Chapter 11
Community-Acquired Pneumonia—Back to Basics

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Background

Lower respiratory tract infections are among the most common infectious diseases worldwide and are caused by the inflammation and consolidation of lung tissue due to an infectious agent.[1] The clinical criteria for the diagnosis include chest pain, cough, auscultatory findings such as rales or evidence of pulmonary consolidation, fever, or leukocytosis. Radiographic evidence, such as the presence of new infiltrates on chest radiograph, and laboratory evidence can support the diagnosis.[2] Elderly and patients with underlying conditions, such as cerebro- and cardiovascular diseases, chronic obstructive pulmonary disease (COPD), and alcoholism, are at increased risk for developing lower respiratory tract infections and complicated courses of infection.[3, 4] Complications include the development of progressive pneumonia, pleural empyema, uncontrolled sepsis, and death, sometimes even despite appropriate antimicrobial treatment.[5]

Because of differences in pathogenesis and causative microorganisms, healthcare-associated and community-acquired pneumonia (CAP) are usually distinguished. CAP represents a broad spectrum of disease severity, ranging from mild pneumonia that can be managed by general practitioners to severe pneumonia with septic shock needing treatment in the intensive care unit (ICU). Most cases of CAP are successfully managed in primary care and approximately 20 and 1% of patients need hospitalization or treatment in ICU, respectively.[6, 7]

Despite the widespread availability of antibiotics and reduced mortality since their introduction, lower respiratory tract infections remain the most important infectious cause of death in the developed world.[8] For instance, absolute mortality due to pneumonia has increased in the past 10 years in the Netherlands and the United States.[8–12]

Estimated annual costs for treating CAP were in excess of 1 billion US$ in the United Kingdom in 1997 and 9.7 billion US$ in the United States in 2001.[8, 13–15]

Lower respiratory tract infections are most frequently caused by bacteria or viruses. Treatment should be directed toward the causative organisms, with antibiotics prescribed only for bacterial infections and being withheld for

nonbacterial causes of inflammation. Yet, causative agents have usually not been identified at the time that treatment must be initiated and empirical therapy should, therefore, cover the most likely pathogens. This implies that it is unavoidable that empirical therapy frequently includes a wider range of pathogens and, thus, a broader antibiotic spectrum than a choice that exclusively covers the pathogen involved.

On a population level, the quantity of antibiotics prescribed is linearly related to antibiotic resistance and unnecessary antibiotic use should, therefore, be prevented. Despite this paradigm, overuse of antibiotics frequently occurs, especially in case of viral infections.[16] Yet, this goal to minimize unnecessary antibiotic use must be balanced constantly against the urge to cover all potential pathogens in order to prescribe optimal treatment for the individual patient. Therefore, optimizing therapeutic efficacy of empirical treatment, while preventing unnecessary antibiotic use have become important issues in the management of lower respiratory tract infections. In this chapter, etiologic, diagnostic, therapeutic, and preventive considerations are described to optimize antibiotic prescription for the individual patient with lower respiratory tract infections, while keeping antibiotic resistance development on a population level in mind.

Etiology

Worldwide, *Streptococcus pneumoniae* is by far the most important pathogen for CAP. Other frequently isolated bacteria are *Haemophilus influenzae* and *Staphylococcus aureus*.[17–23] Incidences of atypical pathogens, such as *Mycoplasma pneumoniae, Chlamydia pneumoniae*, and *Legionella pneumophila*, are generally lower than those of the afore-mentioned bacteria, although variations may be large.[17, 18, 20, 23] *Pseudomonas aeruginosa* can be relevant in patients with structural lung damage, such as those with bronchiectasis or COPD.[24] Most frequent viral causes of CAP include influenza virus and parainfluenza virus.[23, 25] Viral pneumonias due to infection with influenza, respiratory syncytial virus, coronaviruses, parainfluenza virus, and even rhinoviruses can be life threatening in elderly and immunocompromised patients. Influenza pneumonia may be complicated by secondary bacterial infections caused by *S. aureus, S. pneumoniae, H. influenzae*, or other Gram- negative pathogens.[21, 26]

