The correct approach to community-acquired pneumonia in immunocompetent adults: review of current guidelines

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SUMMARY

Community-acquired pneumonia (CAP) often represents a clinical emergency requiring prompt and adequate antimicrobial treatment. The choice of antimicrobials, however, is difficult due to the variety of potential pathogens and to the spread of drug-resistance. Hence, a correct therapeutic approach should be based on the knowledge of the most frequently reported etiologies for the different clinical conditions, specific patient risk factors and the treatment setting (home, hospital, intensive or non intensive care unit) chosen accordingly. The awareness of the local drug-resistance epidemiology and individual patient characteristics, such as age, history of antibiotic treatments and related adverse events, underlying diseases, concurrent therapies and expected adherence to treatment should also be considered. Lastly, an adequate CAP management should address other issues, including therapy duration, monitoring of its efficacy and adverse effects, and supportive measures. The guidelines for CAP management aim to provide the physician with the necessary knowledge and criteria to assist him in these crucial decisions, and their adoption result in a significant reduction of mortality, frequency and length of hospitalization, and costs. Herein, the authors review and discuss some of the main current guidelines for CAP management, highlighting their differences and similarities.

KEY WORDS: Pneumonia, Community-acquired, Guidelines

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INTRODUCTION

Community-acquired pneumonia (CAP) is a common infectious disease associated with a high rate of morbidity and mortality. Even though precise data are not available for most European countries, studies performed in Spain, Finland and England have suggested an annual incidence of 1.6/1 000 to 19/1 000 cases of CAP among adult populations (Woodhead *et al.*, 2005 appendix 2), 22%-51% of whom required hospitalization. The principal risk factors for CAP are the following: older age, alcoholism, smoking, obesity, malnutrition, comorbidities (mainly chronic obstructive pulmonary disease: COPD), recent viral infection, environmental factors, drugs (such as morphine, atropine, sedatives, corticosteroids, salicylates) (Woodhead *et al.*, 2005). While the rate of mortality is low (<1%) among non-hospitalized subjects (Woodhead, 2002), it increases to 5-15% among hospitalized patients, to 15-25% for pneumococcal CAP with bacteremia, to 20-45% for subjects admitted to intensive care units (ICUs) and to 40% among those >80 years old (Suchyta *et al.*, 2001). In the United States, CAP is still the seventh cause of death, and the mortality rate has not remarkably declined since the routine use of penicillin started (Mandell *et al.*, 2007).

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Adoption of guidelines for managing CAP in clinical practice has resulted in a significant reduction of mortality (Dean *et al.,* 2001; Capelastegui *et al.,* 2004; Mortensen *et al.,* 2004), frequency (Marrie *et al.*, 2000; Suchyta *et al.*, 2001) and length of hospitalization (Dean *et al.*, 2001; Capelastegui *el al.*, 2004; Fine *el al.*, 2003), and costs. The guidelines reviewed herein are those released by the Infectious Diseases Society of America in cooperation with the American Thoracic Society (Mandell *et al.*, 2007), the European Respiratory Society in collaboration with the European Society of Clinical Microbiology and Infectious Diseases (Woodhead *et al.*, 2005), and the British Thoracic Society (BTS, revised 2004).

DIAGNOSIS OF CAP

According to IDSA/ATS (Mandell *et al.*, 2007), a diagnosis of pneumonia is suggested by the presence of particular clinical features (such as cough, fever, sputum, chest pain, rales or breath sounds), while the ERS/ESCMID (Woodhead *et al.*, 2005) report that pneumonia should be suspected in a patient with an acute cough and at least one of the following: >4 day fever, dyspnoea, tachypnoea or new focal chest signs (such as dry or humid breath sounds). However, both guidelines underline that, due to the low sensitivity and specificity of these clinical findings (Wipf *et al.*, 1999), a CAP diagnosis can be confirmed only by demonstration of an infiltrate with a chest radiograph or other imaging procedures. In fact, the above-mentioned symptoms and signs are frequently absent or altered in the elderly, and can be present in lower respiratory infections other than pneumonia or even in non-infectious acute diseases or exacerbations of chronic disorders, such as asthma, COPD, heart failure or lung infarction. In patients hospitalized for suspected pneumonia in whom the chest radiograph is normal, the imaging procedure should be repeated after 24-48 hours.

ETIOLOGY

The microbial agents most often responsible for CAP are illustrated in Table 1. Their frequency often differs from one study to another due to several factors including diverse characteristics of the studied population, geographical area, sampling and microbiological procedures. The etiological agent remains undefined in about 50% of cases. Generally, the pathogens most frequently causing CAP vary in relation to the severity of clinical disease, and, consequently, to the setting in which the patient is assisted (home, non-ICU hospital ward, ICU). *Streptococcus pneumoniae* is the responsible agent in most CAP patients. However, the role of atypical pathogens is important, in particular *Mycoplasma pneumoniae,* which is the causative agent especially in patients <50 years old without significant underlying diseases. Viruses can also determine CAP in up to 36% of cases (Templeton *et al.*, 2005). Less frequent pneumonia pathogens include *Streptococcus pyogenes*, *Neisseria meningitidis*, *Pseudomonas multocida,*

TABLE 1 - *The most frequent etiological agents of CAP according to treatment setting.*

Non-hospitalized patients	*Non-ICU hospitalized patients*	*ICU-hospitalized patients*
S. pneumoniae	*S. pneumoniae*	*S. pneumoniae*
M. pneumoniae	*M. pneumoniae*	*Legionella* spp.
H. influenzae	*C. pneumoniae*	*H. influenzae*
C. pneumoniae	*H. influenzae*	*S. aureus*
Respiratory viruses[a]	*Legionella* spp. Respiratory viruses*	Gram-negative bacilli

CAP community-acquired pneumonia, ICU intensive care unit. *Respiratory viruses: Influenza A e B viruses, Parainfluenza virus, Adenovirus, respiratory syncytial virus. Adapted from File T.M. (File, 2003), with permission from Elsevier.

Haemophilus influenzae b and some viruses (e.g. human metapneumovirus, *Herpes Simplex Virus*, *Varicella-Zoster Virus*, measles virus). Table 2 illustrates the agents associated with specific conditions. Lastly, several studies have reported mixed infections in 5-38% of CAP patients (Mandell *et al.*, 2007; Woodhead *et al.*, 2005; Lieberman *et al.*, 1996), and mixed infections involving one atypical pathogen in 2-11% (File, 2001). *S. pneumoniae* was also isolated in about 45% of CAP caused by C*hlamydia pneumoniae* (File *et al.*, 1999).

TABLE 2 - *Epidemiologic and clinical conditions associated to specific pathogens in CAP.*

Characteristics	*Pathogens*	
Epidemiologic:		
• Alcohol abuse	- *S. pneumoniae* - Anaerobes - *K. pneumoniae*	- *Acinetobacter* spp. - *M. tuberculosis*
• Injecting drug abuse	- *S. aureus* - Anaerobes	- *M. tuberculosis* - *S. pneumoniae*
• Hotel stay or ship cruise in previous 2 weeks, especially in Mediterranean coast	- *Legionella* spp.	
• Influenza outbreak in community	- Influenza viruses - *S. pneumoniae*	- *S. aureus*/CA-MRSA[2] - *H. influenzae*
• Exposure to bat or bird droppings	- *H. capsulatum*	
• Exposure to birds	- *C. psittaci (if poultry: avian influenza virus)*	
• Specific epidemiologic conditions	- SARS[1] associated coronavirus	- Avian influenza virus (H5N1)
• Exposure to farm animals or parturient cats	- *C. burnetii (Q fever)*	- *Hantavirus*
• Travel to or residence in south-western United States	- *Coccidioides* spp.	
• Travel to or residence in Southeast and East Asia	- *B. pseudomallei*	- Avian influenza
• In context of bioterrorism	- *B. anthracis* - *Y. pestis*	- *F. tularensis*
Clinical:		
• Chronic obstructive pulmonary disease (COPD), Smokers	- *H. influenzae* - *M. catarrhalis* - *Legionella* spp. - *S. pneumoniae*	- *P. aeruginosa* - *C. pneumoniae* - Enterobacteriaceae
• Structural lung disease (bronchiectasis, cystic fibrosis etc.)	- *P. aeruginosa* - *B. cepacia*	- *S. aureus*
• Cough >2 weeks with whoop or post-tussive vomiting	- *B. pertussis*	
• Aspiration (patients with history of alcohol abuse, drug overdose, or oesophageal motility disorders).	- *Anaerobes* - Enterobacteriaceae	- *P. aeruginosa* - Mixed infections
• Lung abscess	- CA-MRSA[2] - oral anaerobes - endemic fungi	- *M. tuberculosis* - Atypical mycobacteria
• Necrotizing pneumonia	- *CA-MRSA*	
• Cavitary infiltrates	- *M. tuberculosis* - Fungi	- *CA-MRSA*
• HIV infection (early)	- *S. pneumoniae* - *H. influenzae*	- *M. tuberculosis*
• Recent antibiotic therapy or hospitalization	- *Enterobacteriaceae*	- *P. aeruginosa*
• Chronic treatment with steroids	- *P. aeruginosa* - Enterobacteriaceae	- *Aspergillus* spp.

