CHAPTER 14

Antibiotic treatment for nosocomial pneumonia

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The management of nosocomial pneumonia has been an object of intensive investigation during the previous two decades. Up to now some important aspects have been clarified. Firstly the recognition that early and late onset pneumonia represent two separate entities with important differences in epidemiology, risk factors, and prognosis has been established. Secondly, the role of antibiotics has been re-evaluated. Today there is strong evidence that early antibiotic treatment is crucial for a favourable outcome. However, risks associated with prolonged treatment with antimicrobial agents have been recognised. Besides the increasing costs of antibiotics it is apparent that the selection of potentially drug resistant microorganisms, associated with excess mortality, is also important. Although better treatment options, like new broad spectrum antibiotics are available, antimicrobial resistance is increasing.

Many studies have focused on the diagnostic and therapeutic strategies to improve the outcome. While some issues are clear others still remain controversial. Maybe the time has come to leave the individual diagnostic approach and turn to a more epidemiological point of view.

Previously the American Thoracic Society (ATS) made recommendations which emphasised the following aspects: 1) initial antimicrobial therapy for hospital-acquired pneumonia (HAP) must always be empirical; 2) any antibiotic regimen must be guided by the severity of the pneumonia, the time point of the pneumonia occurrence and specific risk factors; and 3) the selection of antimicrobial agents has to consider local microbial and resistance patterns. This framework can be used as a guide for the selection of appropriate antimicrobial agents.

This chapter will review the current present knowledge of antimicrobial treatment in nosocomial pneumonia. Furthermore, several issues of particular interest leading to new perspectives of antibiotic treatment will be addressed.

Aetiology of nosocomial pneumonia

Microorganisms associated with hospital-acquired pneumonia (HAP) differ from those isolated in community-acquired pneumonia (CAP). Responsible pathogens and their epidemiology have been investigated in numerous studies [1–7]. In general a high rate of Gram-negative bacteria like Gram-negative rods (mostly Escherichia coli, Klebsiella spp., Enterobacter spp., Serratia spp. Proteus spp.) and potentially multiresistant pathogens like Pseudomonas aeruginosa, Acinetobacter spp. and
Stenotrophomonas spp. have been repeatedly reported [1, 3–11]. These strains are responsible for 55–85% of HAP cases. As regards Gram-positive bacteria Staphylococcus aureus has increasingly gained importance and it is estimated that it is now involved in 20–30% of HAP events [1, 3–7]. An important proportion of HAP events are polymicrobial, rates ranging between 13–60% [1, 12]. More uncommon microorganisms may appear, as Legionella spp. [13], anaerobes [14], fungi [15] and respiratory viruses [16]. An overview of the different microorganisms responsible for HAP isolated in different series is depicted in table 1.

All reported series, dealing with the aetiology of HAP are heavily influenced by the type of patients selected and the diagnostic methods employed. However some issues are considered to have an important influence in the aetiology of HAP.

**Orotracheal intubation.** Orotracheal intubation favours a specific pathogenesis of infection associated with a different spectrum of microorganisms [2]. Although data are scarce there seems to be evidence that in spontaneous breathing patients multiresistant pathogens are less common and microorganisms as enteric Gram-negative bacilli, Streptococcus pneumoniae and methicillin sensitive S. aureus are more frequent.

**Differentiation of the subgroups.** The differentiation of the subgroups early and late onset pneumonia has been proven to be of paramount importance [7]. Early onset pneumonia is regarded as a consequence of the aspiration of the endogeneous community-acquired pathogens such as S. aureus, S. pneumoniae, and Haemophilus influenzae, with intubation and any type of impaired consciousness being the main risk factors [4, 17, 19]. Late onset pneumonia results from the aspiration of the oropharyngeal and gastric secretions, thereby including potentially drug-resistant nosocomial pathogens.