Recently, coronaviruses have been recognized as causes of severe lower respiratory tract infections. The SARS coronavirus caused severe CAP associated with high mortality rates, even in previously healthy adults.[27, 28] Non-SARS coronaviruses such as the coronavirus OC43 have been associated with lower respiratory tract infections in children and adults.[25, 29–31] Human metapneumovirus is increasingly recognized as a cause of respiratory failure in children and of pneumonia in the elderly.[32, 33] Importantly, up to 60% of episodes of CAP remain of unknown etiology.[6]

Identification of Causative Pathogens

Rapid and reliable diagnostic results are needed for a prudent and pathogen-tailored antibiotic strategy. Currently available methods for etiological diagnosis include clinical, radiological, and laboratory findings, Gram staining of sputum, urinary antigen tests, or specific DNA detection using real-time polymerase chain reactions (PCR).

Clinical, Radiological, and Laboratory Features

Although some clinical features have been associated with specific causative microorganisms—such as high fever, acute onset of disease, chills, productive cough, and thoracic pain with *S. pneumoniae*, and preceding influenza with *S. aureus*—there is consensus that in most cases, the microbial cause of CAP cannot be predicted using clinical or radiographic features.[34–38] New opportunities include the use of systemic levels of C-reactive protein (CRP) and procalcitonin (PCT). Yet, although raised CRP and PCT levels have been claimed to be indicative for bacterial infections, CRP levels could not differentiate between bacterial and viral respiratory tract infections in adults,[39] nor could PCT in children admitted with CAP.[40, 41] From another perspective, though, PCT was used to reduce unnecessary antibiotic prescriptions in patients with clinical symptoms of LRTI, without subsequent adverse effect on patient outcomes. Of note, reduction of antibiotic use was primarily achieved through withholding of antimicrobial therapy for patients with acute bronchitis and only 36% of patients had CAP in this study.[42]

Microbiology and Serology

Routine diagnostic procedures to identify causative microorganisms include microbiological culturing of blood and sputum and serological testing of acute and reconvalescent blood samples. However, the clinical value of these conventional diagnostic methods in guiding treatment of CAP is limited because of low sensitivity and considerable delay.[43–47] Culturing other samples for which more invasive procedures are needed, such as pleural and bronchoalveolar fluids, might increase diagnostic yields, but inherently suffer from the same diagnostic delay. In one study, fiberoptic bronchoscopy provided an etiological diagnosis in 25% of patients in whom conventional diagnostic methods failed to identify a causative microorganism.[48] Yet, pathogen-directed empirical therapy in this study was not associated with better clinical outcome of patients.[49] Fiberoptic bronchoscopy should, therefore, be considered for cases of treatment failure without identified causative microorganism from conventional diagnostics. Importantly, even in study settings with extensive diagnostic testing, approximately 50% of episodes of CAP remain of unknown etiology[17–23, 34–37]

The use of sputum Gram staining in the diagnostic workup of CAP is controversial: its use is recommended by the Infectious Diseases Society of America

(IDSA), but not by the American Thoracic Society (ATS).[50, 51] Advantages of sputum Gram staining include its wide availability and low costs. However, adequate sputum samples cannot always be obtained, either because there is no sputum production or because samples are not adequate for evaluation. Furthermore, sensitivity and specificity are unknown, some bacteria cannot be identified, and a uniform definition of a positive stain does not exist.[45, 46]

Urinary Antigen Testing

Two urinary antigen tests are available for diagnosing the microbial cause of CAP. The NOW *S. pneumoniae* urinary antigen test (Binax, Inc., Portland, Maine) detects, within 15 minutes, the C polysaccharide wall antigen common to all *S. pneumoniae* strains.[52] One study reported 90–100% specificity and 74% sensitivity.[53] Yet, specificity might be reduced due to nasopharyngeal carriage of pneumococci.[54]

The other urinary antigen test detects *L. pneumophila* type I and test accuracy increases with severity of disease, with sensitivities varying from approximately 40% in mild to 95% in severe CAP.[55] Immediate (within 24 hours after hospital admission) therapy for Legionnaires' disease, as detected by this test, increased ICU-free survival as compared to therapy initiated after $>$ 24 hours.[56]

