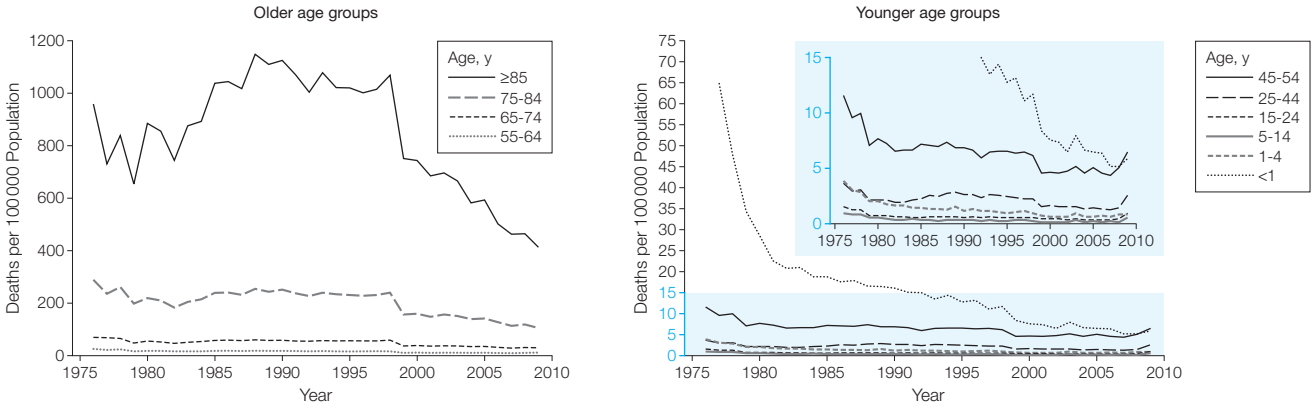
Epidemiology of Influenza and Pneumonia and the Role of Bacterial Coinfection

The overall precise mortality rate associated with influenza and bacterial coinfection is unknown. The National Vital Statistics System collects and presents the leading causes of death in the United States. Cause of death, as typically determined by the treating physician at the time of death, is derived from *International Classification of Diseases* codes on death certificates, and aggregate data are presented annually. Deaths attributable to influenza and bacterial coinfection are not directly measured and so must be extrapolated from available data. Based on these extrapolated data, on average from 1976 to 2009, 66 324 (range, 45 030-91 871) deaths were attributed annually to the combined categories of influenza and pneumonia.[13] Modeling estimates predict that on average 23 607 (range, 3349-48 614) deaths with underlying respiratory and circulatory causes from 1976 to 2007 in the United States were associated with influenza.[14]

Based on National Vital Statistics System data, mortality rates from the combined categories of influenza and pneumonia are highest in individuals 65 years or older and have declined from 1976 to 2009 predominantly in the oldest and youngest age groups (FIGURE 2). Although influenza infection typically results in lower mortality rates in younger individuals, H3N2 influenza viruses that were prevalent in 1997 and 2003 (ie, A/Sydney[H3N2] and A/Fujian[H3N2])[15] and the emergence of the 2009 pandemic influenza A(H1N1) virus resulted in excess mortality in younger age groups.

Bacterial coinfection complicates approximately 0.5% of all influenza cases in healthy young individuals and at least 2.5% of cases in older individuals and those with predisposing conditions.[16] Individuals at high risk of developing

Figure 2. Influenza and Pneumonia Death Rates by Age Group, United States, 1976-2009



Based on data from the National Vital Statistics System.[13]

influenza-related complications including coinfection include adults 65 years or older, children younger than 5 years, pregnant women, people who are morbidly obese (body mass index ≥40, calculated as weight in kilograms divided by height in meters squared), and people with preexisting medical conditions including chronic pulmonary, cardiovascular, renal, hepatic, neurologic, metabolic, or immune-suppressing conditions.[17]

Colonization of the nasopharynx with pathogenic bacteria may predispose to coinfection. Specifically, colonization with *Streptococcus pneumoniae* has been associated with increased risk of ICU admission or death in the setting of influenza infection,[18] and coinfection with *S aureus*, which colonizes the nares of 30% of the adult population,[19] has been associated with increased risk of death in adults and children infected with influenza.[8,20] MRSA coinfection in particular has repeatedly been associated with severe disease and death in adults and children.[20-24]