**Previous antibiotic therapy.** Previous antibiotic therapy is associated with an increased risk of infection with resistant pathogens. There is good evidence that the distribution of microorganisms responsible is markedly influenced by prior antibiotic use [7]. It is known that patients with a prolonged hospital stay and previous antibiotic treatment have the highest risk of infection by multiresistant pathogens such as P. aeruginosa, Acinetobacter baumanii and methicillin resistant S. aureus (MRSA) [7, 10].

**Specific risk factors.** Specific risk factors can modify the spectrum of potentially infecting microorganisms. S. aureus seems to be a common pathogen in patients suffering head injuries, coma incidences, chronic renal failure or diabetes mellitus [4, 18]. Patients with structural lung disease, bronchiectasis and advanced stages of chronic obstructive pulmonary disease (COPD) are prone to infections by P. aeruginosa [20]. A prolonged use

<table>
<thead>
<tr>
<th>Table 1. – Bacteriology of hospital-acquired pneumonia</th>
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<tr>
<td>Early onset pneumonia</td>
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<tr>
<td>Streptococcus pneumoniae</td>
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<tr>
<td>Haemophilus influenzae</td>
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<tr>
<td>Moraxella catarrhalis</td>
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<tr>
<td>Staphylococcus aureus</td>
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<tr>
<td>Aerobic GNB*</td>
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<tr>
<td>Late onset pneumonia</td>
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<tr>
<td>Psuedomonas aeruginosa</td>
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<tr>
<td>Enterobacter sp.</td>
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<tr>
<td>Acinetobacter sp.</td>
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<tr>
<td>Klebsiella. pneumoniae</td>
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<tr>
<td>Serratia marcescens</td>
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<tr>
<td>Escherichia coli</td>
</tr>
<tr>
<td>Other GNB</td>
</tr>
<tr>
<td>S. aureus*</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Anaerobic bacteria</td>
</tr>
<tr>
<td>Legionella pneumophilia</td>
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<tr>
<td>Influenza A and B</td>
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<tr>
<td>Respiratory syncitial virus</td>
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<td>Fungi</td>
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GNB: Gram-negative bacilli; \*: in patients with risk factors; \*: including methicillin resistant S. aureus. Adapted from FRANCIOLI et al [17].
of corticosteroids predisposes to infections caused by *Legionella spp.*, *P. aeruginosa* and *Aspergillus spp.*[20, 21]. The association of nonepidemic HAP caused by *Legionella spp.* and systemic steroid therapy was clearly shown in one study where further risk factors were malignancy, renal failure, neutropenia and cytotoxic chemotherapy [22]. Aspiration will lead to infections, most frequently polymicrobial including anaerobes and Gram-negative bacilli [23].

**Prevalence of infecting microorganisms.** The prevalence of infecting microorganisms shows considerable local differences. Past antimicrobial treatment policies and the dominant patients characteristics (e.g. transplant patients, polytrauma patients or severe respiratory diseases) lead to specific, locally differing microbial and resistance patterns. Therefore each institution varies in its microbiological and susceptibility status [24, 25].

**Aetiology in subsets of patients according to the American Thoracic Society guidelines**

Based on the guidelines released by the ATS patients with an episode of HAP should be stratified into different groups, thereby allowing the most probable infecting agents to be identified. Guidance by the use of three criteria has been suggested, these include: 1) severity of pneumonia; 2) specific risk factors; and 3) the time point of the pneumonia occurrence. According to this determination patients will fall into one of three groups, each with its own set of microorganisms. A detailed description is given in table 2.

**Patients without unusual risk factors.** In patients without unusual risk factors or comorbid diseases, who present with mild-to-moderate HAP with onset at any time during hospitalisation or severe HAP of early onset the following core organisms should be considered: 1) community endogenous pathogens (*S. aureus*, *S. pneumoniae*, and *H. influenzae*); and 2) nonresistant Gram-negative Enterobacteriaceae (GNEB: including *E. coli*, *K. pneumoniae*, *Enterobacter spp.*, *Serratia spp.*, *Proteus spp.*).

