Community-Acquired Respiratory Complications in the Intensive Care Unit: Pneumonia and Acute Exacerbations of COPD

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This chapter will review the two most common lower respiratory tract infections in the intensive care unit (ICU), community-acquired pneumonia (CAP) and acute exacerbations of chronic obstructive pulmonary disease (AECOPD). In addition we will provide an overview of the topics including recommendations for the diagnosis and treatment.

41.1 Severe Community-Acquired Pneumonia in the ICU

Community-acquired pneumonia is the seventh leading cause of death overall and the most common cause of death from infectious diseases in the United States [1, 2]. Based on their clinical condition, patients are admitted to the medical wards, or if severely ill to the ICU. ICU patients carry the highest mortality rates among all patients with CAP [3]. Multiple sets of clinical practice guidelines have been published in the past few years addressing the treatment of CAP, and they all agree that CAP patients admitted to the hospital represent a major concern, and appropriate empiric therapy should be instituted to improve clinical outcomes [3–10]. We will review the current literature related to CAP patients admitted to the ICU; regarding epidemiology, risk factors, severity criteria and reasons to admit the hospitalized patient to the ICU, and the empiric and specific antibiotic therapeutic regimens employed.

41.1.1 Epidemiology

Severe CAP is defined as a clinical syndrome that develops in patients with pneumonia who require hospitalization on the ward service and/or ICU [3]. For the year 2000, over 1 million patients were hospitalized in the United States, and 65,000 deaths were attributable to CAP and influenza [11–13]. There is an estimated cost of approximately nine billion dollars per year [14]. Approximately 10% of all hospitalized patients require ICU admission [15–17]. Hospitalized CAP patients carry significant mortality depending on the severity of illness. Several studies have reported a mortality rate of approximately 10% in hospitalized ward patients, and 30–60% mortality in patients who require ICU admission [3, 18]. CAP is burdensome to health care systems as the duration of hospitalization is 6 days at a cost of approximately $7,500 for ward patients compared to 23 days and $21,144 for ICU patients [11, 19, 20].

The most important determinants for hospitalization and assessment of severity in CAP are the patients' chronic co-morbid conditions and/or the prior antibiotic use (see Table 41.1) [3, 7, 8, 10, 21–27]. Prior antibiotic use has been defined in the CAP clinical practice guidelines as the use of any antibiotic regime in the past 3 months, and is also associated with increased risk of morbidity and mortality [7, 22, 28]. The most common co-morbid illnesses for CAP patients are chronic obstructive pulmonary disease (COPD), which is present in up to half of these patients, followed by alcoholism, chronic heart disease and diabetes mellitus (Table 41.1 shows the risk factors and associated microorganisms) [3, 7, 8, 10, 23–27]. It is important to point out that approximately one-third of patients with CAP were previously healthy [27, 29]. Elderly and nursing home patients are also at significant risk for CAP and have high mortality rates, although some experts consider pneumonia in nursing home patients as health care associated pneumonia due to the similarities in the etiologic pathogens with hospital acquired pneumonia [22, 28, 30]. Hospitalization rates for pneumonia have increased among US adults aged 64–74 years and aged 75–84 years during the past 15 years. Among those aged 85 years or older, at least 1 in 20 patients were hospitalized each year due to pneumonia [31].

The main causes of death in severe CAP patients include refractory hypoxemia, refractory shock, and other pneumonia-related complications, predominantly multi-organ failure [32–37].

The microbial patterns of severe CAP have been extensively studied in the past decade. Consistently, *Streptococcus pneumoniae* is recognized as the most common pathogen causing CAP. Other respiratory

Table 41.1. Risk factors associated with CAP and suggested pathogens

Risk factor	Pathogen
Alcoholism	*Streptococcus pneumoniae* and anaerobes
Cystic fibrosis and other structural lung diseases	*Pseudomonas aeruginosa, Burkholderia cepacia,* and *Staphylococcus aureus*
COPD, smoking and/or bronchiectasis	*S. pneumoniae*, *Haemophilus influenzae*, GNRs, *Pseudomonas aeruginosa*
Chronic aspiration	Mixed infection, anaerobes, GNRs
Chronic steroid use	*Aspergillus* spp.
Nursing home residents, recent antimicrobial therapy (considered HCAP)	*S. aureus* (MRSA), GNRs, *Pseudomonas aeruginosa*
Influenza	*Staphylococcus aureus, S. pneumoniae*, *Haemophilus influenzae*
Injection drug users	*S. aureus*, *S. pneumoniae*, anaerobes, *M. tuberculosis*
Poor dental hygiene	Anaerobes
Exposure to bats or soil with bird droppings	*Histoplasma capsulatum*
Exposure to birds	*Chlamydophila psittaci*
Exposure to cattle	*Coxiella burnetii*
Exposure to rabbits	*Francisella tularensis*
HIV infection (early with high CD4 counts)	*S. pneumoniae*, *Haemophilus influenza, Mycobacterium tuberculosis*
HIV infection (late with low CD4 counts)	In addition to above pathogens: *Pneumocystis jiroveci, Cryptococcus* spp., *H. capsulatum, Coccidioides* spp.
Winter	Influenza, RSV, adenovirus, parainfluenza, rhinovirus
Skin infections	Community-acquired methicillin resistant *Staphylococcus aureus* (CA-MRSA) [141, 142]
Other	Outbreaks: *Legionella* spp., viruses (avian flu, SARS coronavirus [143], metapneumovirus [144], "Sin Nombre" hantavirus [145, 146]
Additional comorbid conditions[a]	*S. pneumoniae*, *Haemophilus influenzae*, GNRs, atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella* spp.)

GNRs Gram-negative rods, *HCAP* health care associated pneumonia, *MSSA* methicillin-susceptible *S. aureus, MRSA* methicillin-resistant *S. aureus, RSV* respiratory syncytial virus

[a] Include renal failure (chronic renal disease), neurological diseases (cerebrovascular diseases), malnutrition, hepatic disease (chronic liver diseases), bacteremia, smoking history and gross aspiration [23–27, 33, 68]

Table 41.2. Pneumonia severity of index score[a] (adapted from Fine et al. [39])

Criteria	Points
Age	
Male	Age (years)
Female	Age (years) –10
Nursing home resident	+10
Preexisting comorbid conditions	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Vital signs abnormalities	
Altered mental status	+20
Respiratory rate > 30 breaths per minute	+20
Systolic blood pressure < 90 mmHg	+20
Temperature < 35° or > 40 °C	+15
Heart rate > 125 per minute	+10
Laboratory or radiographic findings	
Serum blood urea nitrogen > 30 mg/dl	+20
Serum sodium < 130 meq/l	+20
Serum glucose > 250 mg/dl	+10
Hematocrit < 30 %	+10
Arterial pH < 7.35	+30
Arterial oxygen tension (PaO_2) < 60 mmHg or arterial oxygenation saturation < 90 %	+10
Pleural effusion on chest radiograph	+10

[a] For each variable present, the points indicated are added to the score, and the final score is then divided into five risk classes (see Table 41.3)

tract pathogens associated with CAP in the ICU include *Haemophilus influenza*, *Klebsiella pneumoniae*, *Legionella* species, *Staphylococcus aureus* and viral pneumonias (Table 41.2). However, there is an extensive list of pathogens associated with severe CAP in the ICU. The association of individual pathogens and certain comorbid conditions was mentioned earlier (Table 41.1), and specific treatment will be discussed at the end of this chapter.

41.1.2 Severity Assessment and Criteria for Hospital and ICU Admission

One of the most critical decisions for physicians treating patients with CAP is whether to hospitalize patients on the ward or ICU service [38]. This decision is usually made in the outpatient office or in the emergency department, and has implications for the antibiotic class selection, route, and duration of therapy.