Clinical Course and Microbiology of Severe Influenza and Bacterial Coinfection

The typical time course of influenza illness in healthy adults experimentally challenged with influenza virus is as follows: symptom onset occurs within 24 hours of influenza infection; peak viral shedding correlates with peak symptom severity occurring 2 to 3 days postinfection; and symptoms and viral shedding abate by day 8 postinfection.[25]

In a series of 683 adults admitted to 35 ICUs in the United States with severe 2009 pandemic influenza A(H1N1) infection, 207 had clinical evidence of bacterial coinfection, as defined by presumed bacterial pneumonia documented in the medical record or a positive blood culture within 72 hours of ICU admission. The mean time from symptom onset to hospitalization in the coinfected group was 5.2 (SD, 4.9) days.[8] Allowing for a 24-hour asymptomatic period, on average these individuals developed coinfection within the first 6.2 (range, 1.3-11.1) days of influenza infection. This time course of illness suggests that coinfection predominantly occurs during periods of high influenza viral shedding but may occur concurrently with or shortly after influenza infection.

The mean time from symptom onset to hospital admission in this series did not differ significantly between the coinfected group and the influenza-alone group (5.0 [SD, 4.5] days). Similarly, the prevalence of presenting symptoms of fever, cough, dyspnea, and myalgias did not differ between groups. One hundred fifty-four of the 207 patients (74%) with suspected coinfection had positive bacterial cultures. The pathogens most commonly isolated from respiratory cultures were *S aureus* (45%), *S pneumoniae* (16%), and *Streptococcus pyogenes* (4%). Sixty-two percent of the *S aureus* isolates were methicillin resistant.

In a series of 838 critically ill children with 2009 pandemic influenza A(H1N1) infection, 274 (33%) had clinical evidence of bacterial coinfection, defined as a diagnosis of bacterial pneumonia or other evidence of bacterial infection within 72 hours of pediatric ICU admission.[20] One hundred eighty-three of the 274 patients (67%) with suspected coinfection had positive bacterial cultures. The pathogens most commonly isolated from respiratory cultures were *S aureus* (39%), *Pseudomonas* species (16%), *S pneumoniae* (8%), *Haemophilus influenzae* (7%), and *S pyogenes* (4%). Forty-eight percent of *S aureus* isolates were methicillin resistant. Eighty-seven percent of patients with *Pseudomonas* infection had chronic lung disease; many had tracheostomies in place.

Coinfection may also occur in the hospital setting following admission for influenza infection alone. Bacterial pathogens frequently isolated in hospital-associated coinfection include MRSA, *P aeruginosa*, *Acinetobacter* species, and other resistant enterobacteriaceae.[4,26] In summary, coinfection typically occurs within a few days of influenza infection at times of high viral shedding, presents similarly to severe influenza infection alone, and prominent coinfecting bacterial pathogens include *S aureus, S pneumoniae,* and *S pyogenes*, which commonly colonize the nasopharynx.

Pathogenesis of Coinfection

Synergistic lethality of influenza and bacterial coinfection has been observed in animal models since shortly after influenza viruses were first isolated in early 1930s.[27,28] Influenza viral infection contributes to respiratory epithelial cell dysfunction and death through disruption of protein synthesis and induction of apoptosis.[29-31] Viral neuraminidase cleaves respiratory epithelial cell sialic acids, contributing to increased bacterial adhesion and dissemination. This effect is reversed by neuraminidase inhibitors.[32-34] PB1-F2, a proapoptotic influenza protein expressed by many strains—although not by 2009 pandemic influenza A(H1N1)—increases susceptibility to bacterial coinfection through unknown mechanisms.[35] Proteases secreted by certain strains of *S aureus* cleave influenza hemagglutinin,[36,37] a step required for multicycle viral replication. Propagation of virus along the respiratory tree impairs mucociliary clearance of bacteria from the lower respiratory tract,[38,39] and epithelial cell death exposes the basal cell layer and basement membrane, allowing for increased bacterial adherence and invasion (FIGURE 3).[40-44]

