The Infections Causing Acute Respiratory Failure in Elderly Patients

5

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Abbreviations

AECOPD	Acute exacerbations of chronic obstructive pulmonary disease
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
CAP	Community-acquired pneumonia
COPD	Chronic obstructive pulmonary disease
ESBL	Extended-spectrum β-lactamase
ICU	Intensive care unit
MRSA	Methicillin-resistant *Staphylococcus aureus*
NIV	Non-invasive ventilation

5.1 Introduction

Aging is accompanied by profound morphological and physiological alterations. In particular, the immune system undergoes a complex series of remodeling/restructuring events, involving almost all compartments, both cell-mediated immunity and humoral immune responses.

This process termed immunosenescence or immune dysregulation, together changes in lung function who occur with advancing age, play a critical role in the manifestation of age-related pulmonary diseases such as infections (i.e., pneumonia), chronic obstructive pulmonary disease (COPD), and increased the risk for develop sepsis [1].

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Respiratory failure is not a disease per se but a consequence of the problems that interfere with the ability to breathe. The term refers to the inability to perform adequately the fundamental functions of respiration: to deliver oxygen to the blood and to eliminate carbon dioxide from it. Respiratory failure has many causes and can come on abruptly (acute respiratory failure), when the underlying cause progresses rapidly, or slowly (chronic respiratory failure), when it is associated over months or even years with a progressive underlying process. Triggering causes of ARF in advanced aged patients are especially acute heart decompensation, severe community-acquired pneumonia (CAP), acute exacerbations of COPD (AECOPD), and pulmonary embolism. Pneumothorax, lung cancer, severe sepsis, and acute asthma were less frequent (<5%) [2].

Acute respiratory failure is a condition in which the respiratory system fails in one or both of its gas functions, i.e., oxygenation (PaO_2 <60 mmHg) of and/or elimination of carbon dioxide (arterial carbon dioxide tension ($PaCO_2$) >45 mmHg). In practice, it may be classified as either hypoxemic or hypercapnic. Hypoxemic respiratory failure (type I) is characterized by an arterial oxygen tension (PaO_2) lower than 60 mm Hg with a normal or low arterial carbon dioxide tension ($PaCO_2$). This is the most common form of respiratory failure, and it can be associated with virtually all acute diseases of the lung, which generally involve fluid filling or collapse of alveolar units.

The four pathophysiological mechanisms related to hypoxemic ARF are [3, 4]:

1. Ventilation/perfusion inequality which is the main mechanisms in an emergency setting (congestive heart failure or pneumonia)
2. Increased shunt (acute respiratory distress syndrome)
3. Alveolar hypoventilation (chronic obstructive pulmonary disease)
4. Diffusion impairment (pulmonary fibrosis)

Hypercapnic respiratory failure (type II) is characterized by a $PaCO_2$ higher than 45 mmHg. Hypoxemia is common in patients with hypercapnic respiratory failure who are breathing room air. Common etiologies include drug overdose, neuromuscular disease, chest wall abnormalities, and severe airway disorders (e.g., chronic obstructive pulmonary disease).

In case of a COPD exacerbation, an acute inflammation in the airways increases resistance to air flow with consequent air trapping. Increased resistance and elastic load due to air trapping place respiratory muscles at a mechanical disadvantage and increases the work of breathing and leads to ARF.

Infectious factor such as pneumonia with/without sepsis caused by a variety of pathogens, including bacteria, viruses, malaria, and fungal is the medical condition that is most commonly associated with acute respiratory distress syndrome (ARDS). Sepsis due to nonpulmonary infections, aspiration of gastric contents, and major trauma with shock also commonly precipitate the injury [5]. Since the same kinds of immune cells and immune proteins, including immunoglobulins and complements, are observed in the pathologic lesions of pneumonia, ARDS, and other organ-specific pathologic lesions, it may be a reasonable assumption that sepsis and

ARDS have similar underlying mechanisms, characterized by inflammation and endothelial dysfunction [6]. ARDS is a heterogeneous syndrome characterized by increased permeability of pulmonary capillary endothelial cells and alveolar epithelial cells, leading to hypoxemia that is refractory to usual oxygen therapy [7].

The severity of ARDS is associated with poor prognosis and higher mortality, and, by the Berlin definition, diagnostic hypoxemia is defined as decreased arterial PaO_2/FiO_2 ratio with parameters of 201–300 mmHg for mild ARDS, 101–200 mmHg for moderate ARDS, and <100 mmHg for severe ARDS [8].