Two tools have been developed to predict mortality and to determine the site of care for patients with CAP based on the severity of illness, the pneumonia-specific severity of illness (PSI) score and the CURB rule [39–46]. Fine and colleagues developed the PSI score as part of the pneumonia Patient Outcome Research Team Study (PORT) [39]. The PSI is based on 20 parameters including three demographic variables, five

Table 41.3. Pneumonia severity index score risk class stratification[a] (adapted from Fine et al. [39])

Risk class	Points	Mortality (%)	Recommended site of care
I	–[b]	0.1	Outpatient
II	<70	0.6	Outpatient
III	71–90	2.8	Outpatient or brief inpatient
IV	91–130	8.2	Inpatient
V	>130	29.2	Inpatient

[a] Metlay and Fine suggested a three-step process to decide the initial site of CAP treatment based on: (1) assessment of preexisting conditions that compromise safety of home care; (2) calculation of the PSI score; and (3) clinical judgment [47]

[b] Risk class I: age <50 years, no comorbidities and absence of vital-sign abnormalities

Table 41.4. CURB-65 criteria (adapted from Lim et al. [46])

Age >65 years
Altered mental status
Respiratory rate >30 breaths per minute
Diastolic blood pressure <60 mmHg
Serum blood urea nitrogen >19.6 mg/dl

Each criterion has a score of one, and the total score depends on the presence or absence of each of the five criteria. Two or more criteria suggest severe CAP and admission to the hospital is recommended.

co-morbid conditions, five physical examination findings, and seven laboratory/imaging results with the primary goal to identify low risk patients who might be managed safely at home (Tables 41.2, 41.3). In a follow-up paper, the same authors suggested a three-step process to decide the initial site of CAP treatment based on: (1) assessment of preexisting conditions that compromise safety of home care; (2) calculation of the PSI score; and (3) clinical judgment [47]. Similarly, the CURB or CURB-65 (mental status changes, increased blood urea nitrogen, increased respiratory rate, decreased blood pressure, and age above 65 years) was introduced as a much simpler rule to identify patients at low risk of dying and the possible site of care (Table 41.4) [43–46]. Both prognostic tools have been validated in several studies [48–56]. Both tools suggest that CAP patients should be hospitalized if they are included in PSI class IV and V and/or CURB or CURB-65 ≥ 2. It is important to recognize that these tools should not limit the clinical judgment of practicing physicians to decide site of care. In addition, these tools were not developed to identify which patients with CAP should be admitted to the ICU.

The best accepted criteria for the definition of severe CAP are those patients requiring ICU admission. However, there are recommendations based on seven clinical criteria in the 1993 American Thoracic Society (ATS) guidelines [40, 57] that were further refined by Ewig and collaborators in 1998 [42]. The ATS CAP guidelines adopted this new evidence and recommend-

Table 41.5. American Thoracic Society modified criteria (table adapted from Ewig et al. [3, 42])

Major criteria
Need for mechanical ventilation
Requiring vasopressors (septic shock)
Minor criteria
Respiratory rate >30 breaths per minute
PaO_2/FiO_2 ratio <250
Bilateral or multilobar infiltrates

The presence of at least one major criterion or at least two minor criteria defines a pneumonia severe enough to require ICU admission

ed the modified ATS criteria for severe CAP [3]. These investigators included the presence of one of the two major criteria and/or two out of three minor criteria (Table 41.5) [42]. Several studies have validated these criteria to admit patients to the ICU and applied them also in other groups of patients including elderly and HIV-infected patients [19, 42, 49, 50, 53, 58, 59].

Thus, the severity assessment criteria are useful to help physicians identify patients who may need hospitalization or ICU admission, but they are not meant to remove physicians' clinical judgment in the decision-making process.

41.1.3 Diagnosis

All patients suspected of having CAP should receive a chest radiograph to confirm the diagnosis of pneumonia. Several laboratory studies should be performed in patients with CAP admitted to the ICU in order to assess the severity of the disease and possible complications. These tests include: complete blood cell count and differential, basic blood chemistry (urea nitrogen and serum creatinine) electrolytes (sodium and potassium), glucose, and liver function tests. Evaluation of the oxygenation by pulse oxymetry or arterial blood gas analysis is extremely important and mandatory [60]. An attempt to obtain samples to identify the likely etiologic agent is indicated in severe CAP patients [61]. However, there is no supportive evidence that microbiological studies will change favorably the final outcome in these patients. Several microbiological tests are recommended in patients with CAP in the ICU (Table 41.6). In addition, other diagnostic markers including C-reactive protein (CRP) and/or procalcitonin have been used as prognostic indicators with variable results [62, 63].

41.1.4 Antimicrobial Treatment

Treatment guidelines have been developed by several professional organizations to standardize therapy for

CAP, including those patients with severe CAP [3, 6–10]. The published practice guidelines reflect the evolution of expert opinion, changes in resistance patterns and availability of new clinical data regarding the treatment and diagnosis of CAP management in immunocompetent adults. All of these guidelines support the concept that the treatment of ICU patients with CAP should be focused on the possible associated etiologic agents [3, 7, 8, 10]. Appropriate, aggressive and early therapeutic approaches including initiation of antibiotics as early as possible [36, 64] are the main interventions to decrease mortality in patients with CAP in the ICU.

Table 41.6. Laboratory studies recommended in patients with CAP admitted to the ICU

Blood culture [147]
Lower respiratory tract sample
Gram-stain and culture
Sputum [148]
Bronchoscopic or non-bronchoscopic evaluation: including either endotracheal aspirate, bronchoalveolar lavage (BAL), protected specimen brush, for quantitative cultures [149]
Atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella* spp.) culture or PCR
Direct immunofluorescence for influenza and RSV (winter)
BAL for respiratory viruses for PCR
Urinary antigen for:
Legionella spp. [150–153]
Streptococcus pneumoniae [154–156]
Serology testing in the initial and convalescent stages for:
Atypical pathogens (*M. pneumoniae*, *C. pneumoniae*, and *Legionella* spp.) if no PCR is available [157]
Pleural fluid analysis for parapneumonic effusions
Direct rapid viral test by nucleic acid amplification
Influenza, RSV, adenovirus, parainfluenza, rhinovirus

Empiric therapy should be directed against *S. pneumoniae*, *H. influenzae*, and Gram-negative bacilli with beta-lactam medications or new respiratory fluoroquinolones. *Legionella* spp. (and other atypical pathogens) should be covered with a macrolide or a fluoroquinolone [3, 6–8, 10, 65]. Mixed infections with typical and atypical pathogens occur in approximately 5–40% of cases, and should always be considered, to ensure patients are treated with appropriate empiric antimicrobial therapy [3, 6–8, 10, 56, 66, 67]. In cases in which the infecting pathogen can be identified, directed therapy should be employed [3, 6–8, 10]. In all clinical series, approximately 40–70% of patients with CAP have no pathogen identified [25, 68, 69]. The failure to identify a pathogen has not been associated with a worse outcome, but the empiric regimen should cover *S. pneumoniae* and atypical pathogens [15, 16].

The clinical practice guidelines suggest that severe CAP patients admitted to the ICU should be stratified as to whether or not the patients are at risk for *Pseudomonas* spp. infection [3, 7, 10]. If a patient has no risk factors for *Pseudomonas* infection, the treatment should always include two antibiotics, one (beta-lactam) that will cover pneumococcus (including drug resistant isolates) and another (macrolide or respiratory fluoroquinolone) that will cover atypical pathogens especially *Legionella* spp.(Table 41.7) [3, 7, 10, 70]. *Pseudomonas aeruginosa* has been reported in severe CAP patients with specific risk factors, such as chronic or

Empiric treatment	Comments
Intravenous beta-lactam – Third generation cephalosporins (ceftriaxone or cefotaxime) **or** – Beta-lactam/beta-lactamase inhibitor (ampicillin-sulbactam or piperacillin-tazobactam) **plus either**	Covers well *Streptococcus pneumoniae*, *Haemophilus influenzae*, enteric gram-negative bacilli (*Klebsiella* spp.)
Intravenous macrolide – (azithromycin or clarithromycin) **or** Intravenous fluoroquinolone[a] – (levofloxacin, or moxifloxacin)	*Legionella* spp., *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *C. psittaci*
Intravenous beta-lactam – Antipseudomonal beta-lactam/beta-lactamase inhibitor (aztreonam, ceftazidime, cefepime, piperacillin-tazobactam, imipenem, meropenem) **plus either** Intravenous aminoglycoside or intravenous ciprofloxacin/Levofloxacin [750] **plus** Intravenous macrolide – (azithromycin or clarithromycin) if aminoglycoside used, but not with the use of ciprofloxacin/Levofloxacin [750]	*Pseudomonas aeruginosa* (and the other pathogens above)

Table 41.7. Empiric antimicrobial regimen to treat severe community-acquired pneumonia in the ICU (adapted from the clinical practice guidelines [3, 6–10])

[a] Drug resistant *Streptococcus pneumoniae* (DRSP) is also covered by the respiratory fluoroquinolones

prolonged use of broad-spectrum antibiotic therapy, bronchiectasis, malnutrition, HIV and immunosuppression [3, 25, 59, 71, 72]. Patients with risk factors for *P. aeruginosa* admitted to the ICU require specific attention and should receive appropriate antipseudomonal agents as discussed below (Table 41.7).

Only two randomized control trials and several observational studies have evaluated the benefit of using combination therapy versus monotherapy in patients with severe CAP admitted to the ICU [73, 74]. From the limited data and significant heterogeneity between studies, we conclude that there is limited information to compare the differences in mortality for patients with CAP in the ICU. On the other hand, there is strong evidence supporting the clinical practice guidelines [3, 7, 10] by demonstrating statistically significant benefit for those patients receiving guideline concordant therapies in patients with CAP [49, 65, 75–78]. In addition, there is data to support the benefit of using a combination therapy of beta-lactamic agent plus a macrolide for initial empiric therapy to reduce mortality in patients with CAP [77].