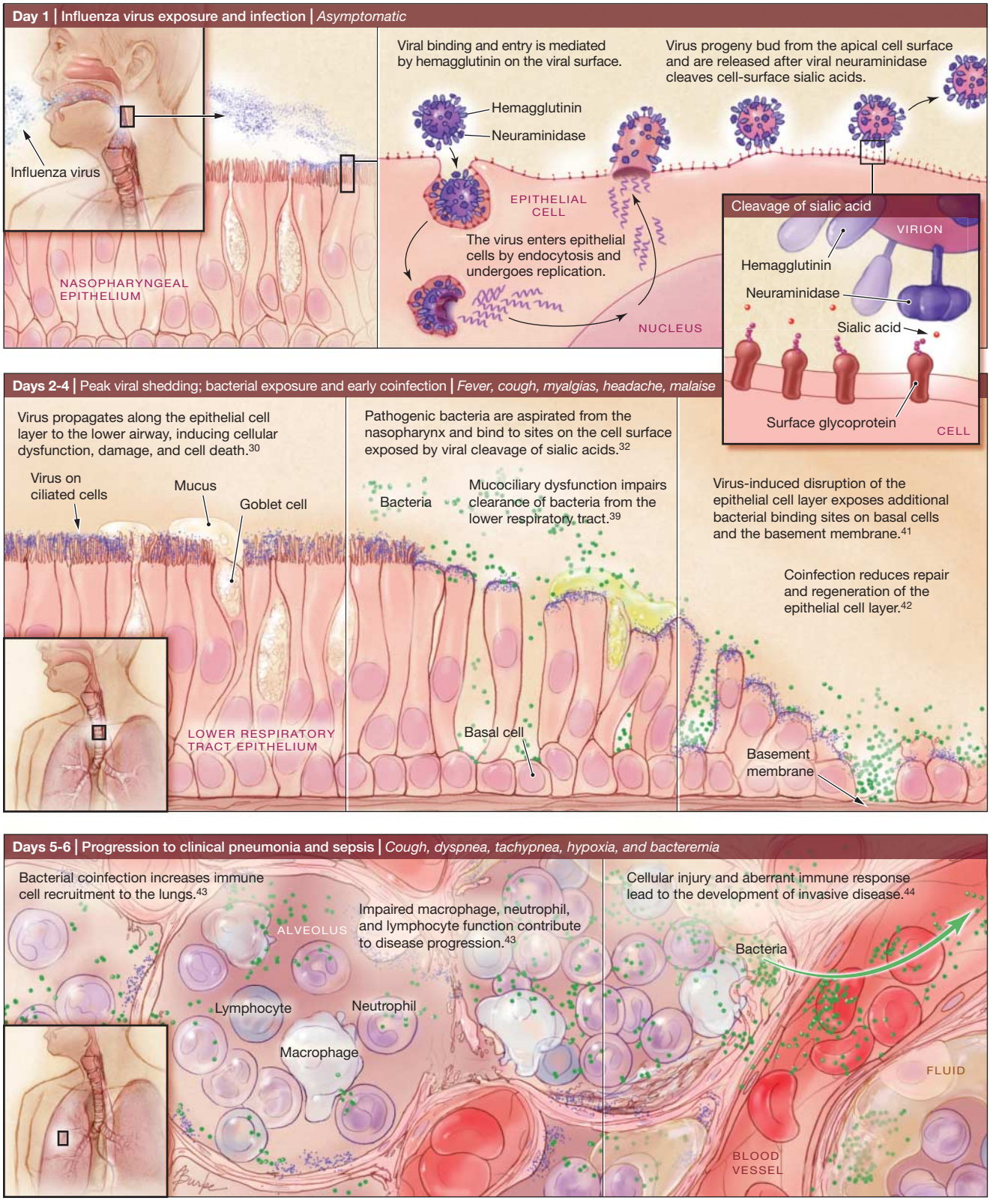
Clinical Management

Clinical management of severe coinfection relies on measures to prevent, diagnose, and treat both influenza and bacterial infection. The following paragraphs and the BOX describe a logical approach to prevention, diagnosis, and treatment of severe coinfection.

