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New Developments in Antibacterial Choice for Lower Respiratory Tract Infections in Elderly Patients

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Abstract

Elderly patients are at increased risk of developing lower respiratory tract infections compared with younger patients. In this population, pneumonia is a serious illness with high rates of hospitalisation and mortality, especially in patients requiring admission to intensive care units (ICUs). A wide range of pathogens may be involved depending on different settings of acquisition and patient's health status. *Streptococcus pneumoniae* is the most common bacterial isolate in community-acquired pneumonia, followed by *Haemophilus influenzae, Moraxella catarrhalis* and atypical pathogens such as *Chlamydia pneumoniae, Legionella pneumophila* and *Mycoplasma pneumoniae*. However, elderly patients with comorbid illness, who have been recently hospitalised or are residing in a nursing home, may develop severe pneumonia caused by multidrug resistant staphylococci or pneumococci, and enteric Gram-negative bacilli, including *Pseudomonas aeruginosa*. Moreover, anaerobes may be involved in aspiration pneumonia. Timely and appropriate empiric treatment is required in order to enhance

the likelihood of a good clinical outcome, prevent the spread of antibacterial resistance and reduce the economic impact of pneumonia.

International guidelines recommend that elderly outpatients and inpatients (not in ICU) should be treated for the most common bacterial pathogens and the possibility of atypical pathogens. The algorithm for therapy is to use either a selected β-lactam combined with a macrolide (azithromycin or clarithromycin), or to use monotherapy with a new anti-pneumococcal quinolone, such as levofloxacin, gatifloxacin or moxifloxacin. Oral (amoxicillin, amoxicillin/clavulanic acid, cefuroxime axetil) and intravenous (sulbactam/ampicillin, ceftriaxone, cefotaxime) β-lactams are agents of choice in outpatients and inpatients, respectively. For patients with severe pneumonia or aspiration pneumonia, the specific algorithm is to use either a macrolide or a quinolone in combination with other agents; the nature and the number of which depends on the presence of risk factors for specific pathogens. Despite these recommendations, clinical resolution of pneumonia in the elderly is often delayed with respect to younger patients, suggesting that optimisation of antibacterial therapy is needed. Recently, some new classes of antibacterials, such as ketolides, oxazolidinones and streptogramins, have been developed for the treatment of multidrug resistant Gram-positive infections. However, the efficacy and safety of these agents in the elderly is yet to be clarified. Treatment guidelines should be modified on the basis of local bacteriology and resistance patterns, while dosage and/or administration route of each antibacterial should be optimised on the basis of new insights on pharmacokinetic/pharmacodynamic parameters and drug interactions. These strategies should be able to reduce the occurrence of risk factors for a poor clinical outcome, hospitalisation and death.

1. Lower Respiratory Tract Infection (LRTI) in the Elderly

In the second half of the 20th century, deaths and morbidities caused by infectious diseases have been consistently reduced in the developed world by public health measures, vaccination and the discovery of new agents, endowed with potent antibacterial activity and broad spectrum. Despite these efforts, infections are currently recognised by the World Health Organization as the second leading cause of death in humans.[1] Lower respiratory tract infections (LRTIs), i.e. acute bronchitis, exacerbations of chronic obstructive pulmonary disease (COPD) and pneumonia, represent the most frequent problems afflicting patients aged ≥65 years, with an incidence that increases proportionally with increasing age.[2-4] As shown in table I, several factors may contribute to the frailty and the increased susceptibility to LRTIs of these patients, including impaired cellular and/or humoral immune responses and/or a variety of comorbidities that in turn may down-regulate the host responses to infections.[2,3,5-11] Moreover, age-related modifications of the nutritional status may induce deficiency of micronutrients, lipids, vitamins and proteins, a condition known to influence host defences.[12,13] In addition, aging itself could enhance the risk of LRTIs through the reduction of lung elasticity and respiratory muscle strength, and the alteration of the secretion clearance.[3,5] Mortality rates for acute bronchitis and exacerbations of COPD are low in the elderly[14] and evidence concerning the influence of antibacterial therapy on the disease outcome are scarce.[15,16] Nevertheless, antimicrobial treatment is generally recommended, especially in aged people with other concomitant lung diseases.[17] Bacteria, such as *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae,* have been isolated in about half of exacer-

bated COPD cases.[18,19] However, whether these findings represent bronchial colonisation or true infection is a controversial issue.[20] Pneumonia is approximately 10-fold more frequent in older rather than younger adults. It represents the leading infectious cause of death in elderly patients (aged ≥80 years).[21] The hospitalisation index for community-acquired pneumonia (CAP) is about 4-fold higher than that observed in the general population[22] and in the elderly requiring admission to intensive care units (ICUs), mortality rates range from 13% to 40%.[4-6,23-27]

In regard to the clinical presentation of pneumonia, some reports indicate only few variations with respect to young adults,[28,29] whereas others show that elderly people sometimes lack the most classic signs of infections (e.g. fever and leucocytosis), showing only atypical clinical manifestations (e.g. weakness, urinary incontinence and changes in mental status).[5,30,31] These atypical findings could be responsible for a delay in diagnosis and treatment, contributing to increased morbidity and mortality. Pneumonia represents the leading cause of morbidity and mortality among the elderly residing in long-term care-facilities, having poor functional status, difficulty swallowing or eating, and COPD as the major risk factors.[32,33]

In developing countries, the percentage of individuals aged ≥65 years is rapidly growing, thus, it is likely that LRTIs, in particular pneumonia, will become the major public health issue in the next half century.[5,21] Results of several controlled clinical trials have demonstrated the safety and efficacy of the pneumococcal vaccine in reducing both hospitalisation and mortality rates, mainly when combined with the influenza vaccine.[34,35] Consequently, large-scale use of this vaccine could offer a preventive measure to reduce the risk of pneumonia in the elderly. However, the international debate on the usefulness of pneumococcal vaccination in preventing pneumonia in the elderly is not completely solved.[3,34,36,37]

It is evident that pneumonia in the elderly requires prompt therapy, employing the most appropriate antibacterial(s) and route of administration, in order to reduce the risk of hospitalisation and death.[38-40] In order to optimise therapy, one has to consider the aetiological agent, the pattern of antibacterial resistance,[41-45] age- and/or nonage-related pharmacokinetic and pharmacodynamic characteristics of antibacterials, the patient's health status and the presence of concomitant diseases or polypharmacy.[5] Finally, it is important to note that the wide use of antibacterials in the elderly population has important social costs, owing not only to drug acquisition, but also to the need for monitoring drug levels and/or to the management of adverse drug reactions. Both the frequency and severity of drug-related adverse effects increase with age, and represent an important and common cause of hospital admission.

