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Hospitalized Patients with Acute Pneumonia

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KEYWORDS

• Community-acquired pneumonia • Hospital-acquired pneumonia
• Emerging infectious diseases • Viral pneumonia • Infection control
• Antibiotic stewardship

HOSPITAL MEDICINE CLINICS CHECKLIST

1. Pneumonia is one of the leading causes of hospital admission, morbidity, and mortality among elderly patients.
2. Choosing the empirical antimicrobial regimen depends on risk factors for multidrug resistance and presenting severity of illness.
3. Risk factors for drug resistance include prior hospitalization, prolonged intensive care unit (ICU) stay, recent surgery, and prior antibacterial therapy.
4. Many scoring systems, including the Infectious Diseases Society of America/American Thoracic Society criteria, pneumonia severity index, and CURB-65 (confusion, blood urea nitrogen >30, respiratory rate $\geq$30, systolic blood pressure <90 mm Hg or diastolic blood pressure $\leq$60 mm Hg, and age $\geq$65 years), can be used to appropriately determine which patients are best suited for a ward or ICU admission.
5. Diagnostic studies, particularly a sputum culture, are recommended for acutely ill patients in the ICU.
6. Therapy should include coverage for the major organisms of acute pneumonia, including *Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis*. This therapy would include a third-generation cephalosporin, such as ceftriaxone, or a fluoroquinolone, such as levofloxacin. If patients are placed in the ICU, vancomycin should be included for *Staphylococcus aureus*.

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7. Atypical coverage for *Mycoplasma* and *Legionella* should be added with azithromycin if a third-generation cephalosporin is used.
8. For unusual or atypical cases, the public health department should be contacted to determine if an additional or emerging organism is present.

Which patients with pneumonia get hospitalized (which groups are most vulnerable)?

Pneumonia is one of the leading causes of mortality and hospitalization among US adults. Studies have shown that hospitalizations for pneumonia have been on the rise, and that trend is particularly true among elderly adults (aged ≥65 years). This fact is particularly relevant because as the population ages and life expectancy increases, the elderly represent an increasing portion of the population. The elderly are thought to be particularly susceptible to pneumonia requiring hospitalization because of the higher prevalence of comorbid diseases, such as chronic cardiac and pulmonary disease or diabetes mellitus, in that population.[1,2] Surrogate markers of multiple comorbidities (multi-morbidity) are also risk factors for pneumonia and include poor performance status, poor oral hygiene, high number of invasive indwelling medical devices, and polypharmacy.[3] **Box 1** outlines the major risk factors for hospital admission. A tool that included factors such as age, smoking status, and pulmonary function was validated in a study and shown to predict the long-term risk of

Box 1
Risk factors for hospitalization and mortality in patients with acute pneumonia

Risk factors for hospitalization

Aged older than 65 years

Greater than 2 comorbidities (eg, diabetes, heart failure, COPD)

Poor oral hygiene

Alcohol or drug abuse

Poor performance status

Underlying structural lung disease

Invasive medical devices

Altered mental status

Renal failure

Risk factors for ICU admission and increased mortality

Mechanical ventilation, invasive and noninvasive

Vasopressor use

Hypercapnia

Hypoxemia

Altered mental status

High predication score (eg, CURB-65, PSI score)

Abbreviations: COPD, chronic obstructive lung disease; CURB-65, confusion, urea, respiration, and blood pressure; PSI, pneumonia severity score.

pneumonia hospitalization among adults in the community.[4] Another significant risk factor for pneumonia hospitalization is alcohol abuse, which is thought to be due to alcohol's effect on immune function, ciliary and surfactant functioning in the lung, aspiration risk, and malnutrition.[5] For patients who are admitted to the hospital and subsequently develop hospital-acquired pneumonia (HAP), certain populations are more vulnerable, including the elderly, men, those with structural lung disease, and those with multiorgan system failure.[6]

How do we determine which patients need to be admitted to the hospital versus discharged from the emergency department?