Influenza Vaccine

Annual influenza vaccination is recommended for persons older than 6 months. In children aged 6 months through 8 years, 2 doses of vaccine are

Figure 3. Model of Severe Influenza and Bacterial Copathogenesis



recommended during their first season of vaccination after July 1, 2010.[28] Evidence supporting efficacy and effectiveness of influenza vaccination for the prevention of severe influenza-related complications, including bacterial coinfection, hospitalization, ICU admission, and death, particularly in the high-risk elderly population, is relatively sparse and of variable quality.

Trials assessing efficacy of new vaccines are limited in that it is unethical to withhold vaccine from a placebo group, and observational studies are limited because of bias inherent in observational study design. A single randomized clinical trial (RCT) evaluating efficacy of influenza vaccine in community-dwelling individuals older than 60 years showed that vaccine was associated with protection against medically attended influenza illness. The incidences of clinical influenza were 2% and 3%, respectively (relative risk, 0.53 [95% CI, 0.39-0.73]). Prevention of bacterial coinfection was not evaluated.[45] Observational studies have shown up to a 45% reduction in pneumonia hospitalizations and a 60% reduction in deaths following influenza vaccination[46,47]; however, these studies have been criticized for their inability to adequately control for patients' baseline health status. Despite data limitations, influenza vaccine remains the best available tool for prevention of severe influenza illness commonly associated with bacterial coinfection.

Pneumococcal Vaccine

The 23-valent pneumococcal polysaccharide vaccine (PPSV23) is recommended in the United States for adults 65 years or older and for persons aged 2 through 64 years with underlying medical conditions predisposing to serious pneumococcal infection.[48] Predisposing conditions include but are not limited to functional or anatomical asplenia; chronic pulmonary, cardiovascular, renal, or hepatic disease; diabetes mellitus; tobacco use; and malignancy and other immune-suppressing conditions or medications. The 13-valent pneumococcal polysaccharide conjugate vaccine (PCV13) is recommended for children aged 2 through 59 months.[49]

A single RCT has evaluated the efficacy of a multivalent pneumococcal polysaccharide vaccine for the prevention of influenza-associated pneumonia in 37 107 African infants. In that trial, a 9-valent conjugate vaccine was associated with 41% efficacy ($P = .006$) for the prevention of influenza-associated pneumonia.[50] No similar RCT has been conducted among adults. However, a population-based observational study in individuals older than 65 years showed an association between combined influenza and pneumococcal vaccine and a reduction in hospital admissions for influenza or pneumonia and a reduction in pneumonia deaths relative to influenza vaccination or pneumococcal vaccination alone.[51]

Indirect vaccine effects (ie, herd effects in unimmunized individuals) significantly reduce invasive pneumococcal disease in all age groups. Since the introduction of 7-valent pneumococcal conjugate vaccine in the United States in 2000 (now replaced by PCV13), rates of invasive pneumococcal disease have decreased in vaccinated as well as unvaccinated age groups. By 2007, invasive pneumococcal disease was reduced by 40% (13.3 to 8.0 per 100 000 population) in persons aged 18 through 49 years, by 18% (24.0 to 19.8 per 100 000 population) in persons 50 through 64 years, and by 37% (60.1 to 37.9 per 100 000 population) in persons 65 years or older.[52]

Diagnosis

Diagnosis of coinfection should be considered in individuals with an influenza-like illness and lower respiratory tract signs or symptoms suggestive of pneumonia (eg, cough with dyspnea, tachypnea, or hypoxia) or evidence of sepsis. Typical, though nonspecific, symptoms of influenza illness include fever, cough, myalgias, malaise, and headache.[53,54] Rapid antigen-based influenza diagnostics, which have false-negative rates of up to 70%,[55] should not be relied on to rule out influenza infection, and although more accurate influenza diagnostics such as viral culture or molecular tests should be performed, treatment decisions should not await their results.