Table I. Major risk factors for lower respiratory tract infections in the elderly[2,3,5-8]

Age-related factors
Age >65 years
Impaired secretion clearance
Chronic obstructive pulmonary disease
Bronchiectasis
Impaired host defences
Swallowing disorders
Cognitive impairment
Multiple illness
Residence in nursing home
Bedridden state
Poor nutritional status (hypoalbuminaemia)
Not strictly age-related factors
Alcoholism
Asthma
Malnutrition
Immunosuppression
Heart diseases
Diabetes mellitus
Recent hospitalisation
Antibacterial treatment during the last month
Feeding by nasogastric tube, oxygen therapy
Exposure to tobacco smoke
Air pollution

2. Bacterial Pathogens Causing Pneumonia in the Elderly

Several bacterial pathogens are known to cause pneumonia in humans, depending on the site of acquisition (community versus hospital or nursing home). Age *per se* has little impact on pneumonia aetiology (table II).[41]

The most common bacterial isolate (about 50% of patients) in the elderly with CAP is *S. pneumoniae*, and recent epidemiological data indicate that age >65 years represents an important risk factor for drug-resistant *S. pneumoniae* pneumonia.[46] The frequency of *H. influenzae* and *M. catarrhalis* is also relatively higher in the elderly population.[3,4] Moreover, *Staphylococcus aureus* may be involved in post-influenza pneumonia and anaerobes of the oropharyngeal micro-flora in aspiration pneumonia.[48] Atypical pathogens cover the remaining 15% of CAPs in the elderly and among these pathogens, *Legionella pneumophila* occurs more frequently than *Mycoplasma* spp.[4] Factors including long periods of hospitalisation, comorbidities, poor health status and malnutrition increase the incidence of pneumonia owing to multiple organisms, Gram-negative rods or drug-resistant strains.[3,49] Finally, severe CAP infections that require the management of patients in ICU and reach mortality rates up to 50%, are due to *S. pneumoniae* (isolated in up to one-third of all ICU patients), *Legionella* spp., *H. influenzae*, *S. aureus* and Gram-negative bacilli, including *Pseudomonas aeruginosa.*[49,50]

Table II. Major pathogens causing pneumonia in the elderly[5,46-48]

Category	Aetiology
Mild-to-moderate CAP, treated in outpatient setting or in hospital ward	*Streptococcus pneumoniae* including DRSP, *Haemophilus influenzae*, *Legionella pneumophila, Chlamydia pneumoniae, Mycoplasma pneumoniae*, respiratory viruses, Gram-negative bacilli, oral anaerobes, *Staphylococcus aureus, Moraxella catarrhalis*
Severe CAP, treated in ICU	*S. pneumoniae* including DRSP, Gram-negative bacilli, including *Pseudomonas aeruginosa*, *S. aureus*, *H. influenzae, L. pneumophila*
Nursing-home acquired pneumonia	*S. pneumoniae* including DRSP, Gram-negative bacilli, oral anaerobes, *H. influenzae*, *M. catarrhalis*, *S. aureus*, *L. pneumophila*, *C. pneumoniae*
Nosocomial pneumonia	Gram-negative bacilli including *P. aeruginosa, S. aureus*, *L. pneumophila*
Aspiration pneumonia	Oropharyngeal colonisation with *S. aureus*, enteric Gram-negative bacilli, anaerobes

CAP = community-acquired pneumonia; **DRSP** = drug-resistant *S. pneumoniae*; **ICU** = intensive care unit.

Agents causing nursing home-acquired pneumonia share some similarities with those responsible for community- and hospital-acquired pneumonia. *S. pneumoniae* and the aerobic Gram-negative bacilli are cultured in about 13% of cases each, while *S. aureus*, *H. influenzae* and *M. catarrhalis* follow in rank order.[2-4] Outbreaks of pneumonia owing to respiratory viruses (influenza and respiratory syncytial viruses) or alternatively to *Chlamydia pneumoniae* and *L. pneumophila* may also occur as a consequence of airborne infection.[51] In addition, aspiration of oropharyngeal secretions into the lung may lead to aspiration pneumonia, an event that more often occurs in patients with cerebrovascular and/or degenerative neurologic diseases, associated with impaired cough reflex and dysphagia. In this case, enteric Gram-negative bacilli colonising dental plaque or oropharynx represent the most frequently isolated organisms, but anaerobes, such as *Prevotella*, *Fusobacterium*, *Bacteroides* and *Peptostreptococcus* spp., may also contribute to the pathogenesis of aspiration pneumonia. However, it remains to be determined whether these microorganisms are simply co-inhabitants of Gram-negative bacteria or represent effective aetiologic agents, thus requiring specific targeted antimicrobial treatment.[48,52]

Finally, organisms most frequently isolated in nosocomial pneumonia are Gram-negative bacilli, in particular *P. aeruginosa* and *Klebsiella pneumoniae* (60–80% of cases), and *S. aureus* (15%). *S. pneumoniae*, anaerobes, *L. pneumophila* and *M. catarrhalis* are the remaining bacterial aetiologic agents.[3,4]

3. Criteria of Antibacterial Selection

While the bacteriological diagnosis of LRTI is generally available in at least 50% of adult patients, the aetiological agent remains undetermined in ma-

Table III. Empirical treatment of pneumonia[46]

Category	Patients' characteristics	Therapy
Group I	Outpatients with no cardiopulmonary diseases and modifying factors[a]	New macrolide (azithromycin, clarithromycin) or doxycycline in patients allergic or intolerant to macrolides
Group II	Outpatients with cardiopulmonary diseases or modifying factors (including residents in nursing homes)	β-Lactam (oral amoxicillin/clavulanic acid or cefuroxime or parenteral ceftriaxone followed by oral β-lactam) plus macrolide or antipneumococcal fluoroquinolone alone
Group III	Inpatients, not in ICU (including patients from a nursing home)	Intravenous β-lactam (cefotaxime, ceftriaxone, sulbactam/ampicillin) plus intravenous or oral macrolide or intravenous antipneumococcal fluoroquinolone
Group IV	ICU-admitted patients (no risks for *Pseudomonas aeruginosa*)	Intravenous β-lactam (cefotaxime, ceftriaxone) plus either intravenous azithromycin or intravenous fluoroquinolone
	ICU-admitted patients (risks for *P. aeruginosa*)	Intravenous antipseudomonal β-lactam (piperacillin/tazobactam, cefepime, imipenem, meropenem) plus intravenous ciprofloxacin or aminoglycoside, plus either intravenous azithromycin or antipneumococcal fluoroquinolone

a (i) Increasing the risk of pneumonia with penicillin-resistant and drug-resistant pneumococci: age >65 years, β-lactam therapy within the past 3 months, alcoholism, immune-suppressive illness, multiple medical comorbidities; (ii) increasing the risks of enteric Gram-negative infection: residence in a nursing home, underlying cardiopulmonary disease, multiple medical comorbidities, recent antibacterial therapy; (iii) increasing the risk of *P. aeruginosa* infection: structural lung disease, corticosteroid therapy, broad-spectrum antibacterial therapy for >7 days in the past month, malnutrition.