DNA Detection

Another approach is to identify viruses and "atypical" bacterial pathogens in respiratory samples through molecular techniques, such as polymerase chain reaction (PCR). Novel real-time Taq-Man PCR techniques are sensitive and specific and able to detect respiratory viruses in clinical specimens within hours.[25, 57] Yet, in a randomized trial, addition of real-time PCR analysis of respiratory viruses and atypical pathogens in nose and throat swabs to routine diagnostic workup, improved diagnostic yields but failed to reduce antibiotic use or healthcare-associated costs among patients admitted with lower respiratory tract infections (of whom 50% had CAP).[58]

Therapy

Microorganisms and Antibiotic Resistance

A detailed description of the underlying mechanisms of antibiotic resistance is beyond the scope of this chapter. In brief, alterations in the bacterial proteins that bind penicillin can decrease binding affinity and antimicrobial susceptibility to penicillins in *S. pneumoniae*. Such strains are also more likely to be resistant to other antibiotics, such as macrolides, tetracyclins, and fluoroquinolones. For the treatment of pneumococcal pneumonia, β-lactam antibiotic concentrations should exceed the MIC for at least 40% of the time.[59] When strains with reduced

susceptibility to penicillin are anticipated, this can be achieved with higher dosages of penicillin (e.g., 2 million units q 6 hours) or amoxicillin (e.g., 1 gram q 6 hours). In clinical studies, mortality rates of patients with bacteremic pneumococcal pneumonia and treated with β-lactam antibiotics were comparable for episodes caused by pneumococci susceptible and nonsusceptible to penicillin.[60]

Macrolide resistance is either due to modification of the target site, encoded by the *ermB* gene, or an active efflux pump that removes macrolides from the cell, encoded by the *mef* gene. In *S. pneumoniae*, the *erm* gene is associated with high levels of resistance to all macrolides. Erythromycin resistance based on efflux mechanisms can be overcome by the use of newer macrolides, such as azithromycin.[60]

The newer fluoroquinolones, such as levofloxacin and moxifloxacin, are active, *in vitro*, against most relevant significant aerobic Gram-positive cocci, the Enterobacteriaceae, *H. influenzae, M. catarrhalis, Legionella* species, *M. pneumoniae*, and *C. pneumoniae*, which make them attractive compounds for treatment of CAP. Development of resistance to fluoroquinolones, which can occur even during treatment, however, is a matter of serious concern.[61, 62] Resistance to fluoroquinolones results from mutations in the target enzymes (DNA gyrase and topoisomerase IV), thereby reducing the inhibitory effects of fluoroquinolones on bacterial DNA synthesis. Strains usually become fully resistant when both target genes are mutated. Other resistance mechanisms include alterations in the bacterial cell membrane and active efflux of the drug.[61, 62]

Importantly, prevalence of antibiotic resistance varies geographically. For instance, prevalence of reduced susceptibility to penicillin among *S. pneumoniae* is around 40% in Spain and $< 1\%$ in the Netherlands (http://www.earss.rivm.nl). Furthermore, over 50% of macrolide resistance in Europe is caused by mutations in the *ermB* gene,[63] whereas presence of an efflux pump is the predominant resistance mechanism of *S. pneumoniae* to macrolides in the United States.[60] Therefore, decisions on empirical antimicrobial treatment should be based on local antibiotic resistance rates.

Recently, an emergence of infections, mostly skin infection but sporadically severe CAP, caused by so-called community-associated methicillin-resistant *S. aureus* (CA-MRSA), have been reported from the United States and Europe.[64, 65] CA-MRSA are resistant to all β-lactam antibiotics, but are frequently still susceptible to clindamycin, co-trimoxazole, and fluoroquinolones.