CAP community-acquired pneumonia. [1]SARS: Severe acute respiratory syndrome. [2]CA-MRSA: community-acquired methicillin-resistant Staphylococcus aureus. Adapted from Mandell L.A., et al. (Mandell et al., 2007), with permission from University of Chicago Press.

CRITERIA FOR HOSPITALIZATION

The correct therapeutic approach for the CAP patient begins with defining the severity of the patient's clinical presentation and the resulting mortality risk. In fact, both the choice of the most appropriate setting for the patient's care and initial antimicrobial therapy rely on this evaluation. To assist the physician in this assessment, the guidelines discussed herein (Mandell *et al.*, 2007; Woodhead *et al.*, 2005; BTS, 2004) consider the following indexes.

Does the patient present ≥1 of the following conditions?
- Age >50 years
- One or more of the following associated pathologies:
  - Neoplasia
  - Congestive heart failure
  - Hepatic disease
  - Cerebrovascular disease
  - Renal disease.
- One or more of the following physical conditions:
  - Alteration of mental status
  - Respiratory rate ≥30 breaths/min
  - Systolic blood pressure <90 mmHg
  - Body temperature <35°C or ≥40°C
  - Pulse rate ≥125 beats/min

NO → Class I risk of mortality

YES → Class II-IV risk of mortality according to total score obtained from the following characteristics.

Characteristics	*Score*	*Characteristics*	*Score*
Demographic:		***Physical examination:***	
Male	Age (years)	Alteration of mental status	20
Female	Age (years) -10	Respiratory rate ≥30 breaths/min	20
Patient in nursing home	10	Systolic blood pressure <90 mmHg	20
		Body temperature <35°C or ≥40°C	15
Coexisting disease		Pulse rate ≥125 beats/min	10
Neoplasia	30		
Hepatic disease	20	***Laboratory and radiographic data:***	
Cardiac disease	10	Arterial pH <7.35	30
Cerebrovascular disease	10	BUN ≥30 mg/dL (11 mmol/L)	20
Renal disease	10	Sodium <130 mEq/L (130 mmol/L)	20
		Glucose ≥250 mg/ dL (14 mmol/L)	10
		Haematocrit <30%	10
		PaO_2 <60 mmHg or SaO_2 <90%	10
		Pleural effusion	10

Risk factors/Total score	*Risk Class*	*Risk*	*% Mortality*	*Recommended site of care*
No risk factor	I	Low	0.1	Home
≥1 risk factors. Total score:				
≤70	II	Low	0.6	Home (observation unit for <24 hours, if needed)
71-90	III	Low	0.9	
91-130	IV	Moderate	9.3	Hospital (non ICU)
>130	V	High	27.0	Hospital (consider ICU admission)

NOTES: CAP community-acquired pneumonia, ICU intensive care unit, PaO_2 arterial oxygen pressure, SaO_2 arterial oxygen saturation, BUN blood urea nitrogen. Adapted from Fine et al. (Fine et al.,1997), with permission (Copyright© 1997Massachusetts Medical Society).

FIGURE 1 - *Pneumonia severity index (PSI). The index, determined according to this algorithm, is used to determine the risk of mortality of the CAP patient and thus can assist the physician in the choice of site of care (home, non-ICU hospital ward, ICU).*

The Pneumonia Severity Index (PSI) (Fine *et al.*, 1997) (Figure 1) ranks patients into five classes from low to high risk of death according to the following parameters: age, presence of at least one of five pathological conditions, and alteration of mental status or vital or laboratory parameters. All patients in Class I and most in Classes II and III, considered at low mortality risk, can be treated at home. The remaining subjects in Classes II and III would be candidates for a short hospital stay (<24 hours), e.g. in an observation unit. Patients in classes IV/V, at increased/high risk of mortality, should be hospitalized; those patients in class V considered for admission to ICU. PSI calculation is rather complex (20 variables, including several laboratory analyses) and thus applicable only in settings with sufficient support resources (Dean *et al.*, 2000).

Furthermore, PSI may underestimate the pneumonia severity in younger patients, due to the influence which age exerts on the final score (Dean *et al.*, 2000).

The "CURB-65" index (Lim *et al.*, 2003) evaluates the risk of mortality by means of a six point score, assigning one point for each of the following: *confusion, blood urea nitrogen (BUN) level* >7 mmol/L (20 mg/dL), *respiratory rate* ≥30 breaths/min, *low blood pressure (systolic <90 mm Hg or diastolic ≤60 mmHg), and age ≥65* years. Patients with a score of 0-1 (risk of mortality 0.7-2.1%) can be treated at home, those with a score of 2 (mortality risk 9.2%) should be hospitalized in a non-ICU ward, and those with a score of ≥3 (mortality risk 14-57%) require urgent hospitalization and consideration for ICU care. The "CURB-65" index, is preferred by both the European (Woodhead *et al.*, 2005; BTS, 2004) and American guidelines (Mandell *et al.*, 2007) because it is much easier to calculate and remember. An even simpler version of this index (CRB-65) which does not require the BUN determination is suitable for assessments outside hospital. In this case, patients with a score of 0 can be treated at home, those with score 1-2 should be considered for hospitalization, and those with a score ≥3 require urgent hospital admission (Mandell *et al.*, 2007; BTS, 2004; Capelastegui *et al.*, 2006).

Pulse oxymetry, in addition to the above mentioned criteria, can greatly assist in judging the severity of clinical conditions, and therefore should be always assessed at hospital presentation (Mandell *et al.*, 2007; Woodhead *et al.*, 2005; BTS, 2004) and become a more widely available tool for general practitioners (BTS, 2004).

As the majority of low-risk patients, as determined by the above indexes, can be safely treated at home (Bartlett *et al.*, 2004), unnecessary hospital-related risks of thromboembolic events and superinfection by "difficult" bacteria (Alikhan *et al.*, 2004), costs (Niederman *et al.*, 1998) and patient discomfort (Carratala *et al.*, 2005) can be avoided.

However, the necessity of hospitalization has to be finally judged by the physician. In fact, several factors may favor hospitalization even in subjects classified as "low risk" according to the above indexes, such as pleural effusion, other pneumonia complications, co-morbidities, difficult patient adherence to therapy, and social impediments for home care.

Since the patient's clinical condition may change over time, a severity reassessment should be performed 24-48 hours after the first evaluation (Woodhead *et al.*, 2005).

CRITERIA FOR ICU ADMISSION

All guidelines considered herein emphasize that a delayed ICU admission for patients with severe CAP appears to be associated with an increased risk of death, and therefore ICU care should not be restricted only to cases requiring mechanical ventilation or management of septic shock. Even though patients with a PSI or CURB-65 score indicating a high risk of mortality should be considered for ICU care, both these indexes were not intended for this purpose and have been found to be oversensitive and non-specific (Angus *et al.*, 2002). This same limit regards the ATS criteria for defining severe CAP (Niederman *et al.*, 2001) recommended by ERS/ESCMID (Woodhead *et al.*, 2005). Therefore, the IDSA/ATS guidelines (Mandell *et al.*, 2007) developed a new proposal (Table 3) in which the CURB parameters (excluding age >65) and the ATS criteria were both included. According to this proposal, a CAP should be defined as "severe" and require ICU admission when at least one major criterion ("strong" recommendation) or three minor criteria ("moderate" recommendation) are met.

TABLE 3 - *Criteria for definition of severe CAP and for ICU admission (IDSA/ATS).*

Minor criteria[a]*:*
- Respiratory rate ≥30 breaths/min
- Severe respiratory failure (PaO2/FiO2 ratio ≤250)
- Need for noninvasive ventilation
- Multilobar infiltrates in chest radiograph
- Confusion/disorientation
- Uremia (BUN level ≥20 mg/dL)
- Leukopenia (WBC count <4 000 cells/mL) infection-related
- Thrombocytopenia (platelet count <100 000 cells/mL)
- Hypothermia (core temperature, <36°C)
- Hypotension requiring aggressive fluid resuscitation

Major criteria:
- Invasive mechanical ventilation
- Septic shock with the need for vasopressors >4h

NOTES: CAP community-acquired pneumonia, IDSA Infectious Diseases Society of America, ATS American Thoracic Society, BUN blood urea nitrogen; PaO2/FiO2 arterial oxygen pressure/fraction of inspired oxygen; WBC white blood cell. [a]Other criteria to consider include hypoglycemia (in nondiabetic patients), acute alcoholism/alcoholic withdrawal, hyponatremia, unexplained metabolic acidosis or elevated lactate level, cirrhosis, and asplenia. Adapted from Mandell L.A., *et al.* (Mandell *et al.*, 2007), with permission from University of Chicago Press.