ICU = intensive care unit.

jority of the elderly, because of the difficulty in attaining adequate bronchial specimens and/or contamination of sputum by oral colonising Gram-negative bacilli. On the other hand, invasive diagnostic tools, such as bronchoscopy or needle aspiration, are difficult to perform and could be dangerous in these patients.[5] Therefore, empiric treatment with broad-spectrum antibacterials or antibacterial combinations is usually performed, in order to cover Gram-positive bacteria, Gram-negative bacteria and/or atypical respiratory pathogens. A number of different guidelines, based on age, severity of pneumonia and presence of comorbidities, have been developed by major international associations.[17,22,46,53-55]

Following the recent indications of the American Thoracic Society (ATS) guidelines,[46] patients with CAP may be categorised into four groups based on the assessment of place of therapy, the presence of cardiopulmonary diseases and modifying factors that increase the risk of infection with penicillin-resistant and drug-resistant *Streptococcus pneumoniae* (DRSP), enteric Gram negatives and *P. aeruginosa*. ATS therapy choices are summarised in table III. Elderly outpatients and inpatients (not in ICU) should be treated for the most common bacterial pathogens and for the possibility of atypical pathogen infection, either as primary infection or as co-pathogen infection. Moreover, all elderly subjects should be treated for DRSP and those with comorbidities for enteric Gram-negative bacteria. The algorithm for therapy is to use either a selected β-lactam combined with a macrolide, or to use monotherapy with a new antipneumococcal fluoroquinolone. The therapy for severe CAP is stratified in relation to *Pseudomonas* risk factors. Patients, both in and out of the ICU, should be treated with either a macrolide or a fluoroquinolone in combination with other antibacterials, the nature and number of which depend on the presence of risk factors. In particular, patients should not receive the following anti-*Pseudomonas* agents: cefepime, piperacillin/tazobactam, imipenem, meropenem and ciprofloxacin unless these risk factors are present. If patients are living in a nursing home, the same choices apply, but the knowledge of specific bacteriology of that nursing home and the local pattern of drug resistance is required for the selection of initial therapy[17,46,53,56] since nursing home acquired pneumonia is associated with high mortality rates.[32,33] Elderly patients with impaired swallowing, neurological illness, impaired consciousness and alcoholism are at risk for aspiration. Aspiration involves

enteric Gram-negative bacilli and anaerobes. Taking this into consideration, monotherapy with an antipneumococcal fluoroquinolone or combination of a broad spectrum β-lactam (such as amoxicillin/clavulanic acid, cefotaxime or ceftriaxone) and a macrolide derivative is recommended.[32,53]

Concerning nosocomial pneumonia, ATS guidelines and some recent reviews have assessed the therapeutic and prophylactic strategies that may significantly contribute to reduce morbidity and mortality in adult patients.[47,57-59] Empiric therapy requires intravenous administration of broad spectrum antibacterials or antibacterial combinations in order to cover the wide range of Gram-positive and Gram-negative pathogens involved. Although the implementation of treatment recommendations has led to the reduction of mortality and length of hospitalisation,[60] the optimal management of pneumonia in the elderly still remains debatable.[2,17,22,46,53-55,61-63]

3.1 Patterns of Drug Resistance Among LRTI Pathogens

Resistance to antibacterials is currently a major problem in human medicine. The emergence of antibacterial resistance among Gram-positive and -negative bacteria has been observed worldwide. This presents a great hurdle for the treatment of bacterial pneumonia in both outpatient and inpatient settings. The minimum inhibitory concentration (MIC) to penicillin in *S. pneumoniae* has been increasing over the past decades. According to criteria of the National Committee for Clinical Laboratory Standards and the Drug-Resistant *S. pneumoniae* Therapeutic Working Group, pneumococci may be considered susceptible to β-lactam derivatives if MIC is ≤1 mg/L, intermediate if MIC is 2 mg/L and resistant if MIC is ≥4 mg/L.[64,65] Decreased susceptibility to penicillin has occurred worldwide from dissemination of several resistant pneumococcal clones.[66] In several European countries, incidence rates of penicillin-resistant pneumococci exceed 30% and, even more worrying is the fact that, often, these isolates are also resistant to common alternative drugs.[43,45,65-70] However, not all countries have such levels of resistance. Results of a recent survey demonstrate that *S. pneumoniae* isolates in Italy maintain a high susceptibility to β-lactam antibacterials,[71] probably as a consequence of a wide use of parenteral antibacterial therapy in the outpatient setting.[72] This suggests that β-lactam antibacterials may still be considered first choice agents for the treatment of community-acquired pneumococcal infections in some countries.

Resistance of pneumococci to macrolides in Europe is mainly due to *ermB*-encoded ribosomal methylases, which confer high levels of resistance to erythromycin (MIC >8 mg/L), while resistance in US isolates is prevalently owing to *mef*A-mediated efflux pump, conferring low resistance (MIC >1 mg/L but <4 mg/L).[62,73] Moreover, the presence of both mechanisms have been recently found in some isolates.[74] Trends in resistance to fluoroquinolones among pneumococci have been monitored in the US by a surveillance programme of the Centers for Disease Control between 1995 and 2000.[75] Results of the study show a low percentage of isolates resistant to levofloxacin (<0.5%) during the observation period. However, data suggest that primary or acquired resistance to newer fluoroquinolones is emerging.[43,44,76-79]

Pneumonia owing to *S. aureus* shows a poor prognosis and high mortality rates,[80,81] especially when bacterial isolates are methicillin-resistant *S. aureus* (MRSA). MRSA strains are more frequently isolated in hospitalised elderly patients with significant comorbidities and represent about half of *S. aureus* isolates in Southern European countries.[80,82] The resistant phenotype, which depends on the appearance of an altered penicillin binding proteins (PBPs), encoded by *mec*A gene, confers resistance to all β-lactam derivatives and is frequently associated with resistance to several widely used antibacterials active on Gram-positive pathogens, including macrolides, fluoroquinolones and cotrimoxazole.[83,84] In addition, resistance to clindamycin, tetracyclines and rifampicin may also be found. MRSA strains are susceptible to glycopeptides, i.e. vancomycin and teicoplanin. Although uncommon, isolates with reduced susceptibility to glycopeptides have been recently reported.[80,81]