**Patients with specific risk factors.** Patients with specific risk factors and/or comorbid diseases who present with mild-to-moderate HAP occurring at any time during hospitalisation or severe HAP of early onset have both core organisms and more specific microorganisms.

In addition to the previously mentioned core organisms the microbiological spectrum is influenced by specific risk factors and the time of onset. Potentially drug-resistant microorganisms must be taken into account. The role of specific risk factors has been commented on previously. According to the ATS guidelines those factors include risks for anaerobes (recent abdominal surgery), *S. aureus* (coma, head trauma, diabetes mellitus, renal failure), *Legionella spp.* (high-dose steroids) and *P. aeruginosa* (prolonged intensive care unit (ICU) stay, steroids, previous antibiotic treatment and structural lung disease). Furthermore if pneumonia develops after a prolonged hospital stay and/or the previous use of antibiotics, the risk of infections with multiresistant microorganisms is increased (MRSA, *P. aeruginosa*, *Acinetobacter spp.*, *Enterobacter spp.* and *Stenotrophomonas maltophilia*).

**Patients with severe hospitalised-aquired pneumonia either of early onset with specific risk factors or of late onset.** Crucial in this patient group is the severity of the disease in addition to the time of onset. The severity criteria suggested by the ATS are as follows: 1) admission to the ICU, respiratory failure (mechanical ventilation or >35%
Table 2. – Risk factors for infections by specific microorganisms according to severity, time of onset and specific risk factors, applicable to nonimmunocompromised patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Group patient characteristics</th>
<th>Core organisms (plus)</th>
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<tbody>
<tr>
<td>Group I</td>
<td>Patients with mild to moderate HAP</td>
<td>Enteric GNB (non-pseudomonal)</td>
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<tr>
<td></td>
<td>No unusual risk factors</td>
<td><em>Enterobacter</em> spp.</td>
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<tr>
<td></td>
<td>Onset any time or</td>
<td><em>Escherichia coli</em></td>
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<td></td>
<td>Patients with severe disease and early onset</td>
<td><em>Klebsiella</em> spp.</td>
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<td></td>
<td><em>Proteus</em> spp.</td>
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<td></td>
<td></td>
<td><em>Serratia marcescens</em></td>
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<td></td>
<td></td>
<td><em>Haemophilus influenzae</em></td>
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<td></td>
<td></td>
<td>MRSA</td>
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<td></td>
<td></td>
<td><em>Streptococcus pneumoniae</em></td>
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<tr>
<td></td>
<td><strong>Specific comments</strong></td>
<td>Risk of multiresistant pathogens</td>
</tr>
<tr>
<td></td>
<td>Early onset VAP in patients with previous antibiotic therapy (within the previous 15 days)</td>
<td>Pseudomonas aeruginosa, <em>Acinetobacter</em> sp., <em>Stenotrophomonas maltophilia</em> (30%)</td>
</tr>
<tr>
<td></td>
<td>Late onset, nonventilated</td>
<td>MRSA (5–18%) TROUILLET et al [7] and IBRAHIM et al [10]</td>
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<tr>
<td></td>
<td></td>
<td>Pseudomonas aeruginosa*</td>
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<td></td>
<td></td>
<td><em>Pseudomonas aeruginosa</em></td>
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<tr>
<td></td>
<td></td>
<td>Risk of resistant GNB possible</td>
</tr>
<tr>
<td>Group II</td>
<td>Patients with mild to moderate HAP</td>
<td>Anaerobes</td>
</tr>
<tr>
<td></td>
<td>With risk factors,</td>
<td>Recent abdominal surgery</td>
</tr>
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<td></td>
<td>Onset any time</td>
<td>Witnessed aspiration</td>
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<td></td>
<td></td>
<td><em>Staphylococcus aureus</em></td>
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<tr>
<td></td>
<td></td>
<td>Coma, head trauma, diabetes, mellitus, renal failure</td>
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<tr>
<td></td>
<td></td>
<td><em>Legionella</em> spp.</td>
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<tr>
<td></td>
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<td>High dose steroids</td>
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<td></td>
<td></td>
<td>Pseudomonas aeruginosa*</td>
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<td></td>
<td></td>
<td>Prolonged ICU stay, steroids</td>
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<td></td>
<td></td>
<td>Antibiotics, structural lung disease, COPD</td>
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<tr>
<td></td>
<td><strong>Specific comments</strong></td>
<td>Risk of multiresistant pathogens</td>
</tr>
<tr>
<td></td>
<td>In case of previous antibiotic treatment</td>
<td>Resistant <em>S. pneumoniae</em> possibly</td>
</tr>
<tr>
<td></td>
<td>Contact with children, &gt;65 yrs, comorbid</td>
<td></td>
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<tr>
<td>Group III</td>
<td>Patients with severe HAP</td>
<td><em>P. aeruginosa</em></td>
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<tr>
<td></td>
<td>With risk factors,</td>
<td><em>Acinetobacter</em> spp.</td>
</tr>
<tr>
<td></td>
<td>Early onset or patients with severe HAP with late onset</td>
<td><em>S. maltophilia</em></td>
</tr>
<tr>
<td></td>
<td>Consider local epidemiology and resistance patterns</td>
<td>MRSA</td>
</tr>
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HAP: hospital-acquired pneumonia; GNB: Gram-negative bacilli; VAP: ventilator-associated pneumonia; MRSA: methicillin resistant *S. aureus*; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease. Data adapted from TROUILLET et al [7], AMERICAN THORACIC SOCIETY [8], IBRAHIM et al [10], LODE et al [26] and EWIG et al [27].