Considering the immunopathogenesis of pneumonia, sepsis, and ARDS, early and appropriate antimicrobial therapy is critical to reduce the number of pathogens and pathogen-originated substances, thereby inducing early recovery from the disease and better outcome.

Similarly, although the knowledge about the effectiveness of antibiotics in the management of acute exacerbations of COPD remains limited by the lack of strong evidence, studies show that early antibiotic administration is associated with improved outcomes among patients hospitalized for acute exacerbations of COPD [9]. Furthermore inadequate antibiotic therapy, which through incomplete resolution of the initial exacerbation and persistent bacterial infection, is likely to influence the risk of relapse.

5.2 Antibiotic Therapy in Exacerbations of Chronic Obstructive Pulmonary Disease

Exacerbations of chronic obstructive pulmonary disease (COPD) are defined as sustained worsening of a patient's condition beyond normal day-to-day variations that is acute in onset, and that may also require a change in medication and/or hospitalization [10].

An acute COPD exacerbation can be viewed as an acute inflammatory event superimposed on chronic inflammation associated with COPD.

Most AECOPD may be due to viral infection or bacterial infection (50%), but irritants such as smoke or environmental factors such as low temperature and air pollution account for 15–20% of exacerbations [11].

In patients with mild disease, *Streptococcus pneumoniae*, Haemophilus influenzae, and *Moraxella catarrhalis* are the predominant microorganisms, whereas in patients with severe COPD, requiring mechanical ventilation, levels of these bacteria are reduced and other microorganism such as Haemophilus parainfluenzae and *Pseudomonas aeruginosa* predominate. It has also been observed that the severity of lung function, measured by FEV1, has an impact on the microbiology of exacerbation [12]. Patients with increased airway obstruction and frequent exacerbations, the microbiology of the exacerbations is often more complex, with a predominance of *Enterobacteriaceae* and *Pseudomonas aeruginosa*.

The role of atypical microorganisms is the subject of debate. According to some authors, there is no association between the presence of organisms such as *Chlamydia pneumoniae*, *Legionella* spp., *Mycoplasma pneumoniae*, and AECOPD [13].

However, in AECB, several older studies and a few recent studies have implicated atypical bacteria in only 5–10% of episodes [14].

Although it is difficult to define precisely the proportion of exacerbations caused by viruses, they are often implicated in AECOPD (up to 30% of cases) [15]. The most common viruses associated with exacerbations of COPD are rhinoviruses, but in more severe exacerbations requiring hospitalization, influenza virus is more common. Viral infection may, also, facilitate subsequent bacterial infection or increase the number of bacteria already present in the lower airways.

5.2.1 Which Patients Should Receive Antibiotic Treatment

The use of antibiotics in exacerbations COPD remains controversial; therefore, in the era of antibiotic resistance, the identification of clinical characteristics that identify patients with AECOPD that can be safely treated without antibiotics is extremely important.

There is evidence supporting the use antibiotics in exacerbations when patients have clinical signs of a bacterial infection, e.g., increased sputum purulence, especially when there are changes in the color of sputum [16].

Antibiotics are also recommended for patients with exacerbations requiring mechanical ventilation, as this has been shown significantly to reduce mortality and the risk of secondary pneumonia.

In summary, antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms: increase in dyspnea, sputum volume, and sputum purulence; have two of the cardinal symptoms if increased purulence of sputum is one of the two symptoms; or require mechanical ventilation (invasive or non-invasive) [10].

5.2.2 Stratification of Patients for Antibiotic Treatment and Type of Treatment (Table 5.1)

After the decision to initiate empirical antibiotic therapy, the choice of empirical antibiotic regimen most appropriate for treating an episode of AECOPD should be based on the following:

1. The severity of COPD, established by FEV1 and the history of more than three exacerbations in the previous 12 months.
2. The patients age (≥ or <65 years).
3. Significant comorbidity (diabetes mellitus, liver cirrhosis, chronic renal failure, or heart disease).
4. The risk of infection due to *P. aeruginosa*, which must be considered in the presence of two of the following risk factors: recent hospitalization, frequent (>4 times/year) or recent (within the previous 3 months) administration of antibiotics, severe disease (FEV1 <30%), or the use of oral corticosteroids (>10 mg of prednisone daily in the previous 2 weeks).