Several mechanisms of resistance have been described in Gram-negative respiratory pathogens. In *H. influenzae* and *M. catarrhalis*, resistance to β-lactams is mediated by the production of β-lactamase,[43,85] but recently, alteration of PBPs has been reported in some ampicillin-resistant *H. influenzae* isolates.[86] In Enterobacteriaceae, β-lactam resistance is usually mediated by the plasmid-encoded β-lactamases e.g. TEMs, SHVs (designations based on the preferred substrate and sulfhydryl reactivity etc.) or by the extended-spectrum β-lactamases, including TEM and SHV mutants and other cephalosporinase.[87,88] Isolates of *Enterobacter cloacae*, *Citrobacter freundii*, *Serratia marcescens* and *P. aeruginosa* overproducing chromosomally-encoded β-lactamases that inactivate third-generation cephalosporins have been described.[88] Moreover, the alteration of the outer-membrane permeability or the presence of efflux pumps, coupled with the production of drug inactivating enzymes, may produce high resistance levels in *P. aeruginosa* isolates.[89-91]

3.2 Age-Related Changes in Antibacterial Pharmacokinetics

Physiological alterations occurring in the course of aging may affect absorption, distribution, metabolism and elimination of antibacterials.[92,93] Drug administration by parenteral route ensures rapid antibacterial effect and better compliance. However, except for aminoglycosides and ceftriaxone, antibacterials should not be administered intramuscularly in the elderly because of an impaired absorption rate owing to decreased muscle mass.[94,95] Moreover, older subjects often show a poor venous access which makes intravenous treatment problematic. Drug absorption following oral administration could be delayed in those patients who have decreased gastric secretory capacity and/or reduced gastrointestinal motility. But this effect is not significant. Consequently, mainly in the outpatient setting, there is an increasing practice to treat, whenever possible, the elderly by oral route or to carry out the so called 'sequential therapy'.[96,97] Changes in body composition may alter the distribution process: the increase of the body fat or the decrease of the lean body mass and total body water may enhance the volume of distribution of lipid-soluble antibacterials, but reduce that of water-soluble agents.[92] In addition, distribution may also be influenced by a decrease of the cardiac output or albumin levels. Drug metabolism in the liver is variably influenced by aging: while the reduction of enzyme activities is generally slight, there is a significant decrease of the hepatic mass and blood flow.[92] Therefore, dosage adjustment of antibacterials eliminated by hepatic route is required only in patients with severe liver impairment, on the basis of clinical judgement.[98,99]

Often, elderly patients have reduced renal function, with progressive decline of the glomerular filtration rate, loss of the tubular function and decrease of renal plasma flow. Thus, renal dysfunction represents the most important parameter to be considered by physicians in prescribing drugs with prominent renal excretion. Dosage or administration intervals of these agents should be adapted to the degree of renal function on the basis of the creatinine clearance rather than serum creatinine levels.[38,92] Finally, antibacterial treatment in elderly patients on dialysis requires careful and complex calculations in order to obtain optimal administration, since haemodialysis and peritoneal dialysis remove drugs in differing amounts.[98]

3.3 Pharmacodynamic and Pharmacokinetic Parameters

A rigourous evaluation of the efficacy of a given antibacterial treatment is achieved by looking at the clinical outcome and the bacteriological eradication, both of which depend on pharmacodynamic/pharmacokinetic (PK/PD) properties of each drug. Pharmacodynamics describes the inter-relationship between the concentration of a given antibacterial at a particular site and its biological effect against the aetiological agent(s). The most important pharmacodynamic parameters are MICs, the bacterial killing over time and the antibacterial persistence effect, such as the post-antibacterial effect (PAE). Bacterial killing may be a time-dependent or a concentration-dependent process, depending on specific

antibacterials. These characteristics are of great relevance in predicting drug efficacy and thus, represent key components for antibacterial selection. In addition, the integration of pharmacokinetic and pharmacodynamic characteristics provides the so called PK/PD indices, that express the capacity of the drug of eradicating pathogens at the concentrations reached during therapy.[100-106] PK/PD parameters related to bacteriological eradication are the time above the MIC (T > MIC), the area under the concentration time curve at 24 hours to MIC (AUC_{24}/MIC) and the maximum serum concentration to MIC (C_{max}/MIC). The evaluation of these indices allows one to ascertain the optimum dosage regimens, as well as allowing direct comparison across agents for the same variables. Moreover, results of recent studies suggest that the magnitude of PK/PD indices also correlate with the prevention of bacterial drug resistance.[100,107]

Studies have shown that eradication by β-lactam derivatives is strictly time-dependent: its capacity cannot be enhanced by increasing drug concentrations above the MIC. Moreover, these antibacterials exhibit only mild or moderate PAE[108] and bacterial regrowth occurs rapidly when their concentrations fall below the MIC. Hence, for β-lactam antibacterials, the main PK/PD determinant of the clinical outcome is represented by T > MIC.[100,101,105] Studies performed in animal models and in humans have shown survival rates exceeding 90% when the time over MIC is about 40% and 40–50% of the administration intervals for penicillins and cephalosporins, respectively.[42,100,101,105] Taking this into account, optimisation of the dosage regimen requires the administration of β-lactam derivatives by continuous infusion. This type of administration better correlates with the clinical efficacy and the prevention of drug resistance.[42]

Studies of the macrolide pharmacodynamics indicate that these agents generally exhibit a concentration-independent bacterial killing.[101,109,110] However, this model is not completely satisfactory for the more recent derivatives that also show an important time-dependent killing. It has been demonstrated that clarithromycin and azithromycin, although unable to reach serum levels above MIC, inhibit *H. influenzae* growth.[109] This effect could depend on the peculiar characteristics of these agents which may achieve concentrations higher than the MIC of the pathogen in several tissues and body fluids, and to their prolonged PAEs.[110] Higher survival rates have been observed in humans when serum concentrations of newer macrolides are kept above the MIC for at least 40–50% of the dosage interval.[100,101] Moreover, recent results of *in vitro* and animal studies suggest that the best parameter correlating with bacteriological eradication and clinical outcome is the AUC_{24}/MIC.[101,104] In addition, some investigators have suggested that the pharmacokinetic properties of macrolides in the epithelial lining fluid could be a better marker compared with serum pharmacokinetics in predicting the clinical outcome in LRTIs.[111]