oxygen to maintain the saturation >90%; and 2) radiographical progression and severe sepsis with hypotension.

Cases of severe HAP with no risk factors, with early onset would rather belong to the first group. Hereby the main microorganisms responsible for infection would be *H. influenza* and Methicillin-sensitive *S. aureus* but further potentially resistant microorganisms must be considered. These include multiresistant MRSAs, GNEB, and *P. aeruginosa*, *Acinetobacter* spp., as well as *S. maltophilia*. This is particularly true in cases of prolonged mechanical ventilation for >7 days and broad spectrum antimicrobial pretreatment [7].

The ATS guidelines do not make specific recommendations for nonventilated patients.
with nosocomial pneumonia. As a consequence patients with HAP, without severity
criteria as well as pneumonia not occurring in the ICU are categorised as nonsevere
pneumonia. They are treated as early onset HAP, with modifications in cases of
additional risk factors. Although the data is scarce, it seems quite probable that the time
point of pneumonia does also play a role in nonintubated patients [2].

As regards the concept of early and late onset ventilator-associated pneumonia some
issues have not yet been satisfactorily resolved. A crucial factor is the starting point for
the definition of early onset pneumonia, the use of hospital admission time, ICU
admission time or intubation time are all possible. If the time of ICU admission is used as
the starting point, patients may already have been extensively colonised during their
previous hospital stay, and consequently, differences between early and late onset
pneumonia are no longer evident [28]. In accordance with the ATS guidelines the use of
the time of hospital admission as starting point appears reasonable. The cut-off time
separating early and late onset ventilator-associated pneumonia (VAP) has been the
subject of many controversies. The ATS suggested the use of the fifth day after hospital
admission [8]. In a study investigating patients with central nervous system injury it was
shown that colonisation patterns markedly changed within 3–4 days. Initially the
oropharynx, nose and tracheobronchial tree were colonised with endogenous commu-
nity-acquired pathogens, this pattern was subsequently replaced by an increasing amount
of typical nosocomial pathogens [4]. TROUILLET et al. [7] could demonstrate that the
length of intubation and previous antimicrobial treatment can reasonably predict the
relation of core and potentially drug-resistant microorganisms. In this study, the cut-off
differentiating early and late onset VAP was seven days. This prospective investigation in
which the microorganisms responsible for infections in 135 consecutive episodes of VAP
was documented lead to the differentiation of four groups. These were early and late
onset pneumonia (>7 days) either with or without previous antibiotic therapy. As regards
early and late onset pneumonia the risk for multiresistant bacteria was significantly
increased by the use of previous antibiotics. Although the conclusions drawn from the
study can only be applied to ventilated patients the results allowed the authors to suggest
a decision tree for selecting initial antimicrobial treatment. However, a different study
study demonstrated that in an ICU setting, even in early onset nosocomial pneumonia,
resistant pathogens were frequent. The authors concluded that probable reasons were
prior antibiotic therapy, severe basic disease and hospital stay [10]. Overall the
importance of prior antimicrobial therapy is not sufficiently reflected in the ATS
guidelines.