The decision to admit patients from the emergency department (ED) versus pursue outpatient treatment is important and has an impact on patient outcomes, patient satisfaction, complications, cost, and resource utilization. For example, studies have shown that patients with pneumonia who were initially managed as an outpatient and subsequently required hospital admission suffered an increased risk of death or delayed recovery.[7] The Infectious Diseases Society of America (IDSA) recommends using a patient severity of illness scale to guide selection of inpatient versus outpatient treatment. There are a variety of severity assessment tools available to physicians, including CURB-65 (confusion, blood urea nitrogen >30, respiratory rate $\geq$30, systolic blood pressure <90 mm Hg or diastolic blood pressure $\leq$60 mm Hg, and age $\geq$65), A-DROP (age, dehydration, respiratory failure, orientation disturbance, and systolic blood pressure), pneumonia severity index (PSI), and IDSA-American Thoracic Society (ATS) criteria, that have all been validated for assessing pneumonia severity and risk of mortality. **Table 1** and Fine and colleagues'[8] article for the pneumonia severity index outline the major scoring systems used to determine hospitalization and poor outcome in acute pneumonia. A criticism of some of these tools is their complexity, which makes them less likely to be used at the bedside.[9] In response to that, a study showed that a real-time electronic ED decision support tool for patients with pneumonia showed improved adherence with guidelines and improved outcomes.[10] Despite the guidelines, patients with low-severity pneumonia are frequently admitted to the hospital. Factors such as access to ambulatory services, physician personality and practice style, social support, and comorbid diseases are not included in severity assessment scores and all influence admission rates.[7,9] In the end, a physician's judgment must be used in determining patients' disposition; but objective tools should be used as an aid in that decision.

What is required to make a reliable diagnosis of pneumonia?

The diagnosis of pneumonia is based on symptoms (cough, shortness of breath), signs (fever, leukocytosis), and radiographic findings. Confirmation via microbiologic studies is not usually obtained because of issues surrounding sample collection and the sensitivity of cultures.[11] Relying on symptoms and signs is difficult because of the variability in presentation and patient factors.[12] This variation is particularly true in the elderly who often present with atypical symptoms and often lack the objective criteria used in diagnosis, such as laboratory and radiographic abnormalities. Rather than symptoms and signs, such as pleuritic chest pain, shortness of breath, cough, fever, and leukocytosis, they often present with falls, decreased functional status, decreased appetite, urinary incontinence, and delirium.[13] A review concluded that individual symptoms and signs are inadequate to rule in or out the diagnosis of pneumonia; in fact, no combination of history and

Table 1
Assessment scores for pneumonia severity

Pneumonia Scoring Systems			
CURB-65	**IDSA**	**SOAR**	**A-DROP**
• Confusion of new onset • BUN >7 mmol/L (19 mg/dL) • Respiratory rate >30 breaths/min • Blood pressure systolic <90 mm Hg or diastolic ≤60 mm Hg • Aged 65 y or older	Major criteria (1 or more = ICU admit) • Endotracheal intubation and mechanical ventilation • Shock requiring vasopressors Minor criteria (3 or more = ICU admit) • Respiratory rate ≥30/min • Pao_2 to FIO_2 ratio ≤250 • Multi-lobar infiltrates • Confusion or delirium • BUN ≥20 mg/dL • Leukopenia (WBC count <4000 cells/mm^3) • Thrombocytopenia (platelet count <100,000 cells/mm^3) • Hypothermia (core temperature <36°C) • Hypotension requiring aggressive fluid resuscitation	• Partial arterial oxygen pressure to FIO_2 ratio (Pao_2/FIO_2 ratio) <250 • Respiratory rate ≥30 breaths/min • Systolic blood pressure <90 mm Hg or diastolic blood pressure <60 mm Hg • Age 65 y or older	• *A*ge (male ≥70 y, female ≥75 y) • *D*ehydration (BUN ≥210 mg/L) • *R*espiratory failure (SaO_2 ≤90% or Pao_2 ≤60 mm Hg) • *O*rientation disturbance (confusion) • Low blood *P*ressure (systolic blood pressure ≤90 mm Hg)