Recommended Treatment

When organisms are known, recommended treatment should be aimed at the isolated pathogen (Table 11.1). However, the initial treatment of CAP, as recommended in recent guidelines, is predominantly based on the clinical severity of presentation rather than the presumed causative pathogen (Table 11.2). For the prediction of clinical severity, several risk classifications exist which include combinations of underlying illnesses, age, and clinical features. In clinical practice, broad-spectrum antibiotics should be prescribed more liberally in patients

TABLE 11.1. Preferred pathogen-directed antimicrobial therapy for patients with community-acquired pneumonia, based on the recommendations for community-acquired pneumonia of the American Thoracic Society (ATS), British Thoracic Society (BTS), Infectious Diseases Society of America (IDSA), and the Dutch Working Party on Antibiotic Policy (SWAB)

Microorganism	Preferred targeted therapy	Alternative antimicrobial therapy
S. pneumoniae		
Penicillin susceptible, (MIC< 2 μg/ml)	• Penicillin G • Amoxicillin	• Cephalosporin • Macrolide • Clindamycin • Fluoroquinolone • Doxycycline • Carbapenem
Penicillin resistant	• Cefotaxime • Ceftriaxone	• Fluoroquinolone • Vancomycin
H. influenzae	• β-Lactam + β-lactamase inhibitor	• Cephalosporin (2nd or 3rd generation) • Doxycycline • Trimethoprim/sulfamethoxazole
M. pneumoniae	• Doxycycline • Macrolide	• Fluoroquinolone
C. pneumoniae	• Doxycycline • Macrolide	• Fluoroquinolone
L. pneumophila	• Macrolide ± rifampicin • Fluoroquinolone	• Doxycycline ± rifampicin
S. aureus		
Methicillin susceptible	• Flucloxacillin ± rifampin	• Cefazolin or cefuroxime • Vancomycin • Clindamycin • Teicoplanin ± rifampicin • Trimethoprim/sulfamethoxazole
Methicillin resistant	• Vancomycin ± rifampin or gentamicin	• Linezolid
M. catarrhalis	• Cephalosporin (2nd or 3rd generation) • Trimethoprim/sulfamethoxazole • Macrolide • β-Lactam + β-lactamase inhibitor	• Fluoroquinolone
Anaerobes	• β-Lactam + β-lactamase inhibitor • Clindamycin	• Imipenem
P. aeruginosa	• Aminoglycoside + antipseudomonal β-lactam (e.g., piperacillin) • Carbapenem	• Aminoglycoside + ciprofloxacin • Ciprofloxacin + antipseudomonal β-lactam
Enteric Gram-negative bacilli	• 3rd or 4th generation cephalosporin ± aminoglycoside • Carbapenem	• β-Lactam + β-lactamase inhibitor • Fluoroquinolone
C. psittacci	• Doxycycline	• Erythromycin • Chloramphenicol
Coxiella burnetii	• Tetracycline	• Chloramphenicol

TABLE 11.2. Preferred empirical therapy for community-acquired therapy (CAP) in lower respiratory tract infections, based on the recommendations for community-acquired pneumonia of the American Thoracic Society (ATS), British Thoracic Society (BTS), Infectious Diseases Society of America (IDSA), and the Dutch Working Party on Antibiotic Policy (SWAB)

Severety of CAP	Recommended treatment in the USA (ATS and IDSA guidelines)	Recommended treatment in the UK (BTS guidelines)	Recommended treatment in the Netherlands (SWAB guidelines)
Mild infection (outpatients)	• Macrolide or doxycycline • Fluoroquinolone	• Amoxicillin	• Amoxicillin • doxycycline
Moderately severe infection (inpatients)	• Extended-spectrum cephalosporin plus macrolide • β-Lactam/β-lactamase inhibitor plus macrolide • Fluoroquinolone	• Amoxicillin + macrolide *if mild infection, but admitted for other reasons than pneumonia, e.g., social situation or other condition* • Amoxicillin	• Amoxicillin • Penicillin *If legionella urinary antigen test positive (performed within 12 h)*: • Macrolide • Quinolone
Severe infection (ICU treatment)	• Extended-spectrum cephalosporin plus macrolide • β-Lactam/β-lactamase inhibitor plus either fluoroquinolone or macrolide *Structural lung disease* • Antipseudomonal agents *Suspected aspiration* • Fluoroquinolone ± clindamycin • Metronidazole • β-Lactam/β-lactamase inhibitor	• β-Lactam + β-lactamase inhibitor plus macrolide • Cephalosporin (2nd/3rd generation) plus macrolide • Fluoroquinolone with enhanced pneumococcal activity plus benzylpenicillin	• Moxifloxacin • Penicillin + iprofloxacin • β-Lactam + macrolide