Table 5.1 Antibiotic choice for COPD exacerbations

Clinical presentation	Risk factors	Suggested antibiotic
Uncomplicated exacerbations	Age <65 years FEV_1 >50% predicted No comorbidity <3 exacerbations per years	• Macrolide (azithromycin, clarithromycin) • 2nd- or 3rd generation plus cephalosporins • Doxycycline • Trimethoprim–sulfamethoxazole • If recent antibiotic exposure (<3 months), use alternative class
Complicated exacerbations	Age ≥65 years FEV_1 ≤50 predicted Comorbidity ≥3 exacerbations per years	• Fluoroquinolone (moxifloxacin, levofloxacin) • Amoxicillin/clavulanate • If recent antibiotic exposure (<3 months), use alternative class
At risk for pseudomonas infection	FEV_1 ≤30% predicted Prior antibiotic use Steroid use Bronchiectasis	• Ciprofloxacin • β-lactam with *P. aeruginosa* activity ± • Aminoglycosides

Between 10% and 20% of patients with moderate to severe exacerbations do not respond to initial empirical therapy and require a change of antibiotic. In these cases, the infection can be caused by *Staphylococcus aureus*, *P. aeruginosa*, or some atypical microorganism not covered by the initial regimen or because of resistant organisms (such as *S. pneumoniae*); hence, a microbiological assessment would help to adjust the antibiotic treatment of second choice [17].

There are not enough data concerning the role of antiviral therapy in respiratory failure due to COPD.

5.2.3 Dosing Strategies of Antibiotics

There are no standard procedures that determine the dose and duration of antibiotic treatment in patients with AECOPD. Therefore, several studies demonstrate that short-term antibiotic use is associated with very important advantages such as reduction of exposure that will result in decreased bacterial resistance, enhanced compliance, and decreased side effects. The recommended length of antibiotics therapy is 5–7 days [10].

5.3 Community-Acquired Pneumonia in the Elderly

The incidence of community-acquired pneumonia increases with age, reaching 25–44 cases per 1000 inhabitants/year in the population over the age of 65 years, up to four times that of younger patients [18].

Elderly patients are more predisposed to pneumonia because of their impaired gag reflex, decreased mucociliary function, waning immunity, impaired febrile response, and chronic disease (diabetes mellitus, chronic obstructive pulmonary

disease, chronic heart failure, cancer and chronic renal insufficiency). Furthermore, central nervous system disorders and/or an impaired gag reflex predispose elderly patients to aspiration pneumonia.

With respect to the youngest population, pneumonia in the elderly subjects is more severe, requires often hospitalization, and is characterized by a longer length of stay and by greater mortality, particularly in patients with comorbidities [19].

It is important to remember that clinical presentation of pneumonia in the elderly may be subtle and may be afebrile. Altered mental status, a sudden decline in functional capacity, worsening of underlying diseases, and falls may be the only findings.

As stated by Sir William Osler [20] "in old age, pneumonia may be latent, coming on without chill, the cough and expectoration are slight, the physical signs ill defined and changeable, and the constitutional symptoms out of all proportion."

5.3.1 Etiology of CAP

As with any infectious disease, identifying the causative agent in CAP can be extremely useful in guiding antimicrobial therapy. Unfortunately, despite the use of more sensitive and specific diagnostic methods to define an etiologic pathogen in community-acquired pneumonia requiring hospitalization, in the majority of patients, a microbiologic diagnosis cannot be made [21].

In most cases, the microbiologic patterns observed in the elderly do not differ significantly from those observed in younger populations although with a different age-related distribution.

Streptococcus pneumoniae is still the most important pathogen in younger as well as older adults and the incidence of pneumococcal pneumonia generally increases with age. Haemophilus influenzae is relatively more common in elderly patients than in non-elderly adults and are the second most frequently identified microorganisms, while *Moraxella catarrhalis* is of particular importance as a cause of community-acquired pneumonia in patients with chronic bronchitis.

The most discernible differences between the two groups were Gram-negatives, especially *Enterobacteriaceae* were found more frequently in the elderly, whereas certain atypical pathogens (*Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Coxiella burnetii*) were more frequent in younger patient [22].

Among the atypical bacteria, *Chlamydophila pneumoniae* is the most common agent, while *Mycoplasma pneumoniae* is less frequently associated with CAP in this age group. Although uncommon, *Legionella pneumophila* should be considered in elderly adults presenting with atypical symptoms (e.g., headache, weakness, altered mental status, gastrointestinal disturbances, or bradycardia in the setting of a paucity of respiratory symptoms) or those with severe pneumonia.

Gram-negative organisms are an uncommon cause of CAP. However, in severely debilitated or chronically ill elderly patients from the community, a high index of suspicion for Gram-negative bacilli may be warranted, especially in those who fail to improve on standard therapy.