Abbreviations: BUN, blood urea nitrogen; FIO_2, fraction of inspired oxygen; SaO_2, oxygen saturation; SOAR, systolic blood pressure, oxygenation, age, respiratory rate; WBC, white blood cell.

physical examination findings is sufficient to confirm the diagnosis of pneumonia.[14] Relying on chest radiographs also has significant limitations. Patient factors, including body habitus, inspiratory effort, and comorbid diseases, all result in difficult-to-interpret radiographs.[15] In addition, studies have shown a lack of concordance between radiologist interpretations of chest radiographs.[16] Another study highlighted the delay between symptoms and radiographic findings as they found that more than half of patients in their study admitted with an initially negative chest radiograph developed radiographic infiltrates within 48 hours.[17] Because of the numerous issues with chest radiographs, studies have looked at computed tomography (CT) scans to aid in the diagnosis or exclusion of pneumonia. One study found the use of CT scans modified medical decisions in two-thirds of cases and ruled out pneumonia in one-third of cases. However, cost-effectiveness and radiation exposure among other limitations were not discussed and would need to be addressed before any change in practice.[18] The diagnosis of pneumonia continues to be challenging, particularly in certain populations, and warrants further research into an improved method of diagnosis to allow patients to receive appropriate treatment and avoid unnecessary adverse events.

What pathogens are responsible for causing pneumonia?

The most common pathogens implicated in pneumonia are *Streptococcus pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Haemophilus influenzae*, *Legionella* species, and respiratory viruses.[19,20] In addition, multiple studies have shown *Staphylococcus aureus* to be one of the most common pneumonia pathogens behind *S pneumoniae*.[21] Regarding HAP, the largest report on the microbiology of HAP showed that most culture-positive cases were due to *S aureus* and gram-negative pathogens. A complicating factor in conventional culture-based testing of samples from patients with suspected HAP is that most likely already received antimicrobials before sampling, which impairs sensitivity of pathogen detection using culture-based techniques.[22] In addition, another study showed that respiratory viruses were as commonly isolated as bacterial organisms in cases of HAP.[23] One significant limitation of studying the cause of pneumonia is that a pathogen is detected in only 30% to 40% of cases.[24,25] However, new studies have shown that comprehensive molecular testing significantly increases the pathogen detection rate.[24] As these technologies become more widespread, we will be able to develop a better understanding of the microbiology of pneumonia. **Box 2** outlines the major organisms associated with acute pneumonia.

What antibiotics are recommended for treatment?

The recommended treatment regimen for community-acquired pneumonia includes a beta lactam (cefotaxime, ceftriaxone, or ertapenem in selected patients) plus a macrolide (azithromycin) or a respiratory fluoroquinolone (levofloxacin or moxifloxacin).[19] The recommended regimen for treatment of HAP per the recent IDSA guidelines stratifies patients by their risk of mortality (based on need for ventilatory support due to pneumonia and septic shock) and likelihood of methicillin-resistant *S aureus* (MRSA) (based on receipt of intravenous antibiotics within the last 90 days, treatment in a

Box 2
Common pathogens of acute pneumonia

Pathogens associated with acute pneumonia in hospitalized patients

Bacteria
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Mycoplasma pneumoniae*
- *Chlamydophila pneumoniae*
- *Legionella pneumophila*

Lesser bacteria (multidrug-resistant risk)
- *Staphylococcus aureus*
- *Pseudomonas aeruginosa*
- *Klebsiella pneumoniae*
- *Escherichia coli*