41.1.4.1 Specific Antimicrobial Therapy

Streptococcus pneumoniae is isolated in up to one-third of all ward and ICU patients [23–26, 34, 59, 68, 69]. Several studies published by Moroney et al. [79], Kalin et al. [80], and Metlay et al. [81] evaluated clinical outcomes in patients with bacteremic pneumococcal pneumonia. Antimicrobial resistance in bacteremic *S. pneumoniae* showed no contribution to mortality or the requirement for ICU admission, but may be associated with an increased risk of adverse outcome such as suppurative complications of infection (such as empyema) [79–81]. Waterer et al. found that single effective drug therapy for severe bacteremic pneumococcal pneumonia was associated with a greater risk of death than dual effective therapy [82]. Several other studies suggested a benefit of having a macrolide added to the beta-lactam therapy in patients with bacteremic pneumococcal pneumonia [83–86]. Not adding a macrolide to a beta-lactam based initial antibiotic regimen was an independent predictor of in-hospital mortality [85]. All

Table 41.8. Specific antimicrobial therapy for patients with CAP

Pathogen specific	Recommended therapy
Streptococcus pneumoniae	
Bacteremic	Combination therapy with beta-lactam plus macrolide or fluoroquinolone
Intermediate resistance to penicillin (≤2 mg/dl)	*Third generation cephalosporin, or respiratory fluoroquinolone*
High level of resistance to penicillin (≤2 mg/dl)	*Respiratory fluoroquinolone, vancomycin, linezolid*
Staphylococcus aureus	
MSSA	Third generation cephalosporin, respiratory fluoroquinolone, or clindamycin
MRSA (CA-MRSA)[a]	Vancomycin or linezolid
Atypicals: *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae* and *Legionella* spp.	Respiratory fluoroquinolone, macrolide or doxycycline (not for *Legionella* spp.)
Haemophilus influenzae	Amoxicillin
Beta-lactamase producer	Third-generation cephalosporin, beta-lactam/beta-lactamase inhibitors or a fluoroquinolone, newer macrolide (clarithromycin or azithromycin), or doxycycline
Enterobacteriaceae including *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus mirabilis*	Third-generation cephalosporin, beta-lactam/beta-lactamase inhibitors or a fluoroquinolone
Pseudomonas aeruginosa	Intravenous antipseudomonal beta-lactam/beta-lactamase inhibitor plus either intravenous aminoglycoside or intravenous ciprofloxacin/Levofloxacin [750], plus an intravenous macrolide if aminoglycoside used, but not with the use of ciprofloxacin/Levofloxacin [750]
Coxiella burnetii or *Chlamydophila psittaci*	Macrolide or tetracycline
Influenza pneumonia [7, 158]	The newer agents oseltamivir or zanamivir cover both influenza A and B [7][b]
Aspiration pneumonia anaerobic infections	Carbapenems, clindamycin or beta-lactam/beta-lactamase inhibitors [159]

[a] CA-MRSA community-acquired methicillin-resistant *S. aureus* usually not multidrug resistant

[b] Influenza; CDC reported high levels of resistance in the 2005–2006 season [160]

other specific antimicrobial therapies for identified CAP pathogens are described in Table 41.8.

41.1.5 Duration of Therapy

Generally, the duration of therapy in patients with severe CAP is 7–10 days, but those with atypical pathogens such as *Legionella* spp. should receive longer treatment for 10–14 days [3, 87]. Several studies report the use of a critical pathway to improve the treatment for CAP patients, including those with severe disease [88–93].

Antimicrobial treatment failure or non-resolving pneumonia is usually underestimated [94]. The most common causes include microbial resistance to the initial antimicrobial regimen, suppurative complications, or the presence of nosocomial pneumonia [95].

After the initial clinical improvement, hospitalized patients should be switched from intravenous to oral antibiotic therapy, while maintaining similar antimicrobial coverage and tissue concentrations as with the parenteral form. Criteria for determining when the patient can make the transition to oral antibiotics include the ability to tolerate antibiotics by mouth, a functioning gastrointestinal tract, a stable blood pressure, a trend towards normalization of the white blood cell count, and improving symptoms such as cough, dyspnea and fevers [96–98]. A meta-analysis by Rhew et al. evaluated early intravenous to oral conversion and discharge strategies in patients with CAP, and demonstrated that these interventions are associated with a significant and safe reduction in the mean length of hospital stay [96].

Several of the quality indicators already mentioned, early administration of antibiotics, appropriate antibiotic use following the clinical practice guidelines, use of a critical pathway, switch to oral therapy and early discharge all show improved clinical outcomes in CAP [3, 7, 8, 10]. In addition, measures directed at prevention such as vaccination for pneumococcal and influenza infections, and counseling to quit smoking for patients at risk, may help to decrease the incidence of CAP [3, 7, 8, 10]. Other important processes of care include the collection of blood cultures before antibiotic administration, or in the first 24 h, a test for *Legionella* infections in ICU patients and an evaluation of oxygenation (measurement of blood gases or pulse oximetry).

41.2 Acute Exacerbations of COPD in the ICU

We will describe the diagnosis and antibiotic treatment of acute exacerbations of chronic obstructive pulmonary disease (AECOPD).

41.2.1 Epidemiology

Chronic obstructive pulmonary disease (COPD) is a condition associated with AECOPD. COPD currently accounts for approximately 110,000 deaths per year, making it, following heart disease, cancer, and stroke, the fourth leading cause of death in the United States. It has been estimated that by the year 2020, AECOPD will be the third leading cause of death [99]. The cost of treating AECOPD is very high, not only because of the economic impact, but also because of the high associated morbidity and early mortality. COPD in the United States annually accounts for 16,000,367 office visits, 500,000 hospitalizations, and 18 billion dollars in direct health care costs [100]. Despite treatment with antibiotics, bronchodilators, and corticosteroids, up to 28% of patients discharged from the Emergency Department with acute exacerbations have recurrent symptoms within 14 days [101] and 17% relapse and require hospitalization [102]. Several investigators have confirmed that relapse is more likely among patients who have lower pretreatment or post-treatment FEV_1, those who receive more bronchodilator treatments or corticosteroids during visits, and those who have higher rates of previous relapse [103].

AECOPD can be associated with significant mortality. In the Study to Understand Prognosis and Preferences for Outcomes and Rates of Treatment (SUPPORT) [104], the 180-day mortality rate was 33% and the 2-year mortality rate was 49%. Significant predictors of mortality include acute physiology and chronic health evaluation (APACHE III) score [105], body mass index, age, functional status 2 weeks prior to admission, lower ratio of PaO_2 to F_iO_2, congestive heart failure, serum albumin level, cor pulmonale, lower activities of daily living scores, lower scores on the Duke Activity Status Index, and number of hospital days before transfer to the ICU [106].

41.2.2 Etiology

Although respiratory infections are assumed to be the main risk factors for exacerbation of COPD, other factors are also involved [107]. Many patients with AECOPD are thought to have a combination of viral and bacterial infections, which contribute to their exacerbation. A variety of microorganisms have been shown to be associated with infectious bacterial AECOPD, including *Haemophilus influenzae, H. parainfluenzae, Moraxella catarrhalis,* and *Streptococcus pneumoniae* [108]. It has also been reported that these patients may be infected with atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, but because of limitations with the diagnosis, the true preva-

lence of these organisms is not known [109–112]. There have been several recent studies demonstrating that patients with the most severe COPD and those that required ICU care have significantly higher prevalence of Gram-negative organisms such as Enterobacteriaceae and *Pseudomonas* species [113–115]. Several investigators have proposed that airway damage from chronic infection or colonization occurs in these patients because the bacteria cause the host to continuously release inflammatory mediators [116, 117]. Persistent infection results in lung inflammation and, as a consequence, lung function progressively decreases.

41.2.3 Diagnostic Procedures

A recent evidence base analysis has summarized the best available information related to the use of diagnostic tests in AECOPD [118, 119]. These reviews concluded that data on the utility of most diagnostic tests are limited. However, chest radiography and arterial blood gas sampling are useful while spirometry is performed at the time of the exacerbation is not [102]. Patients who require ICU care should have a chest radiograph obtained in order to rule out any other abnormalities and arterial blood gases.

41.2.4 Treatment with Antibiotics

There have been a number of clinical trials examining the use of antibiotics in the treatment of AECOPD [101, 107, 108, 120, 121]. The GOLD guideline, (GOLD website, accessed Feb. 2006) and the American Thoracic Society/European Respiratory Society (ATS/ERS) COPD consensus guidelines recommend antibiotic choices on the basis of local sensitivity patterns of the most common pathogens associated with AECOPD, and provide specific guidelines [122, 123].