DIAGNOSTIC APPROACH FOR MICROBIAL ETIOLOGY

In the majority of cases, the initial antimicrobial treatment for CAP is chosen empirically, due to the necessity for an early treatment and the frequency of home-based diagnosis.

However, identification of the causative microbial agent and knowledge of its drug susceptibility would permit both the verification and correction of the initial empirical choice of antimicrobials, with the following benefits for both the patient and the community (Mandell *et al.*, 2007):
- reduction of the risk of therapeutic failure and mortality, both associated with an inadequate antibiotic therapy (Kollef *et al.*, 1999; Roson *et al.*, 2004; Arancibia *et al.*, 2000); this advantage is especially important when drug-resistant and/or unusual pathogens (e.g. *Mycobacterium tuberculosis, Francisella tularensis, Chlamydia psittaci*, endemic fungi) occur;
- de-escalation of unnecessary antimicrobials, thus decreasing the risk of drug-related toxicity, pharmacokinetic interactions and microbial resistance;
- cost-reduction consequent to the above mentioned benefits;
- epidemiological information on the causative agents of CAP and their respective drug-resistance; this information would be valuable for recognizing clusters of specific infections and guiding the empirical therapeutic approach in future patients.

However, these potential advantages of a specific pathogen-directed therapy are hampered by the following limitations of current microbiological investigations (Mandell *et al.*, 2007; Woodhead *et al.*, 2005):
- limited feasibility in home/outpatient settings;
- low yield, especially during antimicrobial therapy;
- limited possibility of sample collection before early start of treatment;
- complications with the use of invasive, more sensitive and specific diagnostic procedures;
- possibility of mixed infections even when a single germ is detected;
- confounding false-positive results;
- cost.

Based on the above considerations, etiologic investigations, regarded as "never incorrect or a breach of the standard of care" (Mandell *et al.*, 2007), are recommended by ERS/ESCMID for all patients requiring hospitalization (Woodhead *et al.*, 2005), and by BTS only for severe CAP patients and those with clinical/epidemiological risk-factors or subjected to prior antibiotic therapy (BTS, 2004). IDSA/ATS recommend microbiological testing in the following circumstances in which this approach is more efficient, either because of a greater yield or more frequent unusual or drug-resistant pathogens (Mandell *et al.*, 2007):
- severe pneumonia/ICU admission;
- failure of empirical antibiotic therapy;
- leukopenia;
- chronic severe liver disease;
- asplenia;
- pleural effusion;
- risk factors or clinical manifestations suggesting tuberculosis;
- specific conditions listed in Table 2.

The recommended diagnostic tests to identify the microbial etiology of CAP are the following (Mandell *et al.*, 2007; Woodhead *et al.*, 2005; BTS, 2004):

- *Blood cultures*: the overall yield is 5-15% (mostly *S. pneumoniae*) in an unselected hospitalized CAP population (Campbell *et al.*, 2003). A higher yield is obtained in patients with severe CAP (Waterer, Wunderink, 2001; Paganin *et al.*, 2004; Ruiz *et al.*, 1999), chronic liver disease (Metersky *et al.*, 2004), asplenia and leukopenia (Metersky *et al.*, 2004). Contamination-related isolation of coagulase-negative staphylococci, if misinterpreted, can lead to a longer hospital stay and overuse of vancomycin.
- *Sputum gram stain and cultures:* the yield greatly varies with the quality of the entire procedure (collection, transport, processing, interpretation). In order to reduce the influence of flora colonizing the upper respiratory tract, thus increasing the clinical significance of testing, good quality specimens (i.e. satisfactorily representative of lower respiratory secretions) should be selected by cytological examination (<10 squamous epithelial cells and >25 polymorphonuclear cells/field, at 100x power) (Woodhead *et al.*, 2005). The reported yield for a gram stain of these valid specimens is the following: predominant morphotype in only 14% of cases (Garcia-Vazquez *et al.*, 2004); sensitivity and specificity for *S. pneumoniae* infection = 35.4 and 96.7%, respectively, and 42.8 and 99.4% for *H. influenzae* (Roson *et al.*, 2000), respectively; sensitivity for *S. pneumoniae* detection in bacteremic pneumococcal pneumonia = 80% (Musher *et al.*, 2004). When positive, the gram stain can soon guide the therapeutic choice and subsequently validate the clinical value of positive sputum cultures which, especially if obtained only from one sample, do not necessarily indicate an etiological role for CAP of the isolated agent. In turn, the sputum culture (sensitivity for *S. pneumoniae* in bacteremic pneumonia up to 93%) (Bartlett, 1977) provides information on the antimicrobial drug-susceptibility (Mandell *et al.*, 2007). Good-quality sputum specimens negative for *S. aureus* or gram-negative bacilli can orientate clinicians to exclude a role for these difficult pathogens and, thus, eliminating the need to broaden the empirical therapy (Mandell *et al.*, 2007).
- *Gram stain and cultures of other respiratory tract specimens:* when compared to sputum, the yield and clinical significance of microscopy and cultures are greater for specimens collected invasively, such as endotracheal aspirates, bronchoscopic or non-bronchoscopic bronchoalveolar lavage (BAL) fluid, protected specimen brushing (PSB), or transthoracic needle aspirates (TNA) (Bartlett, 1977; Jimenez *et al.*, 1993; Ishida *et al.*, 2001). BAL can be considered for non-resolving pneumonia (Woodhead *et al.*, 2005); its clinical significance is improved by the quantitative bacterial culture of BAL fluid, especially with a threshold of 10^3 CFU/mL (sensitivity 90%, specificity 97%) (Cantral *et al.*, 2004) or 10^4 CFU/mL (sensitivity 33%, specificity 100%) (Rasmussen *et al.*, 2001). Several studies have reported a high diagnostic yield with TNA (33-80%) (Woodhead *et al.*, 2005; Skerrett, 1999; Scott, Hall, 1999); however, due to potential complications, ERS/ESCMID recommend considering this procedure only for specific cases of severe CAP failing other less invasive diagnostic methods (Woodhead *et al.*, 2005). In intubated patients, endotracheal aspirates are recommended because they are safe and easy to perform, preferably soon after intubation to avoid tracheal colonization by nosocomial flora (Mandell *et al.*, 2007); it is unclear whether nonbronchoscopic BAL is a better diagnostic tool than endotracheal aspirates (Mandell *et al.*, 2007). IDSA/ATS emphasize that bronchoscopic BAL, PSB and TNA for the initial management of patients with CAP have not been prospectively studied thus far (Mandell *et al.*, 2007).
- *Gram stain and culture of pleural fluid*: thoracentesis is feasible and recommended for subjects with a pleural effusion >5 cm in height on a lateral, upright, chest x-radiograph; it provides a low diagnostic yield but with a high clinical significance (Mandell *et al.*, 2007; Woodhead *et al.*, 2005; Skerrett, 1999).

The above-mentioned yields of microscopic and cultural testing are impaired by antibiotic therapy and, therefore, these investigations should be initiated before treatment (Mandell *et al.*, 2007; Woodhead *et al.*, 2005). However, many pathogens often involved in severe CAP, other than *S. pneumoniae,* are unaffected by a single antibiotic dose (Mandell *et al.*, 2007).
- *S.pneumoniae urinary antigen:* immunochromatography, providing satisfactory sensitivity (50-80%), and specificity (>90%) (Dominguez *et al.*, 2001; Gutierrez *et al.*, 2003; Murdoch *et al.*, 2001), is easy to perform and rapid (about 15 minutes) and often remains positive even after starting

therapy; there is little overlap (28%) of positive tests with positive blood cultures (Roson *et al.*, 2004). Limitations: No information is provided on drug-susceptibility, false-positive results are possible in children colonized with *S. pneumoniae* (Navarro *et al.*, 2004) and in subjects with a CAP episode within the previous 3 months (Murdoch *et al.*, 2003).

- *Legionella pneumophila urinary antigen*: this examination provides good sensitivity (70-90%) and specificity (about 99%), and is easy to perform; it is positive from the first day of illness throughout weeks thereafter (Helbig *et al.*, 2001). Limitations: it detects only the *L. pneumophila* serogroup 1 (responsible for 80-95% of community-associated legionellosis in many areas) (Helbig *et al.*, 2001).

- *Influenza virus A and B antigens:* their sensitivity is 50-70% (according to the type of test and sample, and to the time-interval after onset of symptoms), and specificity is close to 100%. The test is easy and rapid to perform (15-30 minutes) (Bellei *et al.*, 2003; Landry *et al.*, 2004). Limitations: a high rate of false-negatives, especially after 3 days from onset of symptoms; possible false-positives with adenovirus infections (Mandell *et al.*, 2007; Templeton *et al.*, 2005).

- *Influenza A and B direct fluorescent antigen testing on nasopharyngeal aspirates:* their sensitivity and specificity are high (96% and 99.6%, for influenza virus type A, and 87.5% and 96.8% for influenza virus type B respectively); the test is rapid (about 2 hours) and can also detect H5N1 subtype (Chan *et al.*, 2002; Shetty *et al.*, 2003).