Viruses
- Influenza
- Respiratory syncytial virus
- Adenovirus
- Human metapneumovirus

unit where the prevalence of MRSA among *S aureus* isolates is not known or >20%, and prior detection of MRSA by culture or nonculture screening). For those not at high risk of mortality and low likelihood of MRSA, treatment with one of the following agents is recommended: piperacillin-tazobactam, cefepime, levofloxacin, imipenem or ertapenem. For those not at high risk of mortality but with factors that increase the likelihood of MRSA treatment with one of the following agents is recommended: piperacillin-tazobactam, cefepime, levofloxacin or ciprofloxacin, imipenem or meropenem, or aztreonam plus vancomycin or linezolid. For those at high risk of mortality or receipt of intravenous antibiotics within the past 90 days, treatment with one of the following agents is recommended: piperacillin-tazobactam, cefepime, levofloxacin/ciprofloxacin, imipenem/meropenem, amikacin/gentamicin/tobramycin, or aztreonam plus vancomycin or linezolid.[26] **Box 3** outlines the antibacterial choices based on risk factors for patients with acute pneumonia.

Who is at risk for multidrug-resistant organisms?

Identifying which individuals are at risk for multidrug resistant (MDR) organisms has been an area of ongoing research. Choosing an appropriate initial antibiotic regimen is of paramount importance; inappropriate antibiotic choice or treatment failure is associated with increased mortality, length of stay, and hospital charges.[27–29] Although undertreating pneumonia leads to worse outcomes, treating pneumonia with unnecessarily broad-spectrum antibiotics can also lead to worse outcomes, such as antimicrobial resistance and *Clostridium difficile* infection. A confounding factor in the existing studies that may skew toward a higher prevalence of MDR organisms is that resistant organisms may be easier to grow in culture than more common organisms, such as *S pneumoniae*, which distorts the data.[30] In an effort to identify those at risk for MDR organisms, in 2005 the IDSA/ATS created the health care–associated pneumonia (HCAP) classification, which included patients who had

Box 3
Antibacterial therapy in acute pneumonia

Antimicrobial choices in acute pneumonia

- Healthy outpatients (no risk factors): macrolide antibiotics, such as azithromycin or clarithromycin, 3 to 7 days
- Outpatients with underlying illness or risk factors: includes underlying risks (such as emphysema or heart failure); a quinolone (such as levofloxacin) or a β-lactam antibiotic (such as cefpodoxime, cefuroxime, amoxicillin, or amoxicillin/clavulanic acid); and a macrolide antibiotic (such as azithromycin or clarithromycin) for 7 to 10 days
- Hospitalized patients without multidrug-resistant risks: require intravenous antibiotics, with a quinolone (such as levofloxacin) or a β-lactam antibiotic (such as cefotaxime, ceftriaxone, ampicillin/sulbactam) or high-dose ampicillin plus a macrolide antibiotic (such as azithromycin or clarithromycin) for 7 to 10 days
- Intensive-care patients with sulbactam risks: require intravenous antipseudomonal fluoroquinolone (such as levofloxacin), or a β-lactam antibiotic (such as cefotaxime, ceftriaxone, ampicillin/sulbactam), or high-dose ampicillin plus a macrolide antibiotic (such as azithromycin or clarithromycin); an antistaphylococcal agent, such as vancomycin or linezolid, recommended for patients in the ICU; 7- to 10-day treatment

Adapted from American Thoracic Society, Infectious Disease Society, and Canadian Thoracic Society guidelines.