There are limited number of studies that have looked at the use of antibiotics in ICU patients. Some of the recent publications, including a recent meta-analysis [124], demonstrated a benefit of antibiotics during an acute exacerbation of ambulatory patients. The study by Anthonisen et al. [125] reported that patients with all three clinical symptoms (increased shortness of breath, increased sputum production, and a change in sputum purulence) at initial presentation who received antibiotics showed a more rapid improvement in peak flow, a greater percentage of clinical successes, and a smaller percentage of clinical failures than those who received placebo. Furthermore, Allegra, et al. [126] found significant benefit with the use of amoxicillin-clavulanate acid (Augmentin) therapy compared with placebo in patients with severe disease. Patients who received this antibiotic exhibited a higher success rate (86.4% versus 50.3% in the placebo group, $p < 0.01$) and a lower frequency of recurrent exacerbations.

There is only one study that has evaluated the role of antibiotics during AECOPD in ICU patients. Nouira et al. [127] published a prospective, randomized, double-blind, placebo-controlled trial, evaluating the use of ofloxacin in patients with AECOPD who required mechanical ventilation (invasive or non-invasive). This study demonstrated that a significant number of Gram-negative organisms (including *E. coli*, *P. mirabilis*, and *P. aeruginosa*) were identified in their population of patients with severe AECOPD. In addition to supporting the findings of the previously reported studies, this trial demonstrated that treating these pathogens is important for improving outcomes in this high-risk population. The antibiotic-treated group had a significantly lower in-hospital mortality rate and a significantly reduced length of stay in the hospital compared with the placebo group. In addition, the patients receiving ofloxacin were less likely to develop pneumonia than those on placebo.

There are additional potential benefits of antibiotic therapy for patients with AECOPD. Antibiotics can reduce the burden of bacteria in the airway [128]. There is a large percentage of patients with acute exacerbations (50–75% potentially pathogenic microorganisms in addition to significantly higher concentrations of frequently $\geq 10^4$ organisms) of bacteria in the large airways. Because treatment with appropriate antibiotics significantly decreases the bacterial burden at 72-h follow-up bronchoscopy, it is speculated that the proper choice of antibiotic reduces the risk of progression to more severe infections, such as pneumonia [115]. The eradication of bacteria by antibiotics is thought to break the vicious cycle of infection, i.e., lung destruction leading to progression of the lung disease.

If the use of antibiotics to treat AECOPD has all the potential benefits discussed, does it matter which agent is chosen? In the Anthonisen et al. study [125], the assumption was made that all of the antibiotics were equivalent; thus the specific agent prescribed was not considered important. Despite the problems with many of the published antibiotic trials, there are some retrospective trials that emphasize the importance of choosing the correct antibiotic for treatment of patients with AECOPD. A recent retrospective study of outpatients with documented COPD, conducted at our institution, evaluated the risk factors for therapy failure at 14 days after an acute exacerbation [129]. One group of patients received antibiotics and the second group did not. The overall relapse rate (defined as a return visit with persistent or worsening symptoms within 14 days) was 22%. After an extensive multivariate analysis, the major risk factor for relapse was lack of antibiotic therapy (32% versus 19%, $p < 0.001$ compared to the antibi-

otic-treated group). The type of antibiotic used was also an important variable associated with the 14-day treatment failure. Patients treated with amoxicillin had a 54% relapse rate compared with only 13% for the other antibiotics ($p<0.01$). Furthermore, treatment with amoxicillin resulted in a higher incidence of failure, even when compared with those who did not receive antibiotics including amoxicillin, macrolides, and ciprofloxacin ($p=0.006$). Although there may be many explanations for these treatment failures, the most likely is that the pathogens were resistant to amoxicillin. This study showed that the use of antibiotics was associated with a significantly lower rate of therapy failure. In contrast to Anthonisen's data [125], Adams' data show that antibiotics are beneficial regardless of the severity of AECOPD. Furthermore, the patients who received antibiotics, and failed within 14 days, had a significantly higher rate of hospital admissions than those who did not receive antibiotics.

Destache et al. reported the impact of antibiotic selection, antimicrobial efficacy, and related cost in AECOPD [130]. The failure rates were significantly higher (at 14 days) for the first-line (amoxicillin, co-trimoxazole, erythromycin, and tetracycline), compared with the third-line (amoxicillin-clavulanate, azithromycin, and ciprofloxacin) agents (19% versus 7%, $p<0.05$). When compared with those who received the first-line agents, the patients treated with the third-line agents had a significantly longer time between exacerbations, overall fewer hospitalizations, and considerably lower total cost.

41.2.5 End-Point for the Treatment of AECOPD

Conventional end-points for efficacy of antibiotics treatment in AECOPD include the symptoms and bacteriological resolution measured at 2–3 weeks after the treatment was started. Most of these end-points rely solely on the subjective report of symptom improvement. It has been suggested by several investigators that other parameters such as the rate of symptom resolution, the interval between exacerbations, the improvement in quality of life, the need for hospitalization and mortality, may be more suitable end-points in this patient population [131, 132].

41.2.6 Clinical Parameters To Stratify Patients into Risk Groups

The clinical parameters that are implicated as possible risk factors for treatment failure in AECOPD and suggested therapies are summarized in Tables 41.9 and 41.10 [10, 108, 121].

41.2.7 Prevention

The two most important prevention measures in AECOPD and CAP patients are smoking cessation

Table 41.9. Patient profiles from the Canadian Chronic Bronchitis Guidelines (adapted from Balter et al. [108])

Acute tracheobronchitis (Group 0)
Healthy people with cough and sputum without previous respiratory problems

"Simple" chronic bronchitis without risk factors (Group I)
Increased cough and sputum, sputum purulence and increased dyspnea

"Complicated" chronic bronchitis with risk factors (Group II)
As group I **plus** (at least one of the following)
>4 exacerbations per year **or**
Cardiac disease **or**
Home oxygen **or**
Chronic oral steroid use **or**
Antibiotic use in the 3 months prior

Chronic "suppurative" bronchitis (Group III)
As group II with constant purulent sputum, plus:
Bronchiectasis (some patients) **or**
FEV1<35% predicted **or**
Multiple risk factors (frequent exacerbations and FEV1<50%)

Category	Probable pathogen	Recommended therapy
Acute tracheobronchitis	Viral	Symptomatic
"Simple" AECOPD	*Haemophilus* spp. (*H. influenzae*), *M. catarrhalis*, *S. pneumoniae*	Macrolide (azithromycin or clarithromycin), amoxicillin, doxycycline, 2nd or 3rd generation cephalosporins. If treatment failure: beta-lactam/beta-lactamase inhibitor or fluoroquinolone
"Complicated" AECOPD	As above with the addition of Gram-negative organisms (*Klebsiella* spp. etc.), and multi-drug resistant (MDR) pathogens such as *Pseudomonas* spp.	3rd generation cephalosporins, beta-lactam/beta-lactamase inhibitor or fluoroquinolone (ciprofloxacin for *Pseudomonas* spp.) Parenteral inpatient therapy highly considered for MDR pathogens or treatment failures

Table 41.10. Recommendations for antibiotic therapy in AECOPD (adapted from Balter et al [108])

[133 – 135] and active immunizations, including influenza and pneumococcal vaccinations.

Influenza is an important cause of lower respiratory tract infections. Influenza A and B often reach epidemic proportions during the winter months. The impact of influenza is critical to the development of other lower respiratory infections including AECOPD and pneumonia. Epidemiological studies have shown that the frequency of lower respiratory infections, and associated morbidity and mortality, are markedly reduced with influenza vaccination [136 – 138]. The polyvalent vaccine based on pneumococcal capsule serotypes has been shown to be effective in preventing pneumococcal bacteremia and pneumonia [138 – 140]. The vaccine is recommended in patients with COPD.

41.3 Summary

The cost, morbidity, and mortality related to CAP and AECOPD remain unacceptably high. Because these are heterogeneous groups of patients it is important to use risk-stratification based on clinical parameters and prediction tools. Appropriate antibiotic therapy is an important component in the management of both groups of patients. In particular, it is essential to administer an appropriate antimicrobial agent from the initiation of therapy, so that the risks of treatment failure and the morbidity of CAP and AECOPD may be minimized.