Fluoroquinolones exhibit a concentration-dependent killing pattern, and have a satisfactory PAE with both Gram-positive and Gram-negative bacteria.[108,112] The main determinants of the clinical outcome for these drugs may be either the C_{max}/MIC or AUC_{24}/MIC ratios.[113,114] A C_{max}/MIC ratio of about 12 is considered predictive of excellent bactericidal effect against several susceptible pathogens,[113] while AUC_{24}/MIC ratios ≥125 and 40 are considered necessary to have an optimum clinical outcome in patients with *P. aeruginosa* infections[115] and to ensure microbiological eradication of *S. pneumoniae*,[116,117] respectively. Recently, several studies have demonstrated that AUC_{24}/MIC ratios for the so called 'respiratory quinolones' (i.e. levofloxacin, gatifloxacin, moxifloxacin, gemifloxacin), except ciprofloxacin, exceed values that correlate with pneumococcal eradication when the agents are administered in standard dosage for CAP treatment.[100,113,118]

The C_{max}/MIC and AUC_{24}/MIC ratios are the parameters that correlate best with efficacy of aminoglycosides that are characterised by concentration-dependent killing. By virtue of these characteristics and their prolonged PAEs, the once daily administration regimen has been proposed.[101] Meta-analysis studies performed on several clinical

Table IV. Some characteristics of major antibacterials for empirical therapy of pneumonia in the elderly

Antibacterials	Spectrum of activity	Dosage adjustment in renal failure	More frequent adverse reactions
Amoxicillin/clavulanic acid, cefuroxime, sulbactam/ampicillin, ceftriaxone	*Streptococcus pneumoniae* (no DRSP), *Haemophilus influenzae*, *Moraxella catarrhalis*, methicillin-susceptible *Staphylococcus aureus*, enteric Gram-negative bacilli, anaerobes	Generally required when CL_{CR} <30 mL/min[39]	Anaphylaxis, skin rashes[9,39]
Piperacillin/tazobactam, cefepime	Gram-negative bacilli, including *Pseudomonas aeruginosa*	Generally required when CL_{CR} <30 mL/min[39]	Encephalopathy (cefepime)[121]
Imipenem, meropenem	Gram positives (no DRSP), Gram-negative bacilli, including *P. aeruginosa*	Required when CL_{CR} <70 and <50 mL/min for imipenem and meropenem, respectively[122,123]	Seizures (imipenem)[9,39]
Azithromycin, clarithromycin	*H. influenzae*, *M. catarrhalis*, *Mycoplasma pneumoniae*, anaerobes, *Legionella pneumophila*, *Chlamydia pneumoniae*, *S. pneumoniae* (no DRSP)	Required when CL_{CR} <10 mL/min[124,125]	Abdominal cramps, nausea and drug interactions[9,39]
Ciprofloxacin	Gram-negative bacilli including *P. aeruginosa, M. pneumoniae, L. pneumophila*, *C. pneumoniae*	Required when CL_{CR} <30 mL/min[39,126,127]	Hallucination, delirium, sleep disorders, seizure, tendinitis and drug interactions[9,39,128,129]
Levofloxacin, gatifloxacin, moxifloxacin	Wide spectrum including macrolide and β-lactam resistant pneumococci (DRSP)	Required when CL_{CR} <50 mL/min[39,126]	

CL_{CR} = creatinine clearance; **DRSP** = drug-resistant *S. pneumoniae*.

trials indicate that the once daily administration regimen is at least equally effective and no more toxic than the traditional one.[103] However, this once daily aminoglycoside regimen, as yet, has not been adequately studied in elderly patients.[119,120]

4. Antibacterials Currently Used in LRTIs

Penicillins, cephalosporins, macrolides and fluoroquinolones are the most extensively used antibacterials for treating elderly patients with bacterial pneumonia (table IV), whereas the use of aminoglycosides and glycopeptides is reserved only for selected cases.

4.1 β-Lactam Antibacterials

Penicillins and cephalosporins are widely used in the treatment of LRTIs in the elderly because of their efficacy and safety.[3,39,130] Oral derivatives with activity against pneumococci (e.g. amoxicillin, amoxicillin/clavulanic acid or cefuroxime axetil) are effective in outpatients, while the intravenous derivatives, including sulbactam/ampicillin, cefotaxime and ceftriaxone, are highly efficacious in patients requiring hospitalisation.[65] Whether β-lactams may still play a role in the empiric treatment of CAP in countries with a high incidence of penicillin-resistant pneumococci, remains to be seen.[131] Results of some studies suggest that intermediate levels of resistance do not imply treatment failures when patients are treated with β-lactams.[132-135] However, recently, a correlation between penicillin resistance and higher mortality rates in CAP has been demonstrated.[136,137] Certainly, a β-lactam derivative should not be used when the MIC of penicillin for *S. pneumoniae* is ≥4 mg/L,[26,131,136-138] but these resistant strains, detected mainly in hospitalised patients with specific risk factors, are relatively uncommon.[138] Methicillin and the isoxazolylpenicillins are molecules of choice for penicillinase-producing staphylococci, but at present their use is limited by the spread of MRSA strains in elderly inpatients and those residing in nursing homes.[39,83,139] Aminopenicillins, i.e. ampicillin and amoxicillin, are very active against *H. influenzae* and *M. catarrhalis,* but enzymatic resistance to these agents is increasing worldwide.[43,85] Thus, combinations with β-lactamase inhibitors (clavulanic acid or sulbactam) may offer clear advantages for initial empiric therapy of CAP.[65]

Gram-negative bacilli, including *P. aeruginosa* and other resistant nonfermentative bacilli, are not a common cause of CAP, except in elderly patients with bronchiectasis.[46] However, they are a major concern in immunocompromised individuals, patients recovered in ICU, patients undergoing mechanical ventilation, following treatment with broad spectrum antibacterials or after prolonged hospitalisation.[140] Carboxypenicillins and the more recent ureidopenicillins, including the combination piperacillin/tazobactam, with their expanded spectrum, cover all these pathogens and are frequently used in combination with antipseudomonal aminoglycosides.[141] Among first-generation cephalosporins, cephalexin and cefazolin may be used only for mild respiratory infections caused by highly susceptible Gram-positive cocci, while second-generation derivatives with enhanced activity against *H. influenzae* and *M. catarrhalis* may be useful in bacterial bronchitis and CAP. In particular, cefuroxime, which is available in parenteral and oral form, is suitable for the so called 'sequential therapy', while cefonicid and cefotetan, endowed with an extended serum half-life and activity against anaerobes, may represent drugs of choice for aerobic/anaerobic pleuropulmonary infections. Although parenteral third-generation cephalosporins (i.e. cefotaxime, ceftriaxone and ceftazidime) are important agents for treatment of Gram-negative nosocomial pneumonia in elderly patients, cefotaxime and ceftriaxone, are often used in outpatient settings for empirical therapy of CAP, because of their effectiveness against *S. pneumoniae*, while ceftazidime does not provide adequate cover for the pneumococcus. The spectrum of ceftazidime covers several Gram-negative organisms including *P. aeruginosa,* but resistance to this agent is greatly increased among nosocomial pathogens during the last few years.