been hospitalized in the past 90 days, resided at a long-term care facility, received intravenous antibiotics, chemotherapy, or wound care within the past 30 days.[31] Because of the introduction of the HCAP classification, the use of broad-spectrum antibiotics has increased significantly; but that classification has come under scrutiny because of its inconsistent ability to predict the presence of MDR organisms.[32] One population driving the increased use of broad-spectrum antimicrobials is nursing home residents, as one study showed that about 30% of patients hospitalized with pneumonia in industrialized countries lived in nursing homes.[33] Given the large and increasing nursing home population, better means of stratifying their risk of MDR pathogens is of vital importance. Ma and colleagues[34] found that patients admitted with pneumonia coming from a nursing home are at high risk for viral pneumonia, which emphasizes the need for testing for respiratory viruses to allow for appropriate antibiotic stewardship. Others argue that geographic MDR prevalence is an important factor to take into account as one study found that using HCAP criteria to guide antibiotics led to overtreatment in areas with low MDR prevalence and undertreatment in areas of high MDR prevalence.[35,36] Some elements of the HCAP criteria have been shown to be predictive of MDR organisms, particularly the receipt of intravenous antibiotics, as this was included in the more recent 2016 HAP guidelines. Although the HCAP classification may not identify individuals at high risk of MDR pathogens, patients with HCAP do have worse outcomes than those with community-acquired pneumonia and this is thought to be due to the higher prevalence of comorbidities in the HCAP population. Another group conducted a large study and found risk factors for MDR organisms including prior hospitalization, immunosuppression, previous use of antibiotics within the last 90 days, use of gastric acid–suppressive agents, tube feeding, and nonambulatory status. They suggested having 3 or more of those risk factors was when physicians should use broad-spectrum antibiotics.[37] Our knowledge in this field continues to develop and will, it is hoped, lead to better antibiotic selection and ultimately improved patient outcomes. **Box 4** outlines the major risk factors for MDR organisms in acute pneumonia.

What criteria should we use for management of pneumonia in the intensive care unit (either from the emergency department or the floor)?

The importance of correctly identifying patients with pneumonia who would benefit from ICU admission is highlighted by the fact that delayed ICU transfer for severe pneumonia

Box 4
Risk factors for multidrug-resistant organisms in acute pneumonia

- Recent admission (>3 days) in the prior 90 days
- Poor performance status
- Chronic renal failure with hemodialysis
- Immunosuppression
- Active cancer
- Nursing home residence
- Chronic alcohol abuse
- Poor dentition
- Broad-spectrum antibacterial use

is associated with increased mortality.[38] Some criteria for ICU admission, such as mechanical ventilation and use of vasopressors, are fairly universally accepted. Beyond those criteria, most guidelines recommend using severity of illness and risk of mortality to determine the need for ICU admission. To that end, there are multiple severity assessments available, including the IDSA/ATS criteria, PSI, and CURB-65. One limitation in attempting to use severity scores to determine ICU admission is the heterogeneity in ICU admission criteria between different health care systems. For example, whether noninvasive ventilation can be performed on the floor differs between hospitals. In addition, much like deciding between outpatient and inpatient treatment, many factors aside from pneumonia severity are used to determine need for ICU admission.[39] The IDSA/ATS criteria have been criticized because in validation studies there was no reduction in mortality found in patients with only minor criteria who were admitted to the ICU.[40] Another study compared the IDSA/ATS guidelines with PSI and CURB-65 and found it to be more specific and sensitive, respectively, for predicting ICU admission but still had a poor positive predictive value (52.9%).[41] An alternative score (systolic blood pressure <90 mmHg, multilobar chest xray involvement, albumin <3.5 g/dL, respiratory rate, tachycardia >/= 125 bpm, confusion (new onset), low oxygen, arterial pH <7.35 [SMART-COP]) was developed with the aim of predicting the need for invasive respiratory support or vasopressors (IRVS) as these are universal ICU admission criteria. The tool was found to be better at predicting need for IRVS than PSI and CURB-65 and was accurate for patients in the ED or on the floor.[42] Another study examined patients who did not meet ICU admission criteria (mechanical ventilation or vasopressors) on presentation to the ED but subsequently were transferred to the ICU within the first 3 days of admission and identified 11 baseline characteristics that were independently associated with ICU admission on days 1 to 3. They used these characteristics to develop a prediction rule (risk of early admission to the intensive care unit [REA-ICU]) which outperformed other prediction rules (PSI, CURB-65) in predicting ICU admission on days 1 to 3.[43] REA-ICU was validated in another study that also pointed out other factors such as high bacterial load and unexpected or resistant pathogens which are not identified on ED presentation can contribute to ICU admission and encouraged further research into inflammatory and stress biomarkers, such as proadrenomedullin, to improve prediction tools.[44] Furthermore, a study found that hypocapnia and hypercapnia were independent predictors of ICU admission and 30-day mortality even after adjusting for severity of illness and chronic obstructive pulmonary disease and encouraged the use of $Paco_2$ in prediction tools.[45] However, as one study pointed out, most severity scores predict mortality, which includes many patients who are elderly and have multiple comorbidities, so using it as the sole tool to guide ICU admission neglects to consider whether for each particular patient an aggressive management strategy is appropriate. In the end, clinical judgment is necessary and plays an important role, as severity scores are not accurate enough to guide management on their own. Not all high-risk patients require ICU admission and not all low-risk patients can be discharged from the ED for a variety of other reasons that are not included in the score criteria.[46]