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

References

1. Anonymous (1995) Pneumonia and influenza death rates – United States, 1979 – 1994. [erratum appears in MMWR Morb Mortal Wkly Rep 1995 44(41):782]. MMWR 44:535 – 537
2. National Center for Health Statistics CfDCaP (1994) Advance report of final mortality statistics 1992. US Department of Health and Human Services, Public Health Service, Hyattsville, MD
3. Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, Dean N, File T, Fine MJ, Gross PA, Martinez F, Marrie TJ, Plouffe JF, Ramirez J, Sarosi GA, Torres A, Wilson R, Yu VL (2001) Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 163:1730 – 1754
4. Anonymous (1998) ERS Task Force Report. Guidelines for management of adult community-acquired lower respiratory tract infections. European Respiratory Society. Eur Respir J 11:986 – 991
5. Huchon G, Woodhead M (1998) Management of adult community-acquired lower respiratory tract infections. Eur Respir Rev 8:391 – 426
6. Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH (2000) Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. The Canadian Community-Acquired Pneumonia Working Group. Clin Infect Dis 31: 383 – 421
7. Mandell LA, Bartlett JG, Dowell SF, File TM, Jr, Musher DM, Whitney C (2003) Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 37:1405 – 1433
8. Bartlett JG, Dowell SF, Mandell LA, File TM Jr, Musher DM, Fine MJ (2000) Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Diseases Society of America. Clin Infect Dis 31:347 – 382
9. Heffelfinger JD, Dowell SF, Jorgensen JH, Klugman KP, Mabry LR, Musher DM, Plouffe JF, Rakowsky A, Schuchat A, Whitney CG (2000) Management of community-acquired pneumonia in the era of pneumococcal resistance: a report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group. Arch Intern Med 160: 1399 – 1408
10. Woodhead M, Blasi F, Ewig S, Huchon G, Leven M, Ortqvist A, Schaberg T, Torres A, van der Heijden G, Verheij TJM (2005) Guidelines for the management of adult lower respiratory tract infections. Eur Respir J 26:1138 – 1180
11. Kozak LJ, Hall MJ, Owings MF (2002) National Hospital Discharge Survey: 2000 annual summary with detailed diagnosis and procedure data. Vital & Health Statistics – Series 13: Data From the National Health Survey:1 – 194
12. Marston BJ, Plouffe JF, File TM, Jr, Hackman BA, Salstrom SJ, Lipman HB, Kolczak MS, Breiman RF (1997) Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance Study in Ohio. The Community-Based Pneumonia Incidence Study Group. Arch Intern Med 157:1709 – 1718
13. Minino AM, Arias E, Kochanek KD, Murphy SL, Smith BL (2002) Deaths: final data for 2000. National Vital Statistics Reports 50:1 – 119
14. Halm EA, Teirstein AS (2002) Clinical practice. Management of community-acquired pneumonia. N Engl J Med 347:2039 – 2045
15. Leroy O, Santre C, Beuscart C, Georges H, Guery B, Jacquier JM, Beaucaire G (1995) A five-year study of severe community-acquired pneumonia with emphasis on prognosis in patients admitted to an intensive care unit. Intensive Care Med 21:24 – 31
16. Moine P, Vercken JB, Chevret S, Chastang C, Gajdos P (1994) Severe community-acquired pneumonia. Etiology, epidemiology, and prognosis factors. French Study Group for Community-Acquired Pneumonia in the Intensive Care Unit. Chest 105:1487 – 1495
17. Torres A, Serra-Batlles J, Ferrer A, Jimenez P, Celis R, Cobo E, Rodriguez-Roisin R (1991) Severe community-acquired pneumonia. Epidemiology and prognostic factors. Am Rev Respir Dis 144:312 – 318
18. Fine MJ, Smith MA, Carson CA, Mutha SS, Sankey SS, Weissfeld LA, Kapoor WN (1996) Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. JAMA 275:134 – 141
19. Angus DC, Marrie TJ, Obrosky DS, Clermont G, Dremsizov TT, Coley C, Fine MJ, Singer DE, Kapoor WN (2002) Severe community-acquired pneumonia: use of intensive care services and evaluation of American and British Thoracic Society Diagnostic criteria. Am J Respir Crit Care Med 166:717 – 723
20. Niederman MS, McCombs JS, Unger AN, Kumar A, Popovian R (1998) The cost of treating community-acquired pneumonia. Clin Ther 20:820 – 837
21. Gutierrez F, Masia M, Rodriguez JC, Mirete C, Soldan B,

Padilla S, Hernandez I, De Ory F, Royo G, Hidalgo AM (2005) Epidemiology of community-acquired pneumonia in adult patients at the dawn of the 21st century: a prospective study on the Mediterranean coast of Spain. Clin Microbiol Infection 11:788 – 800
22. Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, Lamm W, Clark C, MacFarquhar J, Walton AL, Reller LB, Sexton DJ (2002) Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 137:791 – 797
23. Roson B, Carratala J, Dorca J, Casanova A, Manresa F, Gudiol F (2001) Etiology, reasons for hospitalization, risk classes, and outcomes of community-acquired pneumonia in patients hospitalized on the basis of conventional admission criteria. Clin Infect Dis 33:158 – 165
24. Garcia-Ordonez MA, Garcia-Jimenez JM, Paez F, Alvarez F, Poyato B, Franquelo M, Colmenero JD, Juarez C (2001) Clinical aspects and prognostic factors in elderly patients hospitalised for community-acquired pneumonia. Eur J Clin Microbiol Infect Dis 20:14 – 19
25. Luna CM, Famiglietti A, Absi R, Videla AJ, Nogueira FJ, Fuenzalida AD, Gene RJ (2000) Community-acquired pneumonia: etiology, epidemiology, and outcome at a teaching hospital in Argentina. Chest 118:1344 – 1354
26. Meehan TP, Chua-Reyes JM, Tate J, Prestwood KM, Scinto JD, Petrillo MK, Metersky ML (2000) Process of care performance, patient characteristics, and outcomes in elderly patients hospitalized with community-acquired or nursing home-acquired pneumonia. Chest 117:1378 – 1385
27. Lim WS, Macfarlane JT, Boswell TC, Harrison TG, Rose D, Leinonen M, Saikku P (2001) Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. Thorax 56:296 – 301
28. Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS (2005) Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. Chest 128:3854 – 3862
29. Feldman C, Viljoen E, Morar R, Richards G, Sawyer L, Goolam Mahomed A (2001) Prognostic factors in severe community-acquired pneumonia in patients without comorbid illness. Respirology 6:323 – 330
30. Marrie TJ (2000) Community-acquired pneumonia in the elderly. Clin Infect Dis 31:1066 – 1078
31. Fry AM, Shay DK, Holman RC, Curns AT, Anderson LJ (2005) Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988 – 2002. JAMA 294:2712 – 2719
32. Tejerina E, Frutos-Vivar F, Restrepo MI, Anzueto A, Palizas F, Gonzalez M, Apezteguia C, Abroug F, Matamis D, Bugedo G, Esteban A, International Mechanical Ventilation Study G (2005) Prognosis factors and outcome of community-acquired pneumonia needing mechanical ventilation. J Crit Care 20:230 – 238
33. Marrie TJ, Carriere KC, Jin Y, Johnson DH (2003) Factors associated with death among adults < 55 years of age hospitalized for community-acquired pneumonia. Clin Infect Dis 36:413 – 421
34. Pascual FE, Matthay MA, Bacchetti P, Wachter RM (2000) Assessment of prognosis in patients with community-acquired pneumonia who require mechanical ventilation. Chest 117:503 – 512
35. Mehta R, Groth M (2001) Clinical application of a prognostic model for severe community-acquired pneumonia. Chest 119:312 – 313
36. Meehan TP, Fine MJ, Krumholz HM, Scinto JD, Galusha DH, Mockalis JT, Weber GF, Petrillo MK, Houck PM, Fine JM (1997) Quality of care, process, and outcomes in elderly patients with pneumonia. JAMA 278:2080 – 2084
37. Mortensen EM, Coley CM, Singer DE, Marrie TJ, Obrosky DS, Kapoor WN, Fine MJ (2002) Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. Arch Intern Med 162:1059 – 1064
38. Dean NC, Suchyta MR, Bateman KA, Aronsky D, Hadlock CJ (2000) Implementation of admission decision support for community-acquired pneumonia. Chest 117:1368 – 1377
39. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN (1997) A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 336:243 – 250
40. Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Vandervoort MK, Feagan BG (2000) A controlled trial of a critical pathway for treatment of community-acquired pneumonia. CAPITAL Study Investigators. Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin. JAMA 283:749 – 755
41. Ewig S, Schafer H, Torres A (2000) Severity assessment in community-acquired pneumonia. Eur Respir J 16:1193 – 1201
42. Ewig S, Ruiz M, Mensa J, Marcos MA, Martinez JA, Arancibia F, Niederman MS, Torres A (1998) Severe community-acquired pneumonia. Assessment of severity criteria. Am J Respir Crit Care Med 158:1102 – 1108
43. British Thoracic Society (1993) Guidelines for the management of community-acquired pneumonia in adults admitted to hospital. Br J Hosp Med 49:346 – 350
44. Lim WS, Lewis S, Macfarlane JT (2000) Severity prediction rules in community acquired pneumonia: a validation study. Thorax 55:219 – 223
45. British Thoracic Society Standards of Care Committee (2002) British Thoracic Society guidelines for the management of community acquired pneumonia in childhood. Thorax 57 Suppl 1:i1 – 24
46. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, Lewis SA, Macfarlane JT (2003) Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 58:377 – 382
47. Metlay JP, Fine MJ (2003) Testing strategies in the initial management of patients with community-acquired pneumonia. Ann Intern Med 138:109 – 118
48. Aujesky D, Auble TE, Yealy DM, Stone RA, Obrosky DS, Meehan TP, Graff LG, Fine JM, Fine MJ (2005) Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia. Am J Medicine 118:384 – 392
49. Capelastegui A, Espana PP, Quintana JM, Areitio I, Gorordo I, Egurrola M, Bilbao A (2006) Validation of a predictive rule for the management of community-acquired pneumonia. Eur Respir J 27:151 – 157
50. Ewig S, de Roux A, Bauer T, Garcia E, Mensa J, Niederman M, Torres A (2004) Validation of predictive rules and indices of severity for community acquired pneumonia. Thorax 59:421 – 427
51. Espana PP, Capelastegui A, Quintana JM, Soto A, Gorordo I, Garcia-Urbaneja M, Bilbao A (2003) A prediction rule to identify allocation of inpatient care in community-acquired pneumonia. Eur Respir J 21:695 – 701
52. Arnold FW, Ramirez JA, McDonald LC, Xia EL (2003) Hospitalization for community-acquired pneumonia: the pneumonia severity index vs clinical judgment. Chest 124:121 – 124
53. Ewig S, Kleinfeld T, Bauer T, Seifert K, Schafer H, Goke N (1999) Comparative validation of prognostic rules for