Further, emphasis on previously mentioned local differences in resistance patterns and
microbiology should be made. The aetiology of nosocomial pneumonia varies from
institution to institution and the kind of patients admitted [29, 30]. Further national
differences have been described e.g. Enterobacter spp. was found to be more frequent in
the US whilst Acinetobacter spp. is more prevalent in Europe [1, 31].

Different patient risk factors predispose them to infections by specific pathogens which
may play an important role in early onset HAP. This applies especially to medical
patients. Recent guidelines for the treatment of CAP have stressed that underlying
medical conditions predispose to certain pathogens [32]. As community-acquired
pathogens play an important role in early onset HAP, specific risk factors, present in the
ambulatory setting, do not cease to exist after admission to the hospital. This might be of
particular interest in patients with advanced stages of COPD and/or structural lung
disease which are prone to infections by difficult to treat Gram-negative bacteria i.e.
P. aeruginosa [33]. The role of antibiotic resistant strains of S. pneumoniae in HAP is not
known. Risk factors such as advanced age, alcoholism, multiple medical comorbidities,
living in a nursing home or exposure to children in a day care centre, identified for CAP,
can also be of importance in the nosocomial setting.
The ATS guidelines and the classification of VAP suggested by Trouillet et al. [7] has been validated the focus on microbiological data and the potential adequacy of selected antimicrobial regimens in a recently published study [34]. A total of 124 patients with HAP in a French ICU were retrospectively categorised according to the ATS guidelines [8] and the classification of Trouillet et al. [7]. With the ATS classification patients were included into classes (1 and 3) with an increasing frequency of resistant pathogens (0–30.3%). The subsequently recommended antibiotic treatment appeared valid but proposed combinations including vancomycin for 72.5% of patients. Trouillet et al. [7] classification categorised patients into four groups with a frequency of resistant pathogens from 4.9–35.6%. Vancomycin was proposed for 48.5% of patients. Although the ATS classification was more specific than the one by Trouillet et al. [7] for predicting the absence of resistant causative pathogens in HAP, it lead to a greater use of vancomycin. The authors finally concluded that a stratification combining the two classifications could be an interesting alternative.

In conclusion an alternative option would be to amend the severity-based approach of the ATS guidelines to an algorithm that separates pneumonia in the nonintubated and intubated patient, further differentiates between early and late onset, and allows modifications according to the presence of risk factors allows. The recently established German guidelines for the treatment and prevention of nosocomial pneumonia suggest such an approach [27].

Current recommendations of empirical antimicrobial treatment based on the American Thoracic Society guidelines

Despite intensive investigational activity so far no consensus has been reached in basic issues as the optimal antibiotic treatment or the duration of therapy. Whereas appropriate antimicrobial treatment improves the outcome of HAP, inappropriate therapy is associated with an increased risk of death from pneumonia [29, 35]. Moreover, even if the initially inappropriate antimicrobial treatment is corrected according to diagnostic results, there remains an excess mortality compared with patients treated appropriately from the beginning [36].