A recent report of the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) programme indicates that ceftazidime-resistant *P. aeruginosa* isolates have increased in Italy during the period 1997–2000, reaching 28–45%.[142] In these cases, cefepime (a fourth-generation derivative with enhanced activity against Gram-positive bacteria) and carbapenems represent effective alternative agents. New oral third-generation cephalosporins (cefdinir, ceftibuten, cefixime or the prodrugs cefuroxime axetil, cefpodoxime proxetil and cefetamet pivoxil) have greater efficacy against Gram-negative bacilli, enhanced β-lactamase stability and good pharmacokinetic properties.[143] Because of their enhanced activity against β–lactamase-producing *H. influenzae* and *M. catarrhalis*, oral cephalosporins provide an optimal alternative empiric treatment for CAP, except in countries where penicillin-resistant *S. pneumoniae* strains are widely spread.[144] In addition, they are characterised by a prolonged serum half-life, that permits a twice or once daily (with cefixime) administration, thus favouring patient compliance. Carbapenems, i.e. imipenem and meropenem, are broad spectrum agents, including almost all aerobic and anaerobic Gram-positive and Gram-negative pathogens.[122,123] However, because of their high activity against *P. aeruginosa* and other Gram-negative nosocomial pathogens, their use has to be restricted to patients with high risk of *P. aeruginosa* pneumonias or patients with severe nosocomial LRTIs.[46,47] Although the majority of β-lactams (except cefoperazone) are excreted primarily by renal route, dose reduction is recommended only when creatinine clearance is lower than 30 mL/min.[39] However, for imipenem, dose reduction (to about one-fourth) and prolonged dosage intervals (about 12 hours) are required in patients with creatinine clearance rates <70 mL/min, in order to avoid the risk of seizures.[122] Adverse effects of β-lactam antibacterials are generally mild and no particular attention is required when these agents are administered to the elderly. Developments of *Clostridium difficile* infection, especially following treatment with third-generation cephalosporins, can occur.[145]

4.2 Macrolides

The use of these agents in monotherapy has a limited role in the treatment of LRTIs, at least in Europe, because of the spread of pneumococci with high levels of macrolide resistance.[43,69,146] On the contrary, the low level of erythromycin resistance in

US isolates may be overcome by the use of derivatives, such as azithromycin or clarithromycin, with improved pharmacokinetic properties.[62,73] Although the clinical relevance of the *in vitro* resistance to macrolides is still debatable, some recent data have shown a significant correlation between *in vitro* resistance and clinical failure[147,148] or delayed eradication of pneumococci.[149] On the other hand, the peculiar pharmacodynamics and pharmacokinetics of the new derivatives may allow for high concentrations in bronchial secretions and lung tissues as well as their accumulation into mammalian cells, including alveolar macrophages.[150,151] These characteristics may greatly influence their efficacy *in vivo*.[63] Moreover, macrolides are drugs of choice for *C. pneumoniae, Mycoplasma pneumoniae* and *L. pneumophila* pulmonary infections, clarithromycin being the most active agent against *C. pneumoniae*, while azithromycin against *M. pneumoniae* and *Legionella* spp. In addition, new macrolides show more favourable administration regimens. In adult CAP patients a 3-day azithromycin course has been found to be as effective as a 5-day course.[152] In addition, less gastrointestinal adverse effects and lower risks of drug interactions have been reported, but these adverse effects seem more common in the elderly.[9,150] Cardiac events, such as potentially serious prolongation of the QT interval, torsade de points and ventricular arrhythmias, have been described following the concomitant use of macrolides, erythromycin by intravenous administration in particular, and other drugs including terfenadine, astemizole or cisapride.[150,153] Thus, a careful monitoring of these possible adverse effects is necessary when these antibacterials are administered to elderly patients.

4.3 Fluoroquinolones

Quinolones are broad spectrum synthetic agents, grouped in three generations: first generation includes derivatives used for the treatment of urinary tract infections; second generation comprises fluoroquinolones, such as ciprofloxacin, ofloxacin and pefloxacin, with predominant activity against Gram-negative bacilli and sparfloxacin, with enhanced activity against Gram-positive organisms.[154,155] Third-generation quinolones are the so called 'respiratory quinolones' and include levofloxacin, gatifloxacin and moxifloxacin. These derivatives posses enhanced activity against Gram-positive cocci, including penicillin-resistant pneumococci, anaerobes including *C. difficile* and atypical bacterial respiratory pathogens.[145,156] In addition, gatifloxacin and moxifloxacin provide an effective coverage of oral anaerobes and microaerophilic streptococci that may play a role in aspiration pneumonia.[157] Respiratory quinolones are characterised by extended serum half-lives and concentration-dependent antimicrobial activity, allowing for once daily administration.[158] Because of their activity against β–lactam- and macrolide-resistant *S. pneumoniae*, as well as β–lactamase-producing *H. influenzae*, these drugs may be considered as agents of choice for the empiric treatment of CAP in countries with high rates of resistant isolates. Results of some clinical trials show that third-generation quinolones, used in monotherapy, produce clinical outcomes comparable to those obtained with combinations of cephalosporins and macrolides.[5] However, their use should be reserved for selected CAP patients, including those with infection owing to highly-resistant pneumococci or following treatment failure with first-line regimens, in order to reduce the risk of spreading quinolone-resistance among LRTI pathogens in the outpatient setting.[65] All fluoroquinolones penetrate well into the lung, reaching higher concentrations in alveolar macrophages and epithelial lining fluid than in serum.[156] In addition, their excellent oral bioavailability permits their use in the transitional therapy, allowing for an early hospital discharge and cost reduction.[2,4]