community-acquired pneumonia in an elderly population. Eur Respir J 14:370 – 375
54. Farr BM, Sloman AJ, Fisch MJ (1991) Predicting death in patients hospitalized for community-acquired pneumonia. Ann Intern Med 115:428 – 436
55. Karalus NC, Cursons RT, Leng RA, Mahood CB, Rothwell RP, Hancock B, Cepulis S, Wawatai M, Coleman L (1991) Community acquired pneumonia: aetiology and prognostic index evaluation. Thorax 46:413 – 418
56. Neill AM, Martin IR, Weir R, Anderson R, Chereshsky A, Epton MJ, Jackson R, Schousboe M, Frampton C, Hutton S, Chambers ST, Town GI (1996) Community acquired pneumonia: aetiology and usefulness of severity criteria on admission. Thorax 51:1010 – 1016
57. Niederman MS, Bass JB, Jr, Campbell GD, Fein AM, Grossman RF, Mandell LA, Marrie TJ, Sarosi GA, Torres A, Yu VL (1993) Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. American Thoracic Society. Medical Section of the American Lung Association. Am Rev Respir Dis 148:1418 – 1426
58. Riley PD, Aronsky D, Dean NC (2004) Validation of the 2001 American Thoracic Society criteria for severe community-acquired pneumonia. Crit Care Med 32:2398 –2402
59. Cordero E, Pachon J, Rivero A, Giron JA, Gomez-Mateos J, Merino MD, Torres-Tortosa M, Gonzalez-Serrano M, Aliaga L, Collado A, Hernandez-Quero J, Barrera A, Nuno E (2000) Community-acquired bacterial pneumonia in human immunodeficiency virus-infected patients: validation of severity criteria. The Grupo Andaluz para el Estudio de las Enfermedades Infecciosas. Am J Respir Crit Care Med 162:2063 – 2068
60. Levin KP, Hanusa BH, Rotondi A, Singer DE, Coley CM, Marrie TJ, Kapoor WN, Fine MJ (2001) Arterial blood gas and pulse oximetry in initial management of patients with community-acquired pneumonia. J Gen Intern Med 16: 590 – 598
61. Rello J, Bodi M, Mariscal D, Navarro M, Diaz E, Gallego M, Valles J (2003) Microbiological testing and outcome of patients with severe community-acquired pneumonia. Chest 123:174 – 180
62. Boussekey N, Leroy O, Georges H, Devos P, d'Escrivan T, Guery B (2005) Diagnostic and prognostic values of admission procalcitonin levels in community-acquired pneumonia in an intensive care unit. Infection 33:257 – 263
63. van der Meer V, Neven AK, van den Broek PJ, Assendelft WJ (2005) Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. BMJ 331:26
64. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG (2004) Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. Arch Intern Med 164:637 – 644
65. Restrepo MI, Mortensen EM, Anzueto A, Pugh JA (2003) Mortality in monotherapy versus combination therapy in severe community-acquired pneumonia: a systematic review. Chest 124:190S
66. Lieberman D, Schlaeffer F, Boldur I, Horowitz S, Friedman MG, Leiononen M, Horovitz O, Manor E, Porath A (1996) Multiple pathogens in adult patients admitted with community-acquired pneumonia: a one year prospective study of 346 consecutive patients. Thorax 51:179 – 184
67. Ruiz M, Ewig S, Marcos MA, Martinez JA, Arancibia F, Mensa J, Torres A (1999) Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. Am J Respir Crit Care Med 160:397 – 405
68. El-Solh AA, Sikka P, Ramadan F, Davies J (2001) Etiology of severe pneumonia in the very elderly. Am J Respir Crit Care Med 163:645 – 651
69. Afessa B, Green B (2000) Bacterial pneumonia in hospitalized patients with HIV infection: the pulmonary complications, ICU support, and prognostic factors of hospitalized patients with HIV (PIP) study. Chest 117:1017 – 1022
70. Shefet D, Robenshtok E, Paul M, Leibovici L (2005) Empirical atypical coverage for inpatients with community-acquired pneumonia: systematic review of randomized controlled trials. Arch Intern Med 165:1992 – 2000
71. Arancibia F, Bauer TT, Ewig S, Mensa J, Gonzalez J, Niederman MS, Torres A (2002) Community-acquired pneumonia due to gram-negative bacteria and *Pseudomonas aeruginosa:* incidence, risk, and prognosis. Arch Intern Med 162:1849 – 1858
72. Hatchette TF, Gupta R, Marrie TJ (2000) *Pseudomonas aeruginosa* community-acquired pneumonia in previously healthy adults: case report and review of the literature. Clin Infect Dis 31:1349 – 1356
73. Fogarty C, Siami G, Kholer R, File TM, Jr, Tennenberg AM, Olson WH, Wiesinger BA, Scott Marshall JA, Oross M, Khan JB (2004) Multicenter, open label, randomized study to compare the safety and efficacy of levofloxacin versus ceftriaxone sodium and erythromycin followed by clarithromycin and amoxicillin-clavulanate in the treatment of serious community-acquired pneumonia in adults. Clin Infect Dis 38:S16 – 23
74. Leroy O, Saux P, Bedos JP, Caulin E (2005) Comparison of levofloxacin and cefotaxime combined with ofloxacin for ICU patients with community-acquired pneumonia who do not require vasopressors. Chest 128:172 – 183
75. Bodi M, Rodriguez A, Sole-Violan J, Gilavert MC, Garnacho J, Blanquer J, Jimenez J, de la Torre MV, Sirvent JM, Almirall J, Doblas A, Badia JR, Garcia F, Mendia A, Jorda R, Bobillo F, Valles J, Broch MJ, Carrasco N, Herranz MA, Rello J, Community-Acquired Pneumonia Intensive Care Units Study I (2005) Antibiotic prescription for community-acquired pneumonia in the intensive care unit: impact of adherence to Infectious Diseases Society of America guidelines on survival. Clin Infect Dis 41:1709 – 1716
76. Dean NC, Silver MP, Bateman KA, James B, Hadlock CJ, Hale D (2001) Decreased mortality after implementation of a treatment guideline for community-acquired pneumonia. Am J Med 110:451 – 457
77. Garcia Vazquez E, Mensa J, Martinez JA, Marcos MA, Puig J, Ortega M, Torres A (2005) Lower mortality among patients with community-acquired pneumonia treated with a macrolide plus a beta-lactam agent versus a beta-lactam agent alone. Eur J Clin Microbiol Infect Dis 24:190 – 195
78. Mortensen EM, Restrepo M, Anzueto A, Pugh J (2004) Effects of guideline-concordant antimicrobial therapy on mortality among patients with community-acquired pneumonia. Am J Med 117:726 – 731
79. Moroney JF, Fiore AE, Harrison LH, Patterson JE, Farley MM, Jorgensen JH, Phelan M, Facklam RR, Cetron MS, Breiman RF, Kolczak M, Schuchat A (2001) Clinical outcomes of bacteremic pneumococcal pneumonia in the era of antibiotic resistance. Clin Infect Dis 33:797 – 805
80. Kalin M, Ortqvist A, Almela M, Aufwerber E, Dwyer R, Henriques B, Jorup C, Julander I, Marrie TJ, Mufson MA, Riquelme R, Thalme A, Torres A, Woodhead MA (2000) Prospective study of prognostic factors in community-acquired bacteremic pneumococcal disease in 5 countries. J Infect Dis 182:840 – 847
81. Metlay JP, Hofmann J, Cetron MS, Fine MJ, Farley MM, Whitney C, Breiman RF (2000) Impact of penicillin susceptibility on medical outcomes for adult patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 30:520 – 528
82. Waterer GW, Somes GW, Wunderink RG (2001) Monother-