with "severe" CAP (SCAP). Therefore, a reliable prognostic model might be useful in tailoring empirical therapy in individual patients. Pragmatically, SCAP could be defined by the need of ICU admission. However, this definition does not include objective measurements and depends on local policies for ICU admission that may vary considerably between centers.[66] The ATS proposed to define SCAP on the presence of a certain set of minor and major clinical signs or symptoms.[50] The British Thoracic Society defined SCAP using a more or less similar set of "core," "additional," and "preexisting" adverse prognostic features.[67] Another algorithm to predict mortality risk and thus severity of CAP is the Pneumonia

Severity Index (PSI), which classifies patients in five groups. In the development of this scoring system, 30-day mortality rates gradually increased per class from 0.1% in class I, to 31.1% in class V.The ATS criteria had a high sensitivity but low specificity for predicting ICU admission[68] and in another study only 17% of patients in risk class V of the PSI system had been admitted to ICU.[69] To what extent these criteria and algorithms can be used for choosing empirical therapy remains to be determined.[50, 67, 69, 70] In our view, clinical judgment, which is difficult to describe in objective terms, remains important in the management of patients with CAP.

Results of nonexperimental studies have suggested that, in the initial management of patients hospitalized with CAP who do not require ICU admission, combination therapy consisting of a β-lactam antibiotic plus a macrolide or monotherapy with one of the newer fluoroquinolones reduces mortality and length of hospitalization.[71–78] Naturally, such strategies would increase the use of macrolides and fluoroquinolones and thus the selective antibiotic pressure for resistance.[79–81] The beneficial value of macrolides or fluoroquinolones might be the result of a larger than previously assumed role of atypical pathogens in the etiology of CAP, anti-inflammatory effects of macrolides, or resistance to β-lactams of the most important pathogens. However, the nonexperimental, and in almost all cases retrospective, design of these studies may have resulted in confounding by indication. Up till now, randomized controlled trials do not confirm these outcome differences.

The newer fluoroquinolones (levofloxacin and moxifloxacin) have been compared to β-lactam antibiotics (co-amoxiclav and ceftriaxone) with or without a macrolide in three randomized trials. Clinical and bacteriological success of fluoroquinolone treatment appeared to be better in two studies,[22, 82] and statistically significant differences in fever resolution and duration of hospitalization, in favor of fluoroquinolone treated patients, were also observed in two studies.[82, 83] Yet, the absolute differences were rather small (about 1 day for fever resolution and hospitalization), a significant survival benefit was not found, and results might have been influenced by protocol in at least one study, in which a switch to oral treatment for patients receiving ceftriaxone was not allowed before day 7.[83]

In adults with nonsevere CAP, treatment failures were comparable for empirical regimens with atypical coverage as compared to β-lactam antibiotics in meta-analysis.[84] A similar conclusion was reached in another meta-analysis of 24 trials, evaluating more than 5000 patients, treated for CAP. A trend toward increased clinical success and better bacteriological eradication was found for patients receiving atypical coverage, especially for those infected with *Legionella pneumophila*. Yet, this trend disappeared when only high-quality studies were evaluated.[85] Therefore, the recommendation to use empirical treatment with either a β-lactam/macrolide combination or monotherapy with a new fluoroquinolone for patients hospitalized with CAP is based on studies providing, at most, level III evidence.

Length of Treatment

The recommended length of antimicrobial treatment of CAP is usually based on the causative pathogen, response to treatment, presence of comorbid illness, and complications. Current guidelines recommend to treat CAP caused by *S. pneumoniae* until the patient has been afebrile for 72 hours, whereas episodes caused by bacteria associated with pulmonary necrosis (e.g., *S. aureus, P. aeruginosa, Klebsiella*, and anaerobes) should be treated for about 2 weeks.[51] A duration of 2 weeks is also recommended for CAP caused by *M. pneumoniae, C. pneumoniae*, and legionnaires' disease in immunocompetent individuals. Treatment length could be reduced by using azithromycin, due to its long half-life in tissues, although longer courses are probably needed for *Legionella* infections.[51, 86]