The probability of MRSA in patients hospitalized in conventional wards is low being more frequent in severe CAP understood as the need for admission in an

intensive care unit (ICU). Thus, in the presence of less than two factors of multiresistance (severe pneumonia, hospitalization in the previous 90 days, living in a residence, severe basal dependence for basic daily life activities, immunodepression, or the taking of antibiotics in the previous 6 months) coverage against MRSA should be included if the patient presents severe disease.

Pseudomonas aeruginosa is not a frequent pathogen in CAP; factors increasing the likelihood for Pseudomonas infection are structural lung disease such as bronchiectasis or severe COPD with FEV1 <35%, severe pneumonia requiring ICU admission, frequent or recent use of antibiotics, recent hospital admission and steroid use.

Aspiration pneumonia refers to an infection that develops after the entrance of pathologic oropharyngeal microbes into the lung. Major risk factors for aspiration include depressed consciousness, compromised airway defenses, dysphagia, gastroesophageal reflux disease, and recurrent vomiting. Most patients with community-acquired aspiration pneumonia have a mixed infection with anaerobic and aerobic bacteria, whereas those with hospital-acquired pneumonia will more likely have Gram-negative infections, including *Pseudomonas aeruginosa* [23].

In regard to viral etiology, the influenza virus and respiratory syncytial virus are most important cause of pneumonia in the elderly, often within the context of epidemic outbreaks and may cause both viral primary pneumonias such as bacterial superinfection by *S. pneumoniae*, *S. aureus*, and *Haemophilus influenzae*.

5.3.2 Empirical Antibiotic Therapy (Table 5.2)

Antimicrobials are the cornerstone of therapy for CAP in any population, but limited data are available regarding the specific treatments for elderly patients. The only guidelines for the management of community-acquired pneumonia in the elderly patient are published in the year 2014 in Spanish [24].

Table 5.2 Empiric therapy for community-acquired pneumonia in elderly patients

Inpatient with non-severe CAP	• β-lactam (ceftriaxone, cefotaxime) plus • Macrolide (azithromycin or clarithromycin) or • Respiratory fluoroquinolone (moxifloxacin or levofloxacin) alone
Inpatient with severe CAP	• β-lactam (ceftriaxone, cefotaxime, β-lactam/β-lactamase inhibitor) plus • Macrolide or fluoroquinolone
If risk factors for *Pseudomonas aeruginosa*	• β-lactam (cefepime, ceftazidime) Piperacillin/Tazobactam Imipenem, Meropenem) plus • Fluoroquinolone antipseudomonal (ciprofloxacin or high-dose levofloxacin) or • Aminoglycoside and macrolide (azithromycin)
If risk factors for MRSA	• Add linezolid or vancomycin
Aspiration pneumonia	• β-lactam/β-lactamase inhibitor • Moxifloxacin or levofloxacin • Ceftriaxone plus Metronidazole or clindamycin • Ertapenem
Influenza pneumonia	• Oseltamivir or zanamivir

Initial antibiotic selection for CAP is often empirical, as the causative pathogen cannot be predicted from clinical laboratory or radiological findings and therapy must be started swiftly as rapid antibiotic delivery is associated with a better outcome [25].

Empirical antimicrobial therapy must include coverage for the most prevalent pathogens and should be based on several aspects such as the severity of diseases, local patterns of antimicrobial resistances, multi-drug-resistant risk factors, and drug allergies.

International guidelines agree that patients hospitalized with non-severe CAP should be started on empirical combination therapy using a β-lactam plus a macrolide or a respiratory fluoroquinolone alone (levofloxacin, moxifloxacin, and gatifloxacin). The respiratory quinolones are quinolones that are highly active against both the typical and atypical respiratory pathogens causing CAP. Because ciprofloxacin is relatively inactive against *Streptococcus pneumoniae*, even though it is active against the atypical pathogens, it is not termed a "respiratory quinolone."

In patients with severe community-acquired pneumonia (admission in ICU or intermediate care), the guidelines recommend a minimum of a β-lactam plus either a macrolide or a quinolone. The combination treatment offers an advantage over monotherapy by expanding the antimicrobial coverage and probably by immunomodulation (macrolides, quinolones).

In severe patients with risk factors for MRSA vancomycin or linezolid should be added. CAP patients with risk factors for *P. aeruginosa* should receive empirical combination therapy as an antipneumococcal anti-pseudomonal β-lactam plus either ciprofloxacin or high-dose levofloxacin or the above β-lactam plus an aminoglycoside and azithromycin is an appropriate regimen.