apy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 161:1837 – 1842
83. Baddour LM, Yu VL, Klugman KP, Feldman C, Ortqvist A, Rello J, Morris AJ, Luna CM, Snydman DR, Ko WC, Chedid MB, Hui DS, Andremont A, Chiou CC, International Pneumococcal Study G (2004) Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am J Respir Crit Care Med 170:440 – 444
84. Lujan M, Gallego M, Fontanals D, Mariscal D, Rello J (2004) Prospective observational study of bacteremic pneumococcal pneumonia: Effect of discordant therapy on mortality. Crit Care Med 32:625 – 631
85. Martinez JA, Horcajada JP, Almela M, Marco F, Soriano A, Garcia E, Marco MA, Torres A, Mensa J (2003) Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 36:389 – 395
86. Mufson MA, Stanek RJ (1999) Bacteremic pneumococcal pneumonia in one American City: a 20-year longitudinal study, 1978 – 1997. Am J Med 107:34S–43S
87. Sabria M, Pedro-Botet ML, Gomez J, Roig J, Vilaseca B, Sopena N, Banos V, Legionnaires Disease Therapy G (2005) Fluoroquinolones vs macrolides in the treatment of Legionnaires disease. Chest 128:1401 – 1405
88. Dresser LD, Niederman MS, Paladino JA (2001) Cost-effectiveness of gatifloxacin vs ceftriaxone with a macrolide for the treatment of community-acquired pneumonia. Chest 119:1439 – 1448
89. Halley HJ (2000) Approaches to drug therapy, formulary, and pathway management in a large community hospital. Am J Health Syst Pharm 57 Suppl 3:S17 – 21
90. Yost NP, Bloom SL, Richey SD, Ramin SM, Cunningham FG (2000) An appraisal of treatment guidelines for antepartum community-acquired pneumonia. Am J Obstet Gynecol 183:131 – 135
91. Palmer CS, Zhan C, Elixhauser A, Halpern MT, Rance L, Feagan BG, Marrie TJ (2000) Economic assessment of the community-acquired pneumonia intervention trial employing levofloxacin. Clin Ther 22:250 – 264
92. Fogarty CM, Greenberg RN, Dunbar L, Player R, Marrie TJ, Kojak CM, Morgan N, Williams RR (2001) Effectiveness of levofloxacin for adult community-acquired pneumonia caused by macrolide-resistant *Streptococcus pneumoniae:* integrated results from four open-label, multicenter, phase III clinical trials. Clin Ther 23:425 – 439
93. Clark LC, Davis CW (2000) Experiences at a large teaching hospital with levofloxacin for the treatment of community-acquired pneumonia. Am J Health Syst Pharm 57 Suppl 3:S10 – 13
94. Menendez R, Perpina M, Torres A (2003) Evaluation of nonresolving and progressive pneumonia. Semin Respir Infect 18:103 – 111
95. Arancibia F, Ewig S, Martinez JA, Ruiz M, Bauer T, Marcos MA, Mensa J, Torres A (2000) Antimicrobial treatment failures in patients with community-acquired pneumonia: causes and prognostic implications. Am J Respir Crit Care Med 162:154 – 160
96. Rhew DC, Tu GS, Ofman J, Henning JM, Richards MS, Weingarten SR (2001) Early switch and early discharge strategies in patients with community-acquired pneumonia: a meta-analysis. Arch Intern Med 161:722 – 727
97. Ramirez JA, Bordon J (2001) Early switch from intravenous to oral antibiotics in hospitalized patients with bacteremic community-acquired *Streptococcus pneumoniae* pneumonia. Arch Intern Med 161:848 – 850
98. Eron LJ, Passos S (2001) Early discharge of infected patients through appropriate antibiotic use. Arch Intern Med 161:61 – 65
99. Murray CJ, Lopez AD (1997) Alternative projections of mortality and disability by cause 1990 – 2020: Global Burden of Disease Study. Lancet 349:1498 – 1504
100. Feinleib M, Rosenberg HM, Collins JG, Delozier JE, Pokras R, Chevarley FM (1989) Trends in COPD morbidity and mortality in the United States. Am Rev Respir Dis 140:S9 – 18
101. Ball P, Tillotson G, Wilson R (1995) Chemotherapy for chronic bronchitis. Controversies. Presse Medicale 24: 189 – 194
102. Emerman CL, Effron D, Lukens TW (1991) Spirometric criteria for hospital admission of patients with acute exacerbation of COPD. Chest 99:595 – 599
103. Murata GH, Gorby MS, Kapsner CO, Chick TW, Halperin AK (1992) A multivariate model for the prediction of relapse after outpatient treatment of decompensated chronic obstructive pulmonary disease. Arch Intern Med 152:73 – 77
104. Connors AF, Jr, Dawson NV, Thomas C, Harrell FE, Jr, Desbiens N, Fulkerson WJ, Kussin P, Bellamy P, Goldman L, Knaus WA (1996) Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med 154:959 – 967
105. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A, et al. (1991) The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 100:1619 – 1636
106. Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA (1995) Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. JAMA 274: 1852 – 1857
107. Ball P (1995) Epidemiology and treatment of chronic bronchitis and its exacerbations. Chest 108:43S–52S
108. Balter MS, La Forge J, Low DE, Mandell L, Grossman RF, Canadian Thoracic S, Canadian Infectious Disease S (2003) Canadian guidelines for the management of acute exacerbations of chronic bronchitis. Can Respir J 10 Suppl B:3B–32B
109. Blasi F, Damato S, Cosentini R, Tarsia P, Raccanelli R, Centanni S, Allegra L (2002) *Chlamydia pneumoniae* and chronic bronchitis: association with severity and bacterial clearance following treatment. Thorax 57:672 – 676
110. Seemungal TA, Wedzicha JA, MacCallum PK, Johnston SL, Lambert PA (2002) *Chlamydia pneumoniae* and COPD exacerbation. Thorax 57:1087 – 1088; author reply 1088 – 1089
111. Smieja M, Leigh R, Petrich A, Chong S, Kamada D, Hargreave FE, Goldsmith CH, Chernesky M, Mahony JB (2002) Smoking, season, and detection of *Chlamydia pneumoniae* DNA in clinically stable COPD patients. BMC Infect Dis 2:12
112. Smieja M, Mahony J, Petrich A, Boman J, Chernesky M (2002) Association of circulating *Chlamydia pneumoniae* DNA with cardiovascular disease: a systematic review. BMC Infect Dis 2:21
113. Eller J, Ede A, Schaberg T, Niederman MS, Mauch H, Lode H (1998) Infective exacerbations of chronic bronchitis: relation between bacteriologic etiology and lung function. Chest 113:1542 – 1548
114. Miravitlles M, Espinosa C, Fernandez-Laso E, Martos JA, Maldonado JA, Gallego M (1999) Relationship between bacterial flora in sputum and functional impairment in