These recommendations on treatment duration are not based on results of controlled trials. Recently, treatment durations of 3 and 8 days with amoxicillin ± clavulanic acid were compared in a randomized double-blind trial of 186 adult patients with mild CAP. At day 10, outcomes for clinical success, pathogen eradication, radiological response, and duration of hospitalization were similar for both groups, whereas adverse reactions occurred more frequently among patients receiving 8 days of amoxicillin.[87]

In conventional treatment approaches, intravenous therapy is continued until definite clinical cure has been achieved. Based on nonrandomized studies in patients with mild to moderately severe CAP, patients hospitalized with CAP can be managed safely and more efficiently by an early switch from IV to oral medication.[88–93] For patients with severe CAP, an early switch to oral antibiotic treatment also seems to reduce length of hospital stay (by approximately 2 days) and treatment associated costs, without adverse effects on treatment outcome.[94]

Prevention

Prevention of CAP, for instance through vaccination, may well reduce antibiotic use and thus resistance development. With regard to respiratory infections, vaccines are available against pneumococci and influenza. Currently, a 23-valent pneumococcal polysaccharide vaccine (PPV), covering the 23 most prevalent serotypes of *S. pneumoniae*, is recommended in most Western countries for persons at high risk for developing CAP. However, the available data to support these recommendations are far from consistent. Nonexperimental retrospective studies suggest that PPV is effective and cost-saving in preventing invasive pneumococcal disease.[95, 96] However, confounding by indication might have played a considerable role in these studies affecting the validity of the results. Several clinical studies and systematic reviews yielded conflicting results with regard to the prevention of bacteremic pneumonia even in high-risk patients who were previously hospitalized with CAP.[96–102] Therefore, the

real value of pneumococcal vaccination strategies, in terms of effects on nonbacteremic pneumonia and costs, needs further exploration, preferably in randomized controlled trials.[103, 104]

Influenza vaccination is recommended for patients who have a high risk for influenza complications, like severe viral pneumonia or severe secondary bacterial infection. Patients at high risk for these complications can be identified based on host characteristics such as age, gender, comorbidity, and external factors, such as long-term immunosuppressive drug use or residence in closed communities with high transmission rates.[105] In meta-analysis vaccine effectiveness was 50% for preventing hospitalization and 68% for preventing death in high-risk patients. In addition to elderly patients, younger persons with high-risk medical conditions might also benefit from annual influenza vaccination.[101, 106, 107] Data on clinical effectiveness of the vaccine in reducing postinfluenza complications among high-risk persons of working age are limited and indicate no or at most limited benefits from vaccination.[102, 105, 108] Quantitative effects on antibiotic use of influenza vaccination are unknown, but it is tempting to argue that an effective influenza vaccination program might reduce antibiotic use.

Conclusions

CAP is still among the most frequently encountered infections and accounts for considerable antibiotic consumption. Strategies to fight antibiotic resistance on a population level include several basic approaches: only treat when necessary, prescribe antibiotics for bacterial infections only, only treat causative pathogens, and reduce duration of treatment as much as possible. Physicians caring for CAP patients should balance these principles against the optimal treatment of the individual patient, which frequently includes broad-spectrum antibiotics as empirical therapy, especially in patients with severe CAP. As clinical features cannot adequately predict the causative microorganism, establishing an etiological diagnosis by means of urinary antigen tests or real-time PCR techinques may enhance streamlining of therapy, thereby reducing antibiotic pressure. Current guidelines advise broad spectrum antibiotics either with combinations of β-lactam antibiotics plus macrolides or monotherapy with fluoroquinolones for empirical treatment of severe CAP. Yet, different definitions are used for CAP severity and the recommendation of early broad-spectrum therapy is not supported by high-level evidence. The effects of these recommendations on resistance development are not clear, but should be a reason for concern.

More restrictive and prudent, but still responsible, use of antibiotics for CAP could possibly be achieved by improving techniques to establish etiological diagnoses, by optimizing empirical treatment through randomized trials, by optimizing duration of therapy, and implementation of vaccination strategies. However, these hypotheses remain to be proven.

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