What preventative measures are available for acute pneumonia?

Given the high incidence and mortality of pneumonia, prevention strategies are of utmost importance. The primary means of prevention is via vaccination. Given that *S pneumoniae* is the most common pathogen responsible for pneumonia, the pneumococcal vaccine is recommended for those at risk, which includes the elderly (aged >65 years) and those with certain medical conditions. Vaccination with pneumococcal conjugate vaccine has been shown to be effective in preventing vaccine-type

pneumococcal pneumonia.[47] The Centers for Disease Control and Prevention also recommends influenza vaccination as a preventative strategy for pneumonia, and it has been shown to reduce hospitalizations for pneumonia and influenza as well as death.[48,49] Another study highlighted the debate over influenza vaccine efficacy in the elderly secondary to the tendency for sick and frail elderly who are at higher risk of pneumonia and hospitalization to not receive the vaccine as frequently as those that are relatively more healthy, which creates biased data, the so-called healthy vaccine effect. It also added that attempting to assess outcomes data for influenza vaccination is difficult because of the modest vaccine efficacy and variable yearly prevalence of influenza associated respiratory illnesses.[50,51] Statins have been studied for prevention of pneumonia and found to have a beneficial effect, but it was based on very low-quality data and would benefit from further studies.[52] Given the increased role of comorbid diseases in pneumonia, hospitalization, and mortality, another study suggested focusing efforts on reducing preventable comorbid conditions as a prevention measure.[2] Although there has been a lot of research into ventilator-associated pneumonia prevention, there are few studies investigating HAP prevention. Chemical oral care, treatment of dysphagia, prevention of nosocomial transmission of viral infections with universal use of masks, early mobilization, and hand hygiene have been shown to have positive results; but all need further study to better clarify their role and efficacy as well as feasibility of implementation.[6]

How do you determine whether acute pneumonia is caused by an emerging pathogen?

The worlds of public health and critical care can be disparate, but they often collide in the hospital with patients with acute pneumonia. The recent changes in viral pneumonia emergence and detection, particularly the H1N1 pandemic of 2009, highlighted the need for close contact between these worlds. The initial cases of H1N1 were detected through routine surveillance by sentinel providers. These providers sent reports back to local and state public health officials regarding the caseload of influenza-like illness, along with diagnostic samples for subtyping. Thus, when a sample returned as an unidentified subtype of influenza A, we were able to determine the first cases of this new virus. In addition, other unusual respiratory viruses can present initially as a severe febrile respiratory illness, often with respiratory failure in the ICU. And that close contact between critical care providers and public health officers is essential. Finally, studies illustrate the close association between seasonality and viral pneumonia. Influenza and respiratory syncytial virus (RSV), for example, rarely present outside of the winter season. Public health providers can provide this information to critical care physicians, allowing for early treatment when the virus is circulating and additionally allowing conservative measures when it is not circulating. And finally, the relationship between advanced viral testing of respiratory secretions (for virus agents outside of the standard multiplex technology) often goes through public health. Viral hemorrhagic fevers, severe acute respiratory syndrome, novel influenza, and other novel viruses can appear with acute respiratory failure; the relationship between early recognition and rapid testing cannot be stressed enough.