In patients with risk factors of aspiration, an antibiotic should be used which should also cover *S. pneumoniae* and be effective against anaerobes and *Enterobacteriaceae* since these may be the causal microorganisms involved. In most guidelines, β-lactam/β-lactamase inhibitors (amoxicillin-clavulanate, ampicillin/sulbactam/piperacillin/tazobactam) are considered to be the antibiotics of choice. Ceftriaxone plus clindamycin or metronidazole and respiratory fluoroquinolone are the alternative.

For patients at the increasing rise of resistances of *Enterobacteriaceae ertapenem* this therapeutic option is valid mainly for its sensitivity versus anaerobes, *S. pneumoniae*, and all the *Enterobacteriaceae*, including extended-spectrum β-Lactamase-producing (ESBL).

Antibiotic agents with specific anaerobic activity (metronidazole or clindamycin) are not routinely warranted and may be indicated only in patients with severe periodontal disease, putrid sputum, or evidence of necrotizing pneumonia or lung abscess on radiographs of the chest.

Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza pneumonia and should not be delayed by confirmatory laboratory testing results. Neuraminidase inhibitors, oseltamivir and zanamivir, are the agents of choice. The usual dosing of oseltamivir for the treatment of influenza is 75 mg orally twice daily and of zanamivir is 10 mg (2 inhalations) twice daily. The recommended duration for antiviral treatment is 5 days.

Table 5.3 Posology antibiotics

Antibiotic	Doses iv[a]
Amikacina	15–20 mg/kg/24 h
Amoxicillin/clavulanate	2 g/6–8 h
Azithromycin	500 mg/24 h
Cefepime	2 g/8 h
Cefotaxime	2 g/8 h
Ceftriaxone	1–2 g/12–24 h
Ceftazidime	2 g/8 h
Ciprofloxacin	400 mg/12 h
Clarithromycin	500 mg/12 h
Ertapenem	1 g/24 h
Imipenem	500 mg^{-1} g/6–8 h
Levofloxacin	750 mg/24 h
Linezolid	600 mg/12 h
Meropenem	1 g/8 h
Moxifloxacin	400 mg/24 h
Piperacillin/tazobactam	4/0.5 g/6–8 h
Vancomycin	15–20 mg/kg/8–12 h

[a]Dose adjustment for renal insufficiency

The optimal duration of antibiotic therapy is not yet known. BTS guidelines [26] propose 7–10 days treatment for most patients with severe CAP, whereas European guidelines [27] suggest that the duration of treatment should generally not exceed 8 days in a patient who responds to initial therapy. The use of biomarkers such as procalcitonin or the C-reactive protein may be useful to shorten the duration of antibiotic treatment [28]. The duration of antibiotic treatment may be prolonged in patients receiving initial inadequate antibiotic therapy, patients with extrapulmonary infection (e.g., endocarditis, meningitis), patients infected with multi-drug-resistant organism (e.g., *S. aureus*) and patients with necrotizing pneumonia.

Regarding the dosing (Table 5.3), there are many considerations to be made when caring for elderly patients: multiple comorbidities, polypharmacy potentially resulting in drug interactions, pharmacokinetic and pharmacodynamic changes that can result in altered drug metabolism and subsequent toxic effects of drug accumulation [29]. Despite the complexity of all of these changes, however, the singular impairment that most significantly influences the medical management of infection in older patients is the decline in renal function commonly observed in this group. In patients with impaired renal function, antibiotics should always be started at full initial doses and then adjusted based on renal function.

5.4 Conclusions

Lower respiratory tract infections, including pneumonia and exacerbation of chronic obstructive pulmonary disease, are among the most common causes of ARF in elderly people and the most important cause of hospitalization. Moreover pulmonary infection is also the most frequent single cause of ARDS. In the management

of respiratory failure, it is mandatory reversing and/or preventing tissue hypoxia through conventional oxygen therapy or invasive or non-invasive mechanical ventilation. Besides, early administration of appropriate antimicrobials has been postulated as a key strategy in the survival of patients with very severe infections requiring intensive care unit admission taking into account the most risk of adverse events of an antimicrobial in a frail elderly patient.