Subsequent interpretation of molecular influenza diagnostics must take into account the time course of illness relative to symptom onset and loca-

Box. Key Points Regarding Bacterial Coinfection in Influenza

Epidemiology

Between 1979-2009 there were an average of 66 000 deaths per year attributable to coinfection with influenza and pneumonia

Bacterial coinfection is more common in the elderly, the very young, pregnant women, patients with preexisting conditions, and morbidly obese patients

Prevention

Influenza vaccination in all persons older than 6 mo is recommended

23-Valent pneumococcal vaccine is recommended for adults older than 65 y; 13-valent pneumococcal polysaccharide conjugate vaccine is recommended for children aged 2-59 mo

Diagnosis

Diagnosis of coinfection can be difficult but should be suspected in patients who present with influenza-like illness and dyspnea, tachypnea, hypoxia, or signs and symptoms of sepsis

Treatment

Early empirical antiviral treatment and antibiotic treatment with a respiratory fluoroquinolone or a combination β-lactam plus a macrolide should be initiated in all individuals with suspected coinfection

Antibiotic coverage for methicillin-resistant *Staphylococcus aureus* should be initiated when patients have signs of necrotizing pneumonia, including rapid onset of acute respiratory distress or hemoptysis

tion from which a sample is collected (upper vs lower respiratory tract), because sampling of the nasopharynx late in the course of severe influenza infection has been associated with a 19% false-negative rate relative to concurrent sampling of the lower airway by bronchoalveolar lavage.[56] In addition to suggestive clinical features, a demonstrable infiltrate on chest radiographs is required for the diagnosis of pneumonia[57]; however, pattern of infiltrate cannot reliably differentiate between influenza occurring alone vs coinfection.

Microbiologic testing of sputum for Gram stain and culture should be performed in patients with suspected coinfection and clinical or radiographic evidence of pneumonia. Negative sputum culture may not reliably rule out bacterial coinfection. False-negative results occur in the setting of prior antibiotic use and poor-quality specimen collection or processing. Similar limitations apply to tracheal aspirate and bronchoalveolar lavage specimens. At a minimum, blood cultures should be obtained in patients with evidence of sepsis, and *S pneumoniae* urine antigen testing should be performed when available.

Antiviral Treatment

Early empirical antiviral treatment should be initiated in all individuals with suspected coinfection. Efficacy of oseltamivir and zanamivir for the treatment of influenza infection alone has been evaluated in multiple RCTs; however, lower respiratory tract complication was not the primary or secondary end point in these trials. A meta-analysis of 10 RCTs in patients with confirmed influenza infection found that oseltamivir use started within 36 hours of symptom onset was associated with a 55% reduction in the primary end point (4.6% vs 10.3% with placebo; $P < .001$) of lower respiratory tract complication (defined as bronchitis, lower respiratory tract infection, or pneumonia), resulting in initiation of antibiotic therapy 48 hours after the start of the study and before day 28. However, this result was attributable to reduction in bronchitis and not pneumonia. A statistically nonsignificant reduction in hospitalizations was observed.[58] An independent reanalysis of these 10 trials plus an additional trial similarly found oseltamivir use associated with a 37% reduction in lower respiratory tract complications requiring antibiotic therapy in patients with confirmed influenza infection. Subgroup analysis of bronchitis vs pneumonia prevention was not reported.[59] Validity of these studies has been challenged, given the possibility of publication bias.[60]

No RCT has evaluated the efficacy of neuraminidase inhibitors for the prevention of complications in hospitalized patients with influenza infection. An increasing number of observational studies, however, have found an association between oseltamivir use and reductions in ICU admission and death in this population. Earlier vs later administration has been associated with improved survival.[61-64] A recent meta-analysis of observational studies of antiviral therapy for the treatment of influenza infection supports the association of antiviral therapy and improved survival from influenza infection, yet correctly points out that the confidence in the effects for decision making from these observational studies is low.[65] However, the efficacy of antiviral therapy for the treatment of influenza infection is dependent on susceptibility of circulating influenza strains to available antiviral medications and the prevalence of antiviral-resistant infection could increase unpredictably.