Microscopic, cultural and polymerase chain reaction (PCR) *assays for Mycobacterium species*.

Other diagnostic tests are not recommended in clinical practice either because of low sensitivity (e.g. direct fluorescent antibody testing for respiratory syncytial virus), late positive results after infection (e.g. acute/convalescent antibody seroconversion for *C. pneumoniae, M. pneumoniae, Legionella* spp.) or currently not standardized (e.g. PCR test for *L. pneumophila, C. pneumoniae*).

The clinical use of microbiological procedures should take into account the following general considerations:

- performing microbiological analyses should not delay the start of empirical treatment for acute pneumonia;
- the in vitro antimicrobial susceptibility results should be critically evaluated; in general, the drugs to which the microbe is resistant should be not considered, while the choice between those resulting active should not be casual but performed according to the individual patient characteristics (section 7.3);
- the correct clinical interpretation of the microbiological results (microscopy, cultures, drug-susceptibility testing) and the resulting therapeutic decisions should be carried out with the consultation of an infectious disease specialist.

THERAPEUTIC APPROACH

The recommendations for the initial empirically-reasoned antibiotic therapy in CAP, illustrated by the diverse guidelines, are based on the following steps:

- prediction of the most likely responsible pathogens (based on the treatment setting and individual risk factors (Table 2);
- consideration of the regional and local patterns of anti-microbial drug-resistance;
- consideration of the individual patient risk for toxicity to selected drugs, drug interactions with concurrent therapies, and low adherence to the prescription.

Empirically recommended regimens based on treatment setting and individual risk factors (Tables 4-6)

The guidelines considered herein differentiate the therapeutic approach according to the treatment setting chosen for the patient (home, non-ICU hospital ward, ICU), as these settings reflect the difference in disease severity and mortality risk, the most likely causative pathogens (see Table 1), and the need and feasibility for more aggressive treatments. The "syndromatological approach" of the past, based on the clinical-radiological picture (typical versus atypical pneumonia), is now considered ineffective for the choice of empirical treatment (Woodhead *et al.*, 2005; Ruiz *et al.*, 1999).

Home-treated patients

The U.S. recommendations (Mandell *et al.*, 2007) indicate the use of a macrolide or doxycycline (if the first is not tolerated) as the preferred home-based regimen to guarantee sufficient activity

both for *S. pneumoniae* and atypical pathogens. Conversely, in the European guidelines (Woodhead *et al.*; BTS, 2004), the empirical therapy is centered on *S. pneumoniae*, and therefore amoxicillin (ineffectual for atypical agents however) is recommended as the first-line antibiotic. This discordance is due to the fact that in Europe the *S. pneumoniae* strains are frequently macrolide-resistant. Moreover, the BTS attributes only slight consideration to atypical pathogens because *M. pneumoniae*, the most frequent of these germs, has a five-year periodicity and primarily affects young subjects. The IDSA/ATS underline that the need to treat moderate CAP caused by *Mycoplasma* spp. and *Chlamydophila* spp. is still controversial because these infections

TABLE 4 - *Recommended empirical antibiotic therapy for CAP in adults - IDSA/ATS.*

Setting of care/patient characteristics	*Preferred treatments*	*Alternatives*
Home-treated patients: a. Previously healthy and no use of antimicrobials within the previous 3 months	• Macrolide[a]	• Doxycycline
b. Comorbidities (chronic liver, heart, lung or renal disease; diabetes, alcoholism, malignancy, asplenia; immunosuppressing conditions or drugs). Use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected). Regions with a high rate (>25%) of infection with high-level (MIC ≥16 µg/mL) macrolide-resistant *S. pneumoniae*	• Respiratory fluoroquinolone[b] • β-lactam (high-dose oral amoxicillin [1 g 3 times daily] or amoxicillin-clavulanate [2 g 2 times daily]; ceftriaxone, cefpodoxime or cefuroxime) + macrolide	• β-lactam (same than preferred treatment) + doxycycline
Non-ICU[1] hospitalized patients:	• Respiratory fluoroquinolone • β-lactam (ampicillin, cefotaxime, ceftriaxone; ertapenem for selected patients[c])+ macrolide	• β-lactam (same than preferred treatment) + doxycycline
ICU hospitalized patients:	• β-lactam (ampicillin-sulbactam, cefotaxime, ceftriaxone) +: - azithromycin, or - respiratory fluoroquinolone	• Respiratory fluoroquinolone + aztreonam[d]
Special concerns: a. Risk factors for *Pseudomonas* infection[e]	• Antipneumococcal-antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) or aztreonam[d] +: - ciprofloxacin or levofloxacin, or - aminoglycoside + azithromycin, or - aminoglycoside + respiratory fluoroquinolone	
b. Community-acquired MRSA (CA-MRSA[2])	• Add vancomycin or linezolid	

NOTES: CAP community-acquired pneumonia, IDSA Infectious Diseases Society of America, ATS American Thoracic Society. [1]ICU: intensive care unit. [2]CA-MRSA: community-acquired methicillin-resistant *Staphylococcus aureus*. [a]Azithromycin, clarithromycin, or erythromycin. [b]Moxifloxacin, levofloxacin, or gemifloxacin. [c]Suspected infection by anaerobic agents, drug-resistant *S. pneumoniae* (DRSP), enterobacteriaceae including extended-spectrum β-lactamase (ESBL) producers; subjects recently treated with antibiotics. [d]Indicated for penicillin-allergic patients. [e]Risk factors for *P. aeruginosa* infection include: COPD, bronchiectasis, recent antimicrobial therapies, recent hospitalization, gross aspiration. Adapted from Mandell L.A., *et al.* (Mandell *et al.*, 2007), with permission from University of Chicago Press.

TABLE 5 - *Recommended empirical antibiotic therapy for CAP in adults - ERS/ESCMID.*

Setting of care/patient characteristics	*Preferred treatments*	*Alternatives*[a]
Home-treated patients:	• Amoxicillin • Tetracyclines[b]	• Amoxicillin-clavulanate • Macrolide • Respiratory fluoroquinolone[c]
Non-ICU hospitalized patients:	• β-lactam (penicillin G, aminopenicillind, aminopenicillin-β-lactamase-inhibitord, 2nd or 3rd generation cephalosporin) + macrolide	• Respiratory fluoroquinolone[c,d]
ICU hospitalized patients: - No risk factors for *P. aeruginosae*	• Non antipseudomonal 3rd generation cephalosporin + macrolide	• Non antipseudomonal 3rd generation cephalosporin + respiratory fluoroquinolone
- Risk factors for *P. aeruginosa*[e]	• Antipseudomonal cephalosporin (cefepime) + ciprofloxacin	• Ciprofloxacin +: - ureidopenicillin-β-lactam-inhibitors, or - carbapenem

NOTES: CAP community-acquired pneumonia, ERS European Respiratory Society, ESCMID European Society of Clinical Microbiology and Infectious Diseases. [a]To be used in case of major intolerance or in areas with widespread clinical relevant resistance to "preferred" antibiotics. [b]Tetracycline or doxycycline. [c]In regions with increased pneumococcal resistance rates. [d]Can be applied as sequential treatment (i.v./i.m. → oral) using the same drug. [e]Risk factors for P. aeruginosa infection include: COPD, bronchiectasis, recent antimicrobial therapies, recent hospitalization, gross aspiration. Adapted from Woodhead M., *et al.* (Woodhead *et al.*, 2005), with permission from European Respiratory Society Journals Ltd.

are generally self limiting, and that evidence for treatment benefits (i.e. reduction of morbidity and symptom duration) has been reported only for children thus far (Woodhead *et al.*, 2005; Shefe *et al.*, 2005).