Key Recommendations

1. Acute respiratory failure is a frequent complication in elderly patients.
2. Infections (CAP and AECOPD) are among the most frequent triggering causes of ARF in advanced aged patients.
3. Antimicrobials are the cornerstone of therapy for CAP and in COPD exacerbations when patients have clinical signs of a bacterial infection.
4. Antibiotic duration should be as shorter as possible, based on the pathogen, clinical response, and presence of complications.
5. A judicious use of antibiotic therapy in the respiratory tract infections is critical in the era of antibiotic resistance.

References

1. Murray MA, Chotirmall SH. The impact of immunosenescence on pulmonary disease. Mediators Inflamm. 2015;2015:692546. Published online 2015 Apr 19. Pages 10.
2. Becquemin H, Beigelman C, Isnard R, et al. Acute respiratory failure in the elderly: etiology, emergency diagnosis and prognosis. Crit Care. 2006;10(3):R82.
3. Roussos C, Koutsoukou A. Respiratory failure. Eur Respir J Suppl. 2003;47:3s–14s.
4. Delerme S, Ray P. Acute respiratory failure in the elderly: diagnosis and prognosis. Age Ageing. 2008;37:251–7.
5. Lee K-Y. Pneumonia, acute respiratory distress syndrome, and early immune-modulator therapy. Int J Mol Sci. 2017;18:388–403.
6. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1334–49.
7. Sharma S. Acute respiratory distress syndrome. BMJ Clin Evid. 2010;11:1511.
8. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307:2526–33.
9. Rothberg MB, Pekow PS, et al. Antibiotic therapy and treatment failure in patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease. JAMA. 2010;303(20):2035–42.
10. Global Initiative for Chronic Obstructive Lung Diseases. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease (2017 Report).
11. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. N Engl J Med. 2008;359(22):2355–65.
12. Eller J, Ede A, Schaberg T, Niederman MS, et al. Infective exacerbations of chronic bronchitis: relation between bacteriologic etiology and lung function. Chest. 1998;113(6):1542–8.
13. Diederen BM, van der Valk PD, Kluytmans JA, et al. The role of atypical pathogens in exacerbations of chronic obstructive pulmonary disease. Eur Respir J. 2007;30(2):240–4.
14. Sethi S. Infectious etiology of acute exacerbations of chronic bronchitis. Chest. 2000;117: 380S–5S.

15. Mohan A, Chandra S, Agarwal D, et al. Prevalence of viral infection detected by PCR and RT-PCR in patients with acute exacerbation of COPD: a systematic review. Respirology. 2010;15:536–42.
16. Miravitles M, Kruesmann F, Haverstock D, et al. Sputum colour and bacteria in chronic bronchitis exacerbations: a pooled analysis. Eur Respir J. 2012;39(6):1354–60.
17. Black PN, McDonald CF. Pathogen-directed therapy in acute exacerbations of COPD. Proc Am Thorac Soc. 2007;4:647–58.
18. Janssens J-P, Krause K-H. Pneumonia in the very old. Lancet Infect Dis. 2004;4:112–24.
19. Fernandez-Sabé N, Carratala J, Roson B, et al. Community-acquired pneumonia in very elderly patients: causative organisms, clinical characteristics, and outcomes. Medicine. 2003;82(3):159–69.
20. Berk SL. Bacterial pneumonia in the elderly: the observations of Sir William Osler in retrospect. J Am Geriatr Soc. 1993;42:683–5.
21. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med. 2015;373(5):415–27.
22. Chong CP, Street PR. Pneumonia in the elderly: a review of the epidemiology, pathogenesis, microbiology, and clinical features. South Med J. 2008;101(11):1141–5.
23. Xiaowen H, Lee JS, Pianosi PT, et al. Aspiration-related pulmonary syndromes. Chest. 2015;147(3):815–23.
24. González-Castillo J, Martín-Sánchez FJ, Linares P, et al. Guidelines for the management of community-acquired pneumonia in the elderly patient. Rev Esp Quimioter. 2014;27(1):69–86.
25. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(Suppl 2):S27–72.
26. Lim WS, Baudouin SV, George RC, et al. Guidelines for the management of community-acquired pneumonia in adults: update 2009. Thorax. 2009;64(Suppl 3):1–55.
27. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections. Clin Microbiol Infect. 2011;17(Suppl 6):E1–E59.
28. Schuetz P, Litke A, Albrich WC, Mueller B. Blood biomarkers for personalized treatment and patient management decisions in community-acquired pneumonia. Curr Opin Infect Dis. 2013;26:159–67.
29. Weber S, Mawdsley E, Kaye D. Antibacterial agents in the elderly. Infect Dis Clin N Am. 2009;23:881–98.