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 cattle                                                          | Chlamydia psittaci                                                        |
| Exposure to rabbits                                                         | Coxiella burneti                                                          |
| HIV infection (early with high CD4 counts)                                 | Francisella tularensis                                                   |
| HIV infection (late with low CD4 counts)                                   | S. pneumoniae, Haemophilus influenzae, Mycobacterium tuberculosis        |
| Winter                                                                      | In addition to above pathogens: Pneumocystis jiroveci, Cryptococcus spp., |
| Skin infections                                                             | H. capsulatum, Coccidioides spp.                                         |
| Other                                                                       | Outbreaks: Legionella spp., viruses (avian flu, SARS coronavirus [143],  |
| Additional comorbid conditionsa                                             | metapneumovirus [144], “Sin Nombre” hantavirus [145, 146]               |
|                                                                             | S. pneumoniae, Haemophilus influenzae, GNRs, atypical pathogens (Mycopla- |
|                                                                             | *sma pneumoniae, Chlamydia phila 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 scorea (adapted from Fine et al. [39])

| Criteria                                                                 | Points |
|--------------------------------------------------------------------------|--------|
| Age                                                                      |        |
| Male                                                                     | Age (years) +20 |
| 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 (PaO2) < 60 mmHg or arterial oxygenation satu-  | +10    |
| ration < 90%                                                             |        |
| Pleural effusion on chest radiograph                                    | +10    |

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)

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
41.1 Severe Community-Acquired Pneumonia in the ICU

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 oximetry 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

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

| Risk class | Points | Mortality (%) | Recommended site of care |
|------------|--------|---------------|--------------------------|
| I          | >60    | 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                |

* 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]

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

| Criterion                      | Score |
|--------------------------------|-------|
| Age > 65 years                 | 1     |
| Altered mental status          | 1     |
| Respiratory rate > 30 breaths per minute | 1     |
| Diastolic blood pressure < 60 mmHg | 1     |
| Serum blood urea nitrogen > 19.6 mg/dl | 1     |

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.

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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-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.
Community-Acquired Respiratory Complications in the Intensive Care Unit

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 |
| 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 |

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

| Intravenous beta-lactam |
|-------------------------|
| Covers well Streptococcus pneumoniae, Haemophilus influenzae, enteric gram-negative bacilli (Klebsiella spp.) |
| or |
| – Beta-lactam/beta-lactamase inhibitor (ampicillin-sulbactam or piperacillin-tazobactam) |
| plus either |
| Intravenous macrolide |
| – (azithromycin or clarithromycin) |
| or |
| Intravenous fluoroquinolone* |
| – (levofloxacin, or moxifloxacin) |

| Intravenous beta-lactam |
|-------------------------|
| Pseudomonas aeruginosa (and the other pathogens above) |
| or |
| – Antipseudomonal beta-lactam/beta-lactamase inhibitor (aztreonam, ceftazidine, 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] |

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

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 factors for pneumococcal infection [3, 7, 8, 10]. Appropriate, aggressive and early therapeutic approaches including initiation of antibiotic therapies as early as possible [36, 64] are the main interventions to decrease mortality in patients with CAP in the ICU.

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]. 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
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].

### Table 41.8. Specific antimicrobial therapy for patients with CAP

| Pathogen specific | Recommended therapy |
|-------------------|---------------------|
| *Streptococcus pneumoniae*  | Combination therapy with beta-lactam plus macrolide or fluoroquinolone |
| Bacteremic         | *Third generation cephalosporin, or respiratory fluoroquinolone* |
| Intermediate resistance to penicillin (≤2 mg/dl) | *Respiratory fluoroquinolone, vancomycin, linezolid* |
| High level of resistance to penicillin (≤2 mg/dl) | |
| *Staphylococcus aureus*  | |
| MSSA               | *Third generation cephalosporin, respiratory fluoroquinolone, or clindamycin* |
| MRSA (CA-MRSA)*    | Vancomycin or linezolid |
| Atypicals: *Chlamydia 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 *Chlamydia pneumoniae psittaci* | Macrolide or tetracycline |
| Influenza pneumonia [7, 158] | The newer agents oseltamivir or zanamivir cover both influenza A and B [7] |
| Aspiration pneumonia anaerobic infections | Carbapenems, clindamycin or beta-lactam/beta-lactamase inhibitors [159] |

* CA-MRSA community-acquired methicillin-resistant *S. aureus* usually not multi-drug resistant
* CA-MRSA community-acquired methicillin-resistant *S. aureus* usually not multi-drug resistant

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### 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 supplicative 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
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. Criterias 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 showed 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 FEV1, 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 PaO2 to FiO2, 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 ≥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 anti-
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. \[108\])

| 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. \[108\])

| Acute tracheobronchitis | 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) |
| 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%) |
[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 polyclonal 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.

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