Drug-related toxicities represent a problem for some derivatives: recently, postmarketing surveillance has revealed important phototoxicity with sparfloxacin, severe liver toxicity with trovafloxacin and significant cardiotoxicity with grepafloxacin. Consequently, the use of these agents has been withdrawn.[154,155] Although differences exist between family members, special attention should be paid to the use of fluoroquinolones in the elderly,

especially in those with underlying heart diseases or those treated concomitantly with drugs known to prolong QT intervals, because of higher risks of cardiac arrhythmias. Moreover, tendon ruptures, CNS adverse effects including headache, insomnia and confusion, and gastrointestinal adverse effects are more frequently observed in older than younger individuals.[9,129] Drug interactions are less frequent with newer derivatives, but they may face limitations in the elderly because of polypharmacy. In addition, a reduction of dose may be required in this population depending on renal function: a reduction by 50% of ciprofloxacin and levofloxacin dosage should be made when creatinine clearance values are below 30 and 50 mL/min, respectively. All these findings suggest that in elderly patients, fluoroquinolones should be used only for the treatment of severe pneumonia due to antibacterial-resistant Gram-positive organisms or *P. aeruginosa.*

4.4 Aminoglycosides

The role of aminoglycosides in the treatment of LRTIs is limited by several factors, including their poor penetration of lung tissue, the possible inactivation in the acidic environment and above all, the availability of more safe and equally active agents. In addition, the most severe adverse effects, i.e. nephrotoxicity and ototoxicity, may be particularly problematic in the elderly because of the association between aging and the loss of nephrons and hearing. A new dosage regimen, i.e. a single daily dosage combining the 2–3 daily doses, may reduce the risk and/or severity of aminoglycoside-related adverse effects.[103] However, serious adverse effects associated with once daily administration of gentamicin, including high rates of ototoxicity in febrile neutropenic patients[159] and nephrotoxicity in elderly patients,[160] have been recently reported. Moreover, results of some recent clinical trials in geriatric patients suggest that the once daily administration of aminoglycosides has little or no benefit in this population.[119,120] Since the use of these drugs in the elderly requires stringent controls for administration and monitoring of drug-related adverse effects,[161] their use should be reserved for the hospital setting to treat, in combination with β-lactams, serious infections caused by resistant Gram-negative rods, especially *P. aeruginosa*. However, as previously reported, it is important to note that *P. aeruginosa* strains with high levels of aminoglycoside resistance owing to the production of drug modifying enzymes or the presence of drug efflux mechanisms have been isolated in some countries.[89,162]

4.5 Glycopeptides

On the basis of susceptibility rates from *in vitro* tests, vancomycin and, to a lesser extent, teicoplanin, are considered to be the standard treatment for severe MRSA infections. Vancomycin is characterised by a relatively slow and time-dependent bactericidal effect; thus maintaining tissue levels above pathogen's MIC is required for a successful outcome. One way of achieving this is through continuous infusions, which provide longer time above MIC than intermittent administration.[163] Moreover, glycopeptides are relatively toxic. Vancomycin is potentially nephrotoxic and when administered by infusion, phlebitis and symptomatic histamine release may occur. Variations in mechanical ventilation may influence the volume of distribution of the drug, as well as other pharmacokinetic parameters. In addition, decreased elimination may occur during prolonged treatment.[164] Finally, glycopeptides have only moderate extra-vascular diffusion, and the poor penetration into the lung may lower their effectiveness *in vivo*, even with appropriate administration. Consequently, in the treatment of patients with ventilator-associated pneumonia (VAP), vancomycin serum levels must be monitored to minimise nephrotoxicity and to maximise the best concentrations in the lung.[165]

However, clinical studies in patients with severe pneumonia due to MRSA have shown high mortality rates among patients treated with vancomycin.[166,167] In intubated patients with pneumonia caused by methicillin-susceptible *S. aureus* (MSSA) treated with cloxacillin, Rello et al.[166] have reported a mortality rate below 5%, compared with a 54.5% mortality in patients with VAP due to MRSA and treated by intermittent administration of vanco-

mycin with serum level monitoring. In a recent observational study, Gonzales et al.[167] have reported a high mortality rate among patients treated with vancomycin for pneumonia caused by either MRSA (50%) or MSSA (47%), in contrast with patients with pneumonia because of MSSA and treated with cloxacillin (0%). In the light of the high toxicity combined with poor effectiveness *in vivo* and the recent emergence of staphylococcal isolates with reduced susceptibility to vancomycin,[163,168-172] glycopeptides should no longer be considered as first-line antibacterials for Gram-positive lung infections. The strategy for the treatment of nosocomial pneumonia due to MRSA should be combination therapy, including vancomycin and another agent to which the strain is sensitive.[163,165,173]

5. New Drugs for LRTIs

Recently, some new classes of drugs have been developed that are effective against resistant Gram-positive pathogens and have an excellent safety profile. They include oxazolidinones, ketolides and streptogramins.

5.1 Oxazolidinones

Oxazolidinones are a new class of synthetic narrow spectrum drugs, represented by linezolid, the first marketed member, and eperezolid. Their antibacterial spectrum includes Gram-positive organisms, some Gram-negative anaerobic species, but not Gram-negative aerobes.[174] Moreover, multidrug-resistant organisms, including methicillin-resistant staphylococci, staphylococci with reduced susceptibility to vancomycin, penicillin- or macrolide-resistant pneumococci and vancomycin-resistant enterococci, are fully susceptible to these agents.[175]

Oxazolidinones have a unique mechanism of action, involving the inhibition of the initiation step of protein synthesis, and are not cross-resistant to other classes of antibacterials currently available. Their activity is bacteriostatic against some species (enterococci) and bactericidal against others (pneumococci). Linezolid has almost 100% bioavailability and the AUC is identical after oral and intravenous administration; these characteristics enable its initial oral administration in those patients who can absorb the drug normally. In addition, these drugs are also suitable for the step-down therapy from intravenous to oral administration.[176] Twice daily administration in humans results in blood concentrations which at trough values are in excess of the MIC_{90} for significant Gram-positive pathogens. Linezolid shows excellent penetration in lung tissue and epithelial lining fluid; moreover its pharmacokinetic properties are not affected by age. Since the drug has both renal and nonrenal elimination,[177,178] no dose adjustment is necessary in patients with mild-to-moderate renal function or liver disease.[177] The clinical and microbiological efficacy of linezolid has been recently evaluated in a multicentre, randomised, double-blind controlled trial versus vancomycin in patients with hospital-acquired pneumonia who received aztreonam in addition to cover possible Gram-negative organisms.[179] Microbiological eradication, clinical cure rates and safety were comparable. Other controlled clinical studies have assessed the efficacy and safety of linezolid also in CAP, uncomplicated and complicated skin and soft tissue infections, and infections caused by vancomycin-resistant enterococci.[180]