Among the macrolides, clarithromycin and azithromycin are currently preferred to erythromycin because, although more expensive, they have a better gastrointestinal tolerance, an activity against *H. influenzae* and a more favorable pharmacokinetic profile, thus permitting a simpler administration schedule (Mandell *et al.*; 2007). As for the ketolide, telithromycin, the ERS/ESCMID do not provide specific recommendations, as clinical experience with this molecule is still limited. IDSA/ATS report that, according to several studies, telithromycin is equivalent to first-line drugs (e.g. amoxicillin and clar-

TABLE 6 - *Recommended empirical antibiotic therapy for CAP in adults - BTS.*

Setting	*Preferred treatments*	*Alternatives*[a]
Home-treated patients:	• Amoxicillin	• Macrolide
Non-ICU hospitalized patients:	• β-lactam (amoxicillin, ampicillin or benzylpenicillin) + macrolide	• Respiratory fluoroquinolone
ICU hospitalized patients:	• β-lactam (amoxicillin-clavulanate, cefuroxime, cefotaxime or ceftriaxone) + macrolide ± rifampicin	• Respiratory fluoroquinolone + benzylpenicillin

NOTES: CAP community-acquired pneumonia, BTS British Thoracic Society. [a]To be used in case of allergy or intolerance to preferred regimens, or in case of local concerns over *C. difficile* associated diarrhea related to β-lactams use. Adapted from BTS (BTS, 2004 update), with permission from BMJ Publishing Group.

ithromycin) (Hagberg *et al.*, 2003) and can cause severe hepatotoxicity (Clay *et al.*, 2006).
The IDSA/ATS (Mandell *et al.*, 2007) identify, among home-treated patients, a subgroup with risk factors for drug-resistant strains or with comorbidities which increase the likelihood of infection by gram negative bacteria. For these subjects, a more aggressive therapeutic approach with a β-lactam/macrolide association or a monotherapy using a "respiratory" fluoroquinolone is recommended.
The term "respiratory fluoroquinolones", even if not completely appropriate, emphasizes the utility of these molecules in respiratory infections based on their enhanced activity against gram-positive pathogens (in particular *S. pneumoniae*) when compared to earlier-generation fluoroquinolones. The commercially available respiratory fluoroquinolones are currently represented by levofloxacin, moxifloxacin, and in some countries, gemifloxacin. Moxifloxacin presents a greater activity towards *S. pneumoniae*. Data from comparative clinical trials show that fluoroquinolone monotherapy is a β-lactam/macrolide association (Segreti *et al.*, 2005; Fogarty *et al.*, 2004). In order to limit the spread of fluoroquinolone-resistance, IDSA/ATS discourage the use of these molecules in subjects with mild CAP without comorbidities or risk-factors for drug-resistant strains, and warns against the incorrect dose and duration of treatment (Mandell *et al.*, 2007).

Non-ICU hospitalized patients
For non-ICU hospitalized patients, both European (Woodhead *et al.*, 2005; BTS, 2004) and U.S. (Mandell *et al.*, 2007) guidelines advise the use of a respiratory fluoroquinolone alone or a β-lactam/macrolide association.

ICU hospitalized patients
In patients with severe CAP, a therapy to target *S. pneumoniae*, *Legionella* spp., and most of the clinically relevant enterobacteriaceae species is warranted (Mandell *et al.*, 2007; Woodhead *et al.*, 2005). Therefore, a potent anti-pneumococcal β-lactam should be combined with either a macrolide or a fluoroquinolone.

Additional risk-factors for specific etiologies
Both the IDSA/ATS and ERS/ESCMID differentiate hospital-based treatment recommendations according to the risk of *P. aeruginosa* etiology. A consistent tracheal aspirate gram stain, sputum or blood is the best indicator for *Pseudomonas* coverage (Mandell *et al.*, 2007). In addition, this risk must be taken into account for subjects with structural pathologies of the pulmonary parenchyma (such as bronchiectasis), frequent COPD exacerbations treated repeatedly with steroids and/or antibiotics, previous antibiotic treatment or hospitalization, especially in the ICU(Mandell *et al.*, 2007; Woodhead *et al.*, 2005; Arancibia *et al.*, 2002). For all these patients, the use of a β-lactam active against *P. aeruginosa* (Acylureidopenicillin-β-lactam inhibitors, cefepime, carbapenems) associated with a fluoroquinolone with the same activity (ciprofloxacin, levofloxacin) or with an aminoglycoside/azithromycin combination is advised (Mandell *et al.*, 2007; Woodhead *et al.*, 2005). For patients allergic to β-lactams, aztreonam represents an alternative (Mandell *et al.*, 2007). Aminoglycosides are discouraged for elderly patients.
In all hospitalized patients, the best indicator of a *S. aureu*s etiology is the finding of clusters of gram-positive cocci in a tracheal aspirate or in a good-quality sputum sample; end-stage renal disease, injection drug abuse and prior influenza have been identified as risk-factors for this infection (Mandell *et al.*, 2007; Venezia *et al.*, 2001). New drugs against MRSA, such as daptomycin or tigecycline, are not currently recommended for CAP (Mandell *et al.*, 2007).
Table 2 lists peculiar conditions associated with other specific pathogens responsible for CAP which should consistently influence the antimicrobial choice. In subjects in whom tuberculosis is compatible with clinical characteristics and/or specific risk factors, empirical administration of molecules with antituberculous activity (e.g. fluoroquinolones, aminoglycosides) should represent a second choice, at least until appropriate sampling for micobacterial testing has been obtained.

Consideration regarding regional and local anti-microbial drug-resistance patterns

Due to the great geographical variability of drug-resistance patterns, the choice of antimicrobials to address this problem should be based on the local drug-resistance epidemiology (Mandell *et*

TABLE 7 - *Dosage of principal antimicrobials for treating CAP in adults.*

Antimicrobial	*Dosage*
Benzylpenicillin (penicillin G)	1.2 g/6 h, *i.v.* (9)
Aminopenicillins:	
Amoxicillin	1 g/8 h, *os/i.v.*
Amoxicillin/Clavulanate	2 g/12 h os; 2.2 g/8 h, *i.v.*;
Ampicillin	1.5 g/8 h, *i.v./i.m.*;
Ureidopenicillins:	
Piperacillin- Tazobactam	4.5 g (P= 4 g/T= 0.5 g)/8 h, *i.v.*
Carbapenems:	
Imipenem	500 mg-1 g/8 h, *i.m./i.v.*
Meropenem	1 g/8 h, *i.v.*
2nd generation cephalosporins:	
Cefuroxime	1.5 g/8 h, *i.v.* (9)
Cefaclor	750 mg/12 h (modified release), *os*
Cefuroxime axetil	500 mg/8-12 h, *os*
3rd generation cephalosporins:	
Cefotaxime	1-2 g/8-12 h, *i.v./i.m.*
Ceftazidime	2 g/8 h, *i.v./i.m.*
Ceftriaxone	1-2 g/24 h, *i.v./i.m.*
Cefixime	200-400 mg/12-24 h, *os*
Cefpodoxime proxetil	200 mg/12 h, *os*
4th generation, antipseudomonal cephalosporins:	
Cefepime	2 g/12 h, *i.v.*
Fluoroquinolones:	
Ciprofloxain	500-750 mg/12 h, os; 400 mg/8-12 h, *i.v.*
Levofloxacin	500 mg/12-24 h, os/i.v.; 750 mg/24 h, *i.v.*
Moxifloxacin	400 mg/24 h, *os/i.v.*
Macrolides:	
Azithromycin	500 mg/24 h, *os* (for 3 days)
Clarithromycin	500 mg/12 h, *os/i.v.*
Erythromycin	500 mg-1 g/6 h, *os*
Glycopeptides:	
Vancomycin	7.5-15 mg×kg^{-1}/6-12 h (or continuous infusion), *i.v.*
Teicoplanin	6 mg×kg^{-1}/12 h x 3 times and then 6 mg×kg-1/24 h, *i.v./i.m.*; *S. aureus endocarditis, septic arthritis or burns:* 12 mg×kg^{-1}/12 h x 3 times and then 12 mg×kg^{-1}/24 h, *i.v./i.m.*
Aminoglycosides:	
Amikacin	15 mg×kg^{-1}/24 h, *i.m./i.v.*
Gentamicin	5 mg×kg^{-1}/24 h, *i.m./i.v.*
Tobramicin	5 mg×kg^{-1}/24 h, *i.m./i.v.*
Tetracyclines:	
Doxycyclin	200 mg/24 h, *i.m./i.v.*
Minocyclin	100 mg/12 h, *os*
Tetracyclin	250-500 mg/6 h, os; 500 mg-1 g/12 h, *i.v.*
Others:	
Clindamycin	600-900 mg/8 h, *os/i.v./i.m.*
Linezolid	600 mg/12 h, *os/i.v.*
Metronidazol	7.4 mg×kg^{-1} (~500 mg)/6 h, *i.v.*; 500 mg/6 h, *os*
Rifampin	10 mg×kg^{-1} (450-600 mg)/12 h, *os*; (BTS(9): 600 mg/24 h, os/i.v.)
Quinupristin-Dalfopristin	7.5 mg×kg^{-1}/8 h, *i.v.*

Note: Appendix 3 of the ERS/ESCMID guidelines (8) contains extensive and detailed pharmacodynamic and pharmacokinetic properties of the antimicrobials herein considered. Adapted from Woodhead M., *et al.* (Woodhead *et al.*, 2005 appendix 3), with permission from European Respiratory Society Journals Ltd.

al., 2007; Woodhead *et al.*, 2005). The principal CAP-related drug-resistance issues are the following.