Conversely, antimicrobial treatment is not without risk. Various epidemiological investigations have shown a clear relationship between increasing resistance rates and the use of antimicrobial agents [37, 38]. In a study by Rello et al. [20] antimicrobial pretreatment was the only adverse prognostic factor in a multivariate model. However if pneumonia, due to high-risk organisms (P. aeruginosa, Acinobacter calcoaceticus, Serratia marcescens, Proteus mirabilis and fungi) was included in the model, the presence of these high risk organisms was the only independent predictor and antimicrobial pre-treatment entirely dropped out [29]. Furthermore recommendations for initial empirical antimicrobial treatment must accommodate local variations in infecting organisms and their resistance patterns [25, 39].

Limitations of diagnostic criteria for the diagnosis of HAP in the individual patient have fundamental consequences for any antimicrobial treatment strategy. As a consequence the following issues must be taken into account, partly already described by the American ATS guidelines [8]. These include: 1) the empirical character of any initial antimicrobial treatment; 2) empirical initial antimicrobial treatment can be guided by three criteria, including severity of pneumonia, time point of pneumonia occurrence, and specific risk factors; 3) the selection of particular antimicrobial agents and regimens must be adopted to regional or even local peculiarities of microbial and resistance patterns; and 4) microbiological results of diagnostic measurements may offer additional clues which must be interpreted in the context of the clinical condition of the patient.
Such information (obtained by bronchoalveolar lavage or protected specimen brush: PSB) may be particularly relevant in case of nonresponse to empirical initial antimicrobial treatment.

Based on the ATS guidelines, the following general recommendations for an empirical initial antimicrobial treatment of suspected HAP can be made:

**Patients with early onset hospital acquired pneumonia and no risk factors.** In these patients, core organisms such as community endogeneous pathogens (*S. aureus, S. pneumoniae, and H. influenzae*) and nonresistant GNEB, including *E. coli, K. pneumoniae, Enterobacter spp., Serratia spp., Proteus spp.*) should be appropriately covered. This can be afforded by a monotherapy consisting of a second-generation cephalosporin, third generation cephalosporin (cefotaxime or ceftriaxone) or an aminopenicillin plus β-lactamase inhibitor. Fluorquinolones or a combination of clindamycin and aztreonam are alternatives.

**Patients with late onset hospital-acquired pneumonia and no risk factors.** In addition to these core organisms, potentially drug resistant microorganisms must be taken into account. This is particularly true in cases of prolonged mechanical ventilation for more than 7 days and broad spectrum antimicrobial pretreatment [7]. These include multiresistant MRSA, GNEB, and *P. aeruginosa, Acinetobacter spp.*, as well as *S. maltophilia*. Although not proven by randomised studies, it seems prudent to administer a combination treatment, including an antipseudomonal penicillin (+β-lactamase inhibitor) or cephalosporin, a carbapenem together with a quinolone (ciprofloxacin) or an aminoglycoside. Vancomycin may be added where MRSA is a concern, especially in patients with head injury or in a coma.

**Patients with early or late onset hospital-acquired pneumonia and risk factors.** These patients are at risk of peculiar pathogens and should be treated according to the specific risk factors. Virtually always this treatment is identical to late onset HAP without risk factors, except in the presence of risk factors for *Legionella spp.* In that instance, these pathogens must be covered additionally. A summary of the drugs and dosage regimens are given in table 3.

**Specific considerations**

The principal dilemma of potential over treatment at the cost of increased microbial selection pressure could be addressed more satisfactorily if future approaches could succeed in increasing the pretest probability of the presence of pneumonia according to clinical criteria. This could be afforded by the following investigational tools:

Clinical criteria for the diagnosis of HAP currently in use (a new and persistant infiltrate in