patients with acute exacerbations of COPD. Study Group of Bacterial Infection in COPD. Chest 116:40 – 46
115. Soler N, Torres A, Ewig S, Gonzalez J, Celis R, El-Ebiary M, Hernandez C, Rodriguez-Roisin R (1998) Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. Am J Respir Crit Care Med 157:1498 – 1505
116. Murphy TF, Sethi S (1992) Bacterial infection in chronic obstructive pulmonary disease. Am Rev Respir Dis 146: 1067 – 1083
117. Sethi S, Muscarella K, Evans N, Klingman KL, Grant BJ, Murphy TF (2000) Airway inflammation and etiology of acute exacerbations of chronic bronchitis. Chest 118: 1557 – 1565
118. Bach PB, Brown C, Gelfand SE, McCrory DC, American College of Physicians-American Society of Internal M, American College of Chest P (2001) Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. Ann Intern Med 134:600 – 620
119. Snow V, Lascher S, Mottur-Pilson C, Joint Expert Panel on Chronic Obstructive Pulmonary Disease of the American College of Chest Physicians and the American College of Physicians-American Society of Internal M (2001) Evidence base for management of acute exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 134:595 – 599
120. Ball P, Harris JM, Lowson D, Tillotson G, Wilson R (1995) Acute infective exacerbations of chronic bronchitis. QJM 88:61 – 68
121. Balter MS, La Forge J, Low DE, Mandell L, Grossman RF, Chronic Bronchitis Working G, Canadian Thoracic S, Canadian Infectious Disease S (2003) Canadian guidelines for the management of acute exacerbations of chronic bronchitis: executive summary. Can Respir J 10:248 – 258
122. Celli BR, MacNee W, Force AET (2004) Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 23: 932 – 946
123. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS, Committee GS (2001) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med 163:1256 – 1276
124. Saint S, Bent S, Vittinghoff E, Grady D (1995) Antibiotics in chronic obstructive pulmonary disease exacerbations. A meta-analysis. JAMA 273:957 – 960
125. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA (1987) Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 106:196 – 204
126. Allegra L, Blasi F, de Bernardi B, Cosentini R, Tarsia P (2001) Antibiotic treatment and baseline severity of disease in acute exacerbations of chronic bronchitis: a re-evaluation of previously published data of a placebo-controlled randomized study. Pulm Pharmacol Ther 14:149 – 155
127. Nouira S, Marghli S, Belghith M, Besbes L, Elatrous S, Abroug F (2001) Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomised placebo-controlled trial. Lancet 358:2020 – 2025
128. Cabello H, Torres A, Celis R, El-Ebiary M, Puig de la Bellacasa J, Xaubet A, Gonzalez J, Agusti C, Soler N (1997) Bacterial colonization of distal airways in healthy subjects and chronic lung disease: a bronchoscopic study. Eur Respir J 10:1137 – 1144
129. Adams SG, Melo J, Luther M, Anzueto A (2000) Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of COPD. Chest 117:1345 – 1352
130. Destache CJ, Dewan N, O'Donohue WJ, Campbell JC, Angelillo VA (1999) Clinical and economic considerations in the treatment of acute exacerbations of chronic bronchitis. J Antimicrob Chemother 43 Suppl A:107 – 113
131. Wilson R, Allegra L, Huchon G, Izquierdo JL, Jones P, Schaberg T, Sagnier PP, Group MS (2004) Short-term and long-term outcomes of moxifloxacin compared to standard antibiotic treatment in acute exacerbations of chronic bronchitis [see comment]. Chest 125:953 – 964
132. Wilson R, Schentag JJ, Ball P, Mandell L, Study G (2002) A comparison of gemifloxacin and clarithromycin in acute exacerbations of chronic bronchitis and long-term clinical outcomes. Clin Ther 24:639 – 652
133. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, Conway WA, Jr, Enright PL, Kanner RE, O'Hara P, et al. (1994) Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. JAMA 272:1497 – 1505
134. Fiore MC, Jorenby DE, Baker TB (1997) Smoking cessation: principles and practice based upon the AHCPR Guideline, 1996. Agency for Health Care Policy and Research. Ann Behav Med 19:213 – 219
135. Fiore MC, Jorenby DE, Baker TB, Kenford SL (1992) Tobacco dependence and the nicotine patch. Clinical guidelines for effective use. JAMA 268:2687 – 2694
136. Centers for Disease Control and P (2004) Influenza and pneumococcal vaccination coverage among persons aged > or =65 years and persons aged 18 – 64 years with diabetes or asthma – United States, 2003. MMWR 53:1007 – 1012
137. Centers for Disease Control and P (2005) Influenza vaccination levels among persons aged > or =65 years and among persons aged 18 – 64 years with high-risk conditions – United States, 2003. MMWR 54:1045 – 1049
138. Nichol KL, Mallon KP, Mendelman PM (2003) Cost benefit of influenza vaccination in healthy, working adults: an economic analysis based on the results of a clinical trial of trivalent live attenuated influenza virus vaccine. Vaccine 21:2207 – 2217
139. Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV, Facklam RR (1993) Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. JAMA 270:1826 – 1831
140. Centers for Disease Control and P (2004) Updated recommendations on the use of pneumococcal conjugate vaccine: suspension of recommendation for third and fourth dose. MMWR 53:177 – 178
141. Francis JS, Doherty MC, Lopatin U, Johnston CP, Sinha G, Ross T, Cai M, Hansel NN, Perl T, Ticehurst JR, Carroll K, Thomas DL, Nuermberger E, Bartlett JG (2005) Severe community-onset pneumonia in healthy adults caused by methicillin-resistant *Staphylococcus aureus* carrying the Panton-Valentine leukocidin genes. Clin Infect Dis 40:100 – 107
142. Micek ST, Dunne M, Kollef MH (2005) Pleuropulmonary complications of Panton-Valentine leukocidin-positive community-acquired methicillin-resistant *Staphylococcus aureus:* importance of treatment with antimicrobials inhibiting exotoxin production. Chest 128:2732 – 2738
143. Kahn JS (2003) Human metapneumovirus: a newly emerging respiratory pathogen. Curr Opin Infect Dis 16: 255 – 258
144. Peiris JS, Yuen KY, Osterhaus AD, Stohr K (2003) The severe acute respiratory syndrome. N Engl J Med 349: 2431 – 2441

145. Hawes S, Seabolt JP (2003) Hantavirus. Clin Lab Sci 16:39 – 42
146. Ramos MM, Overturf GD, Crowley MR, Rosenberg RB, Hjelle B (2001) Infection with Sin Nombre hantavirus: clinical presentation and outcome in children and adolescents. Pediatrics 108:E27
147. Metersky ML, Ma A, Bratzler DW, Houck PM (2004) Predicting bacteremia in patients with community-acquired pneumonia. Am J Respir Crit Care Med 169:342 – 347
148. Garcia-Vazquez E, Marcos MA, Mensa J, de Roux A, Puig J, Font C, Francisco G, Torres A (2004) Assessment of the usefulness of sputum culture for diagnosis of community-acquired pneumonia using the PORT predictive scoring system. Arch Intern Med 164:1807 – 1811
149. Rodriguez RM, Fancher ML, Phelps M, Hawkins K, Johnson J, Stacks K, Rossini T, Way M, Holland D (2001) An emergency department-based randomized trial of nonbronchoscopic bronchoalveolar lavage for early pathogen identification in severe community-acquired pneumonia. Ann Emerg Med 38:357 – 363
150. Dominguez J, Gali N, Matas L, Pedroso P, Hernandez A, Padilla E, Ausina V (1999) Evaluation of a rapid immunochromatographic assay for the detection of *Legionella* antigen in urine samples. Eur J Clin Microbiol Infect Dis 18:896 – 898
151. Harrison BD, Farr BM, Connolly CK, Macfarlane JT, Selkon JB, Bartlett CL (1987) The hospital management of community-acquired pneumonia. Recommendations of the British Thoracic Society. J R Coll Physicians Lond 21:267 – 269
152. Helbig JH, Uldum SA, Bernander S, Luck PC, Wewalka G, Abraham B, Gaia V, Harrison TG (2003) Clinical utility of urinary antigen detection for diagnosis of community-acquired, travel-associated, and nosocomial legionnaires' disease. J Clin Microbiol 41:838 – 840
153. Yzerman EP, den Boer JW, Lettinga KD, Schellekens J, Dankert J, Peeters M (2002) Sensitivity of three urinary antigen tests associated with clinical severity in a large outbreak of Legionnaires' disease in The Netherlands. J Clin Microbiol 40:3232 – 3236
154. Dominguez J, Blanco S, Rodrigo C, Azuara M, Gali N, Mainou A, Esteve A, Castellvi A, Prat C, Matas L, Ausina V (2003) Usefulness of urinary antigen detection by an immunochromatographic test for diagnosis of pneumococcal pneumonia in children. J Clin Microbiol 41: 2161 – 2163
155. Dominguez J, Gali N, Blanco S, Pedroso P, Prat C, Matas L, Ausina V (2001) Detection of *Streptococcus pneumoniae* antigen by a rapid immunochromatographic assay in urine samples. Chest 119:243 – 249
156. Smith MD, Derrington P, Evans R, Creek M, Morris R, Dance DA, Cartwright K (2003) Rapid diagnosis of bacteremic pneumococcal infections in adults by using the Binax NOW *Streptococcus pneumoniae* urinary antigen test: a prospective, controlled clinical evaluation. J Clin Microbiol 41:2810 – 2813
157. Templeton KE, Scheltinga SA, van den Eeden WCJFM, Graffelman AW, van den Broek PJ, Claas ECJ (2005) Improved diagnosis of the etiology of community-acquired pneumonia with real-time polymerase chain reaction. Clin Infect Dis 41:345 – 351
158. Khater F, Moorman JP (2003) Complications of influenza. South Medic J 96:740 – 743
159. Marik PE (2001) Aspiration pneumonitis and aspiration pneumonia. N Engl J Med 344:665 – 671
160. Centers for Disease Control and P (2006) High levels of adamantane resistance among influenza A (H3N2) viruses and interim guidelines for use of antiviral agents – United States, 2005 – 06 influenza season. MMWR 55: 44 – 46