- *Penicillin-resistant S. pneumoniae*. The worldwide prevalence is between 18.2% and 22.1% (Felmingham,2002; Jacobs *et al.*, 2003). In Europe (EARSS, 2005), wide differences (1-39%) have been reported between countries. Penicillin resistance is often associated with in vitro resistance toward other antibiotics, such as cephalosporins, macrolides, doxycycline and trimethoprim/sulfamethoxazole (Klugman *et al.*, 2006). Several studies suggest that the current resistance levels to β-lactams do not generally determine clinical failure when these molecules are used for CAP therapy (Mandell *et al.*, 2007; Woodhead *et al.*, 2005, Yu *et al.*, 2003).
- *Macrolide-resistant S. pneumoniae*. The rate in most countries is 10-25% (reaching 31% in Italy and Belgium, and 37% in Hungary). Macrolide resistance seems to lead to clinical failure when these molecules are used in CAP (Woodhead *et al.*, 2005; Lonks *et al.*, 2002). High-level erythromycin resistance (>64 μg/mL, encoded by the *erm* gene), conferring cross-resistance to clindamycin, is common in Europe (File *et al.*, 2004).
- A *dual S. pneumoniae resistance* to both penicillin and macrolides still remains below 5% for most nations, but it has reached high levels in France (32%) and Romania (31%) (EARSS, 2005).
- *Fluoroquinolone-resistant S. pneumoniae*. Although it is low throughout the world (approximately 2%), in some countries it is increasing. In CAP patients, clinical failure has been reported following resistance to ciprofloxacin and levofloxacin but not with resistance to moxifloxacin and gemifloxacin (Mandell *et al.*, 2007; Woodhead *et al.*, 2005; Davidson *et al.*, 2002).

The major risk factor for resistance to β-lactams, macrolides or fluoroquinolones is represented by a recent therapy utilizing antibacterials within the same class (Mandell *et al.*, 2007; Hyde *et al.*, 2001; Ho *et al.*, 2001; Ruhe, Hasbun, 2003). Therefore, in these patients, a different class of molecules should be considered (Mandell *et al.*, 2007; Woodhead *et al.*, 2005). For CAP patients at risk for drug-resistant *S. pneumoniae*, the IDSA/ATS suggest the use of highly active molecules in order to prevent the further spread of the resistant strains (Mandell *et al.*, 2007).

Community-acquired methicillin-resistant S. aureus (CA-MRSA)

An increasing incidence of pneumonia caused by CA-MRSA has been described worldwide, mainly in North-America (Mandell *et al.*, 2007; Gorak *et al.*, 1999). When compared with hospital-acquired strains, CA-MRSA often affects subjects without known risk-factors and is generally characterized by a different type (IV) of the SCC*mec* gene, by the presence of a gene encoding for a toxin (Panton-Valentine leukocidin) associated with necrotizing pneumonia, abscesses, empyemas, shock and respiratory failure, and by the resistance to fewer classes of antibacterials (mainly β-lactams) (Deresinski, 2005). Risk-factors for CAP caused by CA-MRSA regard living in areas in which infections by this strain have been reported, in addition to other factors illustrated in Table 6.

Considerations on individual patient characteristics

The final choice among the therapeutic options the above-mentioned criteria should not be at random but should take into account various host factors, such as:

- history of intolerance or toxicity developed to certain molecules;
- advanced age (associated with a greater risk of adverse events, especially with drugs such as aminoglycosides and fluoroquinolones);
- coexisting comorbidities, such as hepatic or renal disease;
- coexisting extrapulmonary sites of infection (favoring the choice of molecules with greater diffusion in the sites in question);
- expected low out-patient adherence to prescriptions (encouraging the choice of simpler regimens);
- concomitant therapies (favoring antimicrobials with lower risk of additive toxicity and/or pharmacokinetic interactions).

TIME TO INITIATE ANTIMICROBIAL THERAPY

Acute CAP represents a clinical emergency and the early start of an appropriate antibiotic therapy appears to lower mortality (Mandell *et al.*, 2007; Woodhead *et al.*, 2005; Simpson *et al.*, 2000;

Houck *et al.*, 2004) and, therefore, it should not be delayed by diagnostic procedures or other reasons. ERS/ESCMID recommend that the first antibiotic dose be administered within 2 hours after hospital admission and 1 hour after ICU admission (Woodhead *et al.*, 2005). For IDSA/ATS, the first administration of antimicrobials should occur while the patient is still in the emergency room, or even better, at the office of the physician who first diagnosed CAP (Mandell *et al.*, 2007).

MONITORING OF THERAPEUTIC EFFICACY AND NONRESPONDING PNEUMONIA

Failure to respond to initial antibiotic therapy is observed in 6-15% of all hospitalized CAP patients and in up to 40% of those initially admitted to ICU (Mandell *et al.*, 2007; Houck *et al.*, 2004).
The monitoring of antimicrobial efficacy should be based on the improvement and stabilization of the clinical and laboratory findings at presentation (Woodhead *et al.*, 2005). The relevant stabilization criteria are: body temperature ≤37.8°C, respiratory rate <25/min, arterial oxygen saturation ≥90%, or pO_2 ≥60 mmHg, arterial systolic pressure ≥90 mmHg, heart rate ≤100/min, ability to maintain oral intake, and normal mental status (Mandell *et al.*, 2007; Woodhead *et al.*, 2005). The moment for judging the adequacy of therapy depends on the severity of pneumonia at presentation. For instance, patients with PSI IV and V at admission show a median stabilization time of 3 and 5 days, respectively (Arancibia *et al.*, 2000; Halm *et al.*, 1998); for this reason, a well-reasoned empirical antibiotic choice should not be considered ineffective and changed before 72 hours, in the absence of clinical deterioration or new evidence for a different etiology (Mandell *et al.*, 2007). Abnormal radiological findings usually improve more slowly, and therefore cannot represent an early criteria for the efficacy evaluation of treatment.
Based on the stabilization criteria mentioned above, a *"non responding pneumonia"* is defined as an absent or inadequate clinical response to initial antimicrobial therapy, and can occur in three different patterns (Mandell *et al.*, 2007):
a) *progressive pneumonia or clinical deterioration*;
b) *persistent pneumonia* (failure to improve within 72 hours of treatment);
c) *slow-resolving pneumonia* (failure of complete resolution of clinical alterations after initial improvement (Woodhead *et al.*, 2005), or persistence of radiological infiltrates for >30 days (Mandell *et al.*, 2007).

Particularly in non-response patterns a) and b), diagnostic reassessment should regard the following possible factors (Mandell *et al.*, 2007; Woodhead *et al.*, 2005):
- non-adequate antimicrobial therapy (molecules, route of administration, dosage);
- drug-resistant and/or peculiar pathogens;
- CAP complications (e.g. parapneumonic effusion/empyema, abscess, acute respiratory distress syndrome) or BOOP (bronchiolitis obliterans organizing pneumonia);
- extrapulmonary complications (e.g. endocarditis, meningitis, arthritis, other deep-site and intravascular catheter infections);
- pulmonary or extrapulmonary superinfections;
- non-infectious disease (e.g. pulmonary embolus, acute eosinophilic pneumonia, interstitial lung disease, malignancy, congestive heart failure, myocardial infarction, vasculitis, renal failure).

The principal tools for diagnostic re-investigation in non-responding pneumonia are represented by computed tomography scan, bronchoscopy with BAL and transbronchial biopsies, and microbiological tests. In particular, blood cultures can have a significant yield even with prior antibiotic therapy and, if positive, they can increase the suspicion of either drug-resistant pathogens and/or other deep-site infections (e.g. endocarditis or arthritis) (Mandell *et al.*, 2007). *L. pneumophila* and *S. pneumoniae* antigens, as discussed above, are not affected by antibiotics. In the case of persisting fever in spite of clinical stabilization, the withholding of β-lactam antibiotics could safely clarify the possibility of a drug-related fever (Woodhead *et al.*, 2005). The timing and extent of diagnostic re-assessment should be more aggressive in progressive and persistent pneumonia than in slow-resolving cases; in the same manner, a different empirical antimicrobial regimen should be started soon after sample collection for microbiology testing in the former patterns of non-response, whereas it could be delayed in the latter (Woodhead *et al.*, 2005).

DURATION OF THERAPY

There are only a few clinical trials which have specifically evaluated the optimal duration of antibiotic therapy for CAP patients; the decision is usually determined by the specific pathogen, the eventual complications, and the underlying pathologies.
Available studies have demonstrated that treatment of CAP caused by *S. pneumoniae* should be administered for at least 72 hours after fever has ceased (Bartlett *et al.*, 2000).
The use of fluoroquinolones and macrolides has shown that 7-10 days of therapy is the optimal duration (File, 2003). IDSA/ATS recommend to stop treatment after at least 5 days of treatment, when patients are afebrile for 48-72 hours with ≤1 sign of clinical instability (see section 9) (Mandell *et al.*, 2007).
The use of short high-dose cycles appears to increase the efficacy and reduce the appearance of resistance (Clay *et al.*, 2006; Halm *et al.*, 1998).
A longer therapy duration is needed in the case of cavities or other signs of tissue necrosis (Mandell *et al.*, 2007), complications (e.g. endocarditis or meningitis) (Mandell *et al.*, 2007), or specific pathogens (e.g. *Legionella* spp or *Pseudomonas* spp., which should be treated for at least 14 days) (Mandell *et al.*, 2007; Woodhead *et al.*, 2005).