What is the impact of a viral and bacterial coinfection?

The impact of respiratory viruses in critical illness can be broad, from a potential trigger of acute respiratory or cardiac failure in compromised individuals to a potential protective effect. Up to 22% of patients admitted to an ICU with respiratory or heart

failure can have a virus isolated from their tracheobronchial tree or nasal lavage. In general, these patients tend to be older (mean age 69 years), male (68%), and have a higher rate of respiratory failure as compared with heart failure (94%).[53,54] The most common viral isolates in one study were *Rhinovirus* (42%), herpes group (22%), and influenza A (16%).[54] Another study showed influenza (38%), RSV (29%), and rhinovirus (19%) as the most common.[53] In both cohorts, influenza and RSV were not linked to worse outcomes when corrected for severity of illness. *Rhinovirus*, on the other hand, had a protective effect and was independently associated with improved survival (hazard ratio 0.273, 95% confidence interval [CI] 0.096–0.777, $P<.006$).[54]

However, the addition of a bacterial coinfection seems to worsen outcomes in patients with a viral respiratory infection. A large cohort of critically ill patients (n = 209,695) over a 3-year span evaluated the impact of viral and bacterial coinfection of the respiratory tract. The patients were subgrouped into 4 cohorts: no infection, viral infection only, bacterial infection only, and coinfection in the same hospitalization. Influenza and RSV were the community-acquired viruses associated with worse outcomes. The presence of viral pneumonia was associated with an increased risk of pneumonia (relative risk [RR] 1.30, 95% CI 1.10–1.55), sepsis (RR 1.18, 95% CI 1.10–1.28), and septic shock (RR 1.48, 95% CI 1.23–1.78). Only influenza was associated with an increased risk of respiratory failure (RR 3.19, 95% CI 1.96–5.17). Adenovirus and the coronavirus group were associated with an increased risk of pneumonia as well. However, a coincident bacterial infection was associated with the most severe outcomes, especially death (RR 6.58, 95% CI 5.47–7.91), multi-organ system failure (RR 8.25, 95% CI 7.50–9.07), and septic shock (RR 271.1, 95% CI 188–391) when compared with the reference cohort. Finally, the interaction between viral and bacterial infection suggested an enhanced effect (synergy index 1.5, 95% CI 1.2–1.9).[55]

An evaluation of bacterial coinfection during the influenza H1N1 pandemic in 2009 showed similar results. Among patients with influenza A subtype H1N1, 30.3% of patients had a bacterial coinfection on ICU admission. *S aureus* was the most common (27.5%), followed by *S pneumonia* (9.1%).[56] Bacterial coinfection patients were more likely to present with shock (21% vs 10%, $P = .0001$), require mechanical ventilation (63% vs 52%, $P = .005$), have a longer ICU stay (7 vs 6 days, median, $P = .05$), and a higher mortality (31% vs 21%, $P = .002$). Immunosuppression and *S aureus* infection were independently associated with a higher mortality.

The isolation of a respiratory virus from the respiratory tract may be associated with a protective effect (eg, rhinovirus) or worse outcomes (eg, influenza and RSV) and largely depends on the pathogen isolated. Coinfection with a bacterial pathogen does carry increased risks for death, prolonged ICU stay, sepsis, and multi-organ dysfunction when compared with patients with only a viral infection. Particularly influenza and RSV, when combined with a bacterial infection, carry the highest risk for death, respiratory failure, sepsis, and multi-organ dysfunction. In addition, the relationship between viral and bacterial infections seems to enhance these poor outcomes. Because of this increased risk for poor outcomes, particularly with influenza and RSV, the winter virus season should include early antiviral therapy along with timely, adequate, and appropriate antibacterial therapy in order to diminish the potential synergistic effect of both infections.

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