Antibiotic Treatment

Patients with a clinical syndrome compatible with pneumonia with or without suspected influenza infection should receive initial empirical antibiotic treatment.[57] Recommended empirical antibiotic choices for hospitalized patients with community-associated pneumonia that do not distinguish between presence or absence of influenza infection include a respiratory fluoroquinolone or a combination β-lactam (ie, ceftriaxone or cefotaxime) plus a macrolide. Empirical coverage for MRSA with vancomycin or linezolid should be initiated in patients with severe or necrotizing pneumonia and or sepsis. Clinical features of necrotizing pneumonia include hemoptysis, pleural effusion, rapid onset of acute respiratory distress, and leukopenia.[66] Empirical antibiotic treatment for health care–associated pneumonia in patients with suspected or confirmed influenza infection should include coverage for MRSA and resistant gram-negative pathogens dependent on local antimicrobial patterns and susceptibility. Antibiotics should be tailored for specific bacterial pathogens isolated from blood or a high-quality sputum specimen.

Antibiotic treatment within 4 to 8 hours of hospital admission for community-associated pneumonia has been associated with reduced mortality in large observational studies,[67,68] and inappropriate use of initial empirical antibiotics for health care–associated pneumonia has been associated with increased mortality.[69,70] Although optimal timing of antibiotic administration in patients with suspected or confirmed influenza and bacterial coinfection has not been determined, early administration should be targeted.

Supportive Care

Aside from early administration of antiviral medications and antibiotics, management of severe coinfection is largely supportive. Progressive hypoxia results in the need for mechanical ventilation in most patients admitted to the ICU with severe influenza infection with or without coinfection, and rescue modalities such as prone positioning, bi-level or high-frequency oscillatory ventilation, or extracorporeal membrane oxygenation have been used in cases in which hypoxia persists despite use of standard ventilator modes.[5,6,71,72] Septic shock from invasive bacterial infection necessitates vasopressor use in more than one-third of critically ill patients with coinfection, and acute renal failure requiring renal replacement therapy occurs in up to 20%.[8]

CONCLUSIONS

Influenza and bacterial coinfection result in significant morbidity and mortality. Influenza vaccine remains the best available tool for prevention of severe influenza illness commonly associated with bacterial coinfection and should be encouraged in individuals older than 6 months. PCV13 administered to children aged 2 through 59 months and PPSV23 administered to adults 65 years or older and to persons aged 2 through 64 years with underlying medical conditions reduce invasive pneumococcal disease through both direct and indirect herd effects. Despite these benefits, in a large observational study using US state inpatient databases, timing of highest 2009 pandemic influenza A(H1N1) virus activity from late August to mid December 2009 was associated with a significant increase in pneumococcal hospitalizations relative to a seasonal baseline from the previous 6 years in individuals older than 5 and younger than 65 years—those not routinely vaccinated against pneumococcal disease.[73] Similarly, mortality rates from the combined categories of influenza and pneumonia increased significantly from prior seasonal baseline in this age range in 2009. Expanded use of PPSV23 in individuals older than 5 years and younger than 65 years may further reduce morbidity and mortality related to influenza and bacterial coinfection.

Severe bacterial coinfection presents similarly to severe influenza infection occurring alone but confers an increased risk of death in adults and children. Diagnosis of coinfection should be considered in individuals with an influenza-like illness and lower respiratory tract signs or symptoms suggestive of pneumonia, such as cough with dyspnea, tachypnea, or hypoxia or with evidence of sepsis. Early empirical antiviral therapy should be administered to all individuals with suspected coinfection. Bacterial pathogens isolated in coinfection typically colonize the nasopharynx and cause disease during periods of high influenza viral shedding and clinical symptoms. MRSA is the bacterial pathogen most frequently isolated from critically ill patients with coinfection in the United States[8,20] and is not covered by standard antibiotic therapy for community-acquired pneumonia. Vancomycin or linezolid should be administered in addition to standard therapy for community-acquired pneumonia to patients with severe or necrotizing pneumonia, sepsis, or health care–associated coinfection. Delayed administration of antiviral or antibiotic therapy may result in worse outcomes.

Critical care supportive services including mechanical ventilation, vasopressor therapy, and renal replacement therapy are often required for the management of severe coinfection. Despite advances in supportive care, up to one-third of patients with coinfection admitted to ICUs in developed countries die.[7,8] Further advances in vaccine technology for influenza and common bacterial copathogens (specifically *S aureus*) are needed, as are improved rapid and accurate diagnostics for influenza and bacterial infection and novel therapeutics addressing the complex mechanisms contributing to influenza and bacterial copathogenesis.

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