OTHER ISSUES

The following management aspects of CAP are discussed in one or more of the guidelines mentioned but are not considered in this review:
- therapy for specific, identified pathogens;
- non-antimicrobial supportive measures;
- route of administration and switch from parenteral to oral therapy (sequential therapy);
- monitoring for adverse effects;
- time and criteria for hospital discharge;
- prevention;
- rank of recommendations.

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REFERENCES

ALIKHAN R., COHEN A.T., COMBE S., ET AL. (2004). Risk factors for venous thromboembolism in hospitalized patients with acute medical illness: analysis of the MEDENOX Study. *Arch. Intern. Med.* **164**, 963-968.

ANGUS D.C., MARRIE T.J., OBROSKY D.S., ET AL. (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.

ARANCIBIA F., BAUER T.T., EWIG S., ET AL. (2002). Community-acquired pneumonia due to gram-negative bacteria and *Pseudomonas aeruginosa:* incidence, risk, and prognosis. *Arch. Intern. Med.* **162**, 1849-1858.

ARANCIBIA F., EWIG S., MARTINEZ JA., ET AL. (2000). Antimicrobial treatment failures in patients with community-acquired pneumonia. *Am. J. Respir. Crit. Care Med.* **162**, 154-160.

BARTLETT J.G. (1977). Diagnostic accuracy of transtracheal aspiration bacteriologic studies. *Am. Rev. Respir. Dis.* **115**, 777-782.

BARTLETT J.G., DOWELL S.F., MANDELL L.A., ET AL. (2000). Guidelines from the Infectious Diseases Society of America. Practice guidelines for the management of community-acquired pneumonia in adults. *Clin. Infect. Dis.* **31**, 347-382.

BELLEI N., BENFICA D., PEROSA A.H., CARLUCCI R., BARROS M., GRANATO C. (2003). Evaluation of a rapid test (QuickVue) compared with the shell vial assay for detection of influenza virus clearance after antiviral treatment. *J. Virol. Methods* **109**, 85-88.

BRITISH THORACIC SOCIETY (BTS) PNEUMONIA GUIDELINES COMMITTEE. (2004 update). BTS guidelines for the management of community acquired pneumonia in adults. Published online on the BTS website www.brit-thoracic.org.uk/ on 30 Apr 2004.

CAMPBELL S.G., MARRIE T.J., ANSTEY R., DICKINSON G., ACKROYD-STOLARZ S. (2003). The contribution of blood cultures to the clinical management of adult patients admitted to the hospital with community-acquired pneumonia: a prospective observational study. *Chest.* **123**, 1142.

CANTRAL D.E., TAPE T.G., REED E.C., SPURZEM J.R., RENNARD S.I., THOMPSON A.B. (1993). Quantitative culture of bronchoalveolar lavage fluid for the diagnosis of bacterial pneumonia. *Am. J. Med.* **95**, 601-607.

CAPELASTEGUI A., ESPANA P.P., QUINTANA J.M., ET AL. (2004). Improvement of process-of-care and outcomes after implementing a guideline for the management of community-acquired pneumonia: a controlled before and after design study. *Clin. Infect. Dis.* **39**, 955-963.

CAPELASTEGUI A., ESPANA P.P., QUINTANA J.M., ET AL. (2006). Validation of a predictive rule for the man-

agement of community-acquired pneumonia. *Eur. Respir. J.* **27**, 151-157.

Carratala J., Fernandez-Sabe N., Ortega L., et al. (2005). Outpatient care compared with hospitalization for community-acquired pneumonia: a randomized trial in low-risk patients. *Ann. Intern. Med.* **142**, 165-172.

Chan K.H., Maldeis N., Pope W., et al. (2002). Evaluation of the Directigen FluA+B test for rapid diagnosis of influenza virus type A and B infections. *J. Clin. Microbiol.* **40**, 1675-1680.

Clay K.D., Hanson J.S., Pope S.D., Rissmiller R.W., Purdum P.P. III, Banks P.M. (2006). Brief communication: severe hepatotoxicity of telithromycin: three case reports and literature review. *Ann. Intern. Med.* **144**, 415-420.

Davidson R., Cavalcanti R., Brunton J.L., et al. (2002). Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia. *N. Engl. J. Med.* **346**, 747-750.

Dean N.C., Silver M.P., Bateman K.A., James B., Hadlock C.J., Hale D. (2001). Decreased mortality after implementation of a treatment guideline for community-acquired pneumonia. *Am. J. Med.* **110**: 451-457.

Dean N.C., Suchyta M.R., Bateman K.A., Aronsky D., Hadlock C.J. (2000). Implementation of admission decision support for community-acquired pneumonia. *Chest.* **117**, 1368-1377.

Deresinski S. (2005). Methicillin-resistant *S. aureus:* an evolutionary, epidemiologic, and therapeutic odyssey. *Clin. Infect. Dis.* **40**, 562-573.

Dominguez J., Gali N., Blanco S., et al. (2001). Detection of *S. pneumoniae* antigen by a rapid immunochromatographic assay in urine samples. *Chest*. **119**, 243-249.

Dunbar L.M., Wunderink R.G., Habib M.P., et al. (2003). High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. *Clin. Infect. Dis.* **37**, 752-760.

European Antimicrobial Resistance Surveillance System (EARSS). Annual report, 2005, available on line at the website http://www.rivm.nl/earss

Felmingham D. (2002) Evolving resistance patterns in community-acquired respiratory tract pathogens: first results from the PROTEKT global surveillance study. *J. Infection.* **44** (suppl A), 3-1.

File T.M. Jr. (2003). Community acquired Pneumoniae. *Lancet* **362**, 1991-2001.

File T.M. Jr, Garau J., Blasi F., et al. (2004). Guidelines for empiric antimicrobial prescribing in community - acquired pneumonia. *Chest.* **125**, 1888-1901.

File T.M. Jr, Plouffe J.F. Jr, Breiman R.F., Skelton S.K. (1999). Clinical characteristics of Chlamydia pneumoniae infection as the sole cause of community-acquired pneumonia. *Clin. Infect. Dis.* **29**, 426-428.

Fine M.J., Auble T.E., Yealy D.M., et al. (1997). A prediction rule to identify low-risk patients with community-acquired pneumonia. *N. Engl. J. Med.* **336**, 243-250.

Fine M.J., Stone R.A., Lave J.R., et al. (2003). Implementation of an evidence-based guideline to reduce duration of intravenous antibiotic therapy and length of stay for patients hospitalized with community acquired pneumonia: a randomized controlled trial. *Am. J. Med.* **115**, 343-351.

Fogarty C., Siami G., Kohler R., et al. (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** (suppl), S16-S23.

Garcia-Vazquez E., Marcos M.A., Mensa J., et al. (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.

Gorak E.J., Yamada S.M., Brown J.D. (1999). Community-acquired methicillinresistant *S. aureus* in hospitalized adults and children without known risk factors. *Clin. Infect. Dis.* **29**, 797-800.

Gutierrez F., Masia M., Rodriguez J.C., et al. (2003). Evaluation of the immunochromatographic Binax NOW assay for detection of *S. pneumoniae* urinary antigen in a prospective study of community-acquired pneumonia in Spain. *Clin. Infect. Dis.* **36**, 286-292.

Hagberg L., Carbon C., van Rensburg D.J., Fogarty C., Dunbar L., Pullman J. (2003). Telithromycin in the treatment of community-acquired pneumonia: a pooled analysis. *Respir. Med.* **97**, 625-633.

Halm E.A., Fine M.J., Kapoor W.N., Singer D.E., Marrie T.J., Siu A.L. (2002). Instability on hospital discharge and the risk of adverse outcomes in patients with pneumonia. *Arch. Intern. Med.* **162**, 1278-1284.

Halm E.A., Fine M.J., Marrie T.J., et al. (1998). Time to clinical stability in patients hospitalized with communityacquired pneumonia: implications for practice guidelines. *JAMA* **279**, 1452-1457.

Helbig J.H., Uldum S.A., Luck P.C., Harrison T.G. (2001). Detection of *Legionella pneumophila* antigen in urine samples by the BinaxNOW immunochromatographic assay and comparison with both Binax *Legionella* Urinary Enzyme Immunoassay (EIA) and Biotest *Legionella* Urin Antigen EIA. *J. Med. Microbiol.* **50**, 509-516.

Ho P.L., Tse W.S., Tsang K.W., et al. (2001). Risk factors for acquisition of levofloxacin-resistant *S. pneumoniae:* a case-control study. *Clin. Infect. Dis.* **32**, 701-707.

Houck P.M., Bratzler D.W., Nsa W., Ma A., Bartlett J.G. (2004). Timing of antibiotic administration and

outcomes for Medicare patients hospitalized with community-acquired pneumonia. *Arch. Intern. Med.* **164**, 637-644.

HYDE T.B., GAY K., STEPHENS D.S., ET AL. (2001). Macrolide resistance among invasive *S. pneumoniae* isolates. *JAMA* **286**, 1857-1862.