Oxazolidinones are generally well tolerated. The most common adverse reactions are gastrointestinal disturbances (nausea, diarrhoea), followed by headache and rash. The most serious adverse effect reported in phase III clinical trials is thrombocytopenia, being recorded in 2–4% of linezolid recipients. *In vitro* testing has revealed linezolid to be a very weak reversible inhibitor of monoamine oxidase, but no clinical evidence of enzyme inhibition has emerged in clinical trials so far. Nonetheless, product information suggests that patients should avoid large quantities of tyramine-containing food while on linezolid therapy. In addition, the drug has the potential for interaction with adrenergic and serotonergic agents: a reversible enhancement of the pressor response to agents such as dopamine or epinephrine and a risk of serotonin syndrome, including hyperpyrexia and cognitive dysfunction, in patients receiving concomitant serotonergic agents

may occur. Although the US FDA has recently approved linezolid for the empirical treatment of nosocomial pneumonia and CAP,[179,181] oxazolidinones should be used as second-line agents for treatment of LRTIs caused by drug resistant Gram-positive organisms, in order to avoid the emergence of drug resistance. In addition, clinical studies specifically addressed to confirm the efficacy and safety of these drugs in the elderly are needed.

5.2 Ketolides

This family of antibacterials, derived from macrolides, has been developed with the goal of overcoming the problem of macrolide-resistance.[182] Telithromycin is potent against macrolide-resistant Gram-positive cocci, penicillin-resistant pneumococci, *H. influenzae*, *M. catarrhalis* and atypical respiratory bacterial pathogens. This agent has a low potential to select for or induce cross-resistance, and a low propensity for drug interactions.[183] The pharmacokinetic profile reveals that telithromycin penetrates rapidly into lung tissues and fluids, reaching concentrations higher than that found in serum. The drug does not require dose reduction in elderly patients, including those with hepatic impairment and can be administered effectively once daily.[184,185] Results of an international, multicentre trial comparing telithromycin with amoxicillin, clarithromycin or trovafloxacin in the management of CAP, in both out- and inpatients, have demonstrated that all regimens may ensure high clinical and bacteriological success rates (superior to 90%).[186] Telithromycin-related adverse events, such as those of newer macrolides, are mild or moderate in intensity. Thus, because of their potency, the satisfactory pharmacological properties and safety, ketolides could represent substitutes for macrolide derivatives in the empiric treatment of LRTIs in the elderly population, especially in countries with high rates of Gram-positive isolates resistant to macrolides.

5.3 Streptogramins

Quinupristin/dalfopristin, a combination of streptogramin A and B in a 30 : 70 ratio, is the first commercially available injectable streptogramin derivative. This drug combination inhibits protein synthesis by preventing peptide-chain formation and blocking the extrusion of newly formed peptide chains.[187] Conformational alteration of the target ribosomal binding sites represents the most common mechanism of bacterial resistance to streptogramins. However, resistance to the combination product occurs rarely, since it requires multiple point mutations. Recently, other possible resistance mechanisms, including drug-efflux and enzymatic inactivation, have been described. The spectrum of activity of quinupristin/dalfopristin includes multidrug resistant Gram-positive aerobic bacteria, in particular methicillin-resistant *S. aureus* and coagulase-negative staphylococci, vancomycin-resistant *E. faecium*, penicillin- or erythromycin-resistant *S. pneumoniae*. Results of a recent multicentre, prospective randomised study have shown comparable clinical response rates between quinupristin/dalfopristin and vancomycin in adult patients with nosocomial pneumonia, who also received aztreonam to cover Gram-negative bacteria.[188] However, the efficacy of this combination in pneumonia owing to MRSA requires further evaluation, since MRSA strains only moderately susceptible *in vitro* to this combination have been isolated. Although quinupristin/dalfopristin undergoes hepatic metabolism as the parent drug, and their major metabolites are eliminated primarily via the faecal route (75%), no recommendations are available in cases of liver or renal dysfunction.

Streptogramin combination is well tolerated. The most common adverse effects are infusion-site reactions (e.g. pain, oedema and inflammation), thrombophlebitis, elevation of serum bilirubin and liver enzyme levels, myalgia and arthralgia. In addition, interactions with drugs metabolised by cytochrome P-450 3A4 enzymes may occur.[189] To date, no data are available in the elderly population, thus caution is necessary.

6. Conclusion

Due to the progressive rise in the elderly population, researchers and physicians must make a concerted effort to solve the complex dilemmas related to geriatric pharmacology, and clarify the multi-

faceted aspects of empirical antibacterial treatment in these patients. Pneumonia in elderly patients is a particularly common and serious illness, carrying a significant clinical and economic burden. Bacteriological diagnosis is often not available and diagnosis may be obscured by a nonclassical presentation in an elderly patient. Severity assessment is the key to stratifying appropriate therapy and to predicting outcome. Moreover, the determination of the site of care, based on clinical and social factors, represents an important clinical variable. Timely and appropriate empiric treatment is required in order to assure a positive impact on clinical outcome, reduce hospitalisation and mortality. The choice of antibacterial therapy must take into account several risk factors, including age, triage location, comorbidities, disease severity, as well as drug PK/PD parameters that predict clinical efficacy, bacterial eradication and prevent the emergence of drug resistance. The viability of several recent guidelines, proposing therapeutic schemes for CAP, nursing home- or hospital-acquired pneumonia, depends on the constant monitoring and control of specific local bacteriology, the knowledge of local patterns of antibacterial resistance and the assessment of drug-related adverse effects.

Particular attention should be paid to the spread of old pathogens with new resistance patterns. In addition to methicillin-resistant staphylococci, vancomycin-resistant or intermediate Gram-positive isolates and penicillin- or macrolide-resistant pneumococci are now a consideration in elderly patients, as an age of >65 years represents a recognised risk factor for infection with these organisms. Treatment of these infections is problematic and the use of novel agents with improved potency and new spectra of activity, including ketolides, oxazolidinones and streptogramin combination, may be necessary. However, the use of these and other new agents has to be carefully controlled and reserved for the management of serious or complicated LRTIs likely to be caused by drug resistant Gram-positive organisms, which are poorly responsive to glycopeptides. Controlled clinical trials are needed to assess their efficacy and safety in the elderly, as well as establishing optimal dosage regimens in this population. Moreover, prevention of bacterial pneumonia is important for all population groups but especially in elderly subjects who are at a higher risk of frequent infections, more severe course of illness and delayed clinical resolution. Therefore, preventive measures, such as stopping smoking and pneumococcal and influenza vaccines, are recommended in the elderly.

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