ISHIDA T., HASHIMOTO T., ARITA M., ET AL. (2001). Efficacy of transthoracic needle aspiration in community-acquired pneumonia. *Intern. Med.* **40**, 873-877.

JACOBS M.R., FELMINGHAM D., APPELBAUM P.C., GRUNEBERG R.N. AND THE ALEXANDER PROJECT GROUP (2003). The Alexander Project 1998-2000: susceptibility of pathogens isolated from community-acquired lower respiratory tract infection to commonly used antimicrobial agents. *J. Antimicrob. Chemother.* **52**, 229-246.

JIMENEZ P., SALDIAS F., MENESES M., SILVA M.E., WILSON M.G., OTTH L. (1993). Diagnostic fiberoptic bronchoscopy in patients with community-acquired pneumonia: comparison between bronchoalveolar lavage and telescoping plugged catheter cultures. *Chest.* **103**, 1023-1027.

KLUGMAN K.P., LOW K.P., METLAY J., PECHEREE J.C., WEISS K. (2004). Community-acquired pneumonia: new management strategies for evolving pathogens and antimicrobial susceptibilities. Review. *International Journal of Antimicrobial Agents* **24**, 411-422.

KOLLEF M.H., SHERMAN G., WARD S., FRASER V.J. (1999). Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest.* **115**, 462-474.

LANDRY M.L., COHEN S., FERGUSON D. (2004). Comparison of Binax NOW and Directigen for rapid detection of influenza A and B. *J. Clin. Virol.* **31**, 113-115.

LIEBERMAN D., SCHLAEFFER F., BOLDUR I., ET AL. (1996). Multiple pathogens in adult patients admitted with community-acquired pneumonia: a one year prospective study of 346 consecutive patients. *Thorax.* **51**, 179-184.

LIM W.S., VAN DER EERDEN M.M., LAING R., ET AL. (2003). Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax.* **58**, 377-382.

LONKS J.R., GARAU J., GOMEZ L., ET AL. (2002). Failure of macrolide antibiotic treatment in patients with bacteremia due to erythromycin-resistant *S. pneumoniae. Clin. Infect. Dis.* **35**, 556-564.

MANDELL L.A., WUNDERICK R.G., ANZUETO A., ET AL. (2007). Infectious Diseases Society of America/America Thoracic Society. Consensus guidelines on the management of community acquired pneumonia in adults. *Clin. Infect. Dis.* **44** (Suppl 2).

MARRIE T.J., LAU C.Y., WHEELER S.L., WONG C.J., VANDERVOORT M.K., FEAGAN B.G. (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.

METERSKY M.L., MA A., BRATZLER D.W., HOUCK P.M. (2004). Predicting bacteremia in patients with community-acquired pneumonia. *Am. J. Respir. Crit. Care Med.* **169**, 342-347.

MORTENSEN E.M., RESTREPO M., ANZUETO A., PUGH J. (2004). Effects ofguideline-concordant antimicrobial therapy on mortality among patients with community-acquired pneumonia. *Am. J. Med.* **117**, 726-731.

MURDOCH D.R., LAING R.T., COOK J.M. (2003). The NOW *S. pneumoniae* urinary antigen test positivity rate 6 weeks after pneumonia onset and among patients with COPD. *Clin. Infect. Dis.* **37**, 153-154.

MURDOCH D.R., LAING R.T., MILLS G.D., ET AL. (2001). Evaluation of a rapid immunochromatographic test for detection of *S. pneumoniae* antigen in urine samples from adults with community-acquiredp-neumonia. *J. Clin. Microbiol.* **39**, 3495-3498.

MUSHER D.M., MONTOYA R., WANAHITA A. (2004). Diagnostic value of microscopic examination of Gram-stained sputum and sputum cultures in patients with bacteremic pneumococcal pneumonia. *Clin. Infect. Dis.* **39**, 165-169.

NAVARRO D., GARCIA-MASET L., GIMENO C., ESCRIBANO A., GARCIA-DE-LOMAS J. (2004). Performance of the Binax NOW S. pneumoniae urinary antigen assay for diagnosis of pneumonia in children with underlying pulmonary diseases in the absence of acute pneumococcal infection. *J. Clin. Microbiol.* **42**, 4853-4855.

NIEDERMAN M.S., MANDELL L.A., ANZUETO A., ET AL. (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.

NIEDERMAN M.S., MCCOMBS J.S., UNGER A.N., KUMAR A., POPOVIAN R. (1998). The cost of treating community-acquired pneumonia. *Clin. Ther.* **20**, 820-837.

PAGANIN F., LILIENTHAL F., BOURDIN A., ET AL. (2004). Severe community-acquired pneumonia: assessment of microbial aetiology as mortality factor. *Eur. Respir. J.* **24**, 779-785.

RASMUSSEN T.R., KORSGAARD J., MOLLER J.K., SOMMER T., KILIAN M. (2001). Quantitative culture of bronchoalveolar lavage fluid in community-acquired lower respiratory tract infections. *Respir. Med.* **95**, 885-890.

ROSON B., CARRATALA J., FERNANDEZ-SABE N., TUBAU F., MANRESA F., GUDIOL F. (2004). Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia. *Arch. Intern. Med.* **164**, 502-508.

ROSON B., CARRATALA J., VERDAGUER R., DORCA J.,

Manresa F., Gudiol F. (2000). Prospective study of the usefulness of sputum Gram stain in the initial approach to communityacquired pneumonia requiring hospitalization. *Clin. Infect. Dis.* **31**, 869-874.

Roson B., Fernandez-Sabe N., Carratala J., et al. (2004). Contribution of a urinary antigen assay (Binax NOW) to the early diagnosis of pneumococcal pneumonia. *Clin. Infect. Dis.* **38**, 222-226.

Ruhe J.J., Hasbun R. (2003). *S. pneumoniae* bacteremia: duration of previous antibiotic use and association with penicillin resistance. *Clin. Infect. Dis.* **36**, 1132-1138.

Ruiz M., Ewig S., Marcos M.A., et al. (1999). Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. *Am. J. Respir. Crit. Care Med.* **160**, 397-405.

Scott J.A., Hall A.J. (1999). The value and complications of percutaneous transthoracic lung aspiration for the etiologic diagnosis of community-acquired pneumonia. *Chest.* **116**, 1716-1732.

Segreti J., House H.R., Siegel R.E. (2005). Principles of antibiotic treatment of community-acquired pneumonia in the outpatient setting. *Am. J. Med.* **118** (Suppl. 1), 21-28.

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.

Shetty A.K., Treynor E., Hill D.W., Gutierrez K.M., Warford A., Baron E.J. (2003). Comparison of conventional viral cultures with direct fluorescent antibody stains for diagnosis of community-acquired respiratory virus infections in hospitalized children. *Pediatr. Infect. Dis. J.* **22**, 789-794.

Simpson J.C., Macfarlane J.T., Watson J., Woodhead M.A. (2000). A national confidential enquiry into community-acquired pneumonia deaths in young adults in England and Wales. British Thoracic Society Research Committee and Public Health Laboratory Service. *Thorax.* **55**, 1040-1045.

Skerrett S.J. (1999). Diagnostic testing for community-acquired pneumonia. *Clin. Chest. Med.* **20**, 531-548.

Suchyta M.R., Dean N.C., Narus S., Hadlock C.J. (2001). Effects of a practice guideline for community-acquired pneumonia in an outpatient setting. *Am. J. Med.* **110**, 306-309.

Templeton K.E., Scheltinga S.A., van den Eeden W.C., Graffelman A.W., van den Broek P.J., Claas E.C. (2005). Improved diagnosis of the etiology of community-acquired pneumonia with real-time polymerase chain reaction. *Clin. Infect. Dis.* **41**, 345-351.

Venezia R.A., Domaracki B.E., Evans A.M., Preston K.E., Graffunder E.M. (2001). Selection of high-level oxacillin resistance in heteroresistant *S. aureus* by fluoroquinolone exposure. *J. Antimicrob. Chemother.* **48**, 375-381.

Waterer G.W., Wunderink R.G. (2001). The influence of the severity of community- acquired pneumonia on the usefulness of blood cultures. *Respir. Med.* **95**, 78-82.

Wipf J.E., Lipsky B.A., Hirschmann J.V., et al. (1999). Diagnosing pneumonia by physical examination: relevant or relic? *Arch. Intern. Med.* **159**, 1082-1087.

Woodhead M. (2002). Community-acquired pneumonia in Europe: causative pathogens and resistance patterns. *Eur. Respir. J* **20**, 20S-27S.

Woodhead M., Blasi F., Ewig S., et al. (2005). European Respiratory Society Task Force in collaboration with the European Society for Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections. *Eur. Respir. J.* **26** (suppl 6), 1138-1180.

Yu V.L., Chiou C.C., Feldman C., et al. (2003). An international prospective study of pneumococcal bacteremia: correlation with in vitro resistance, antibiotics administered, and clinical outcome. *Clin. Infect. Dis.* **37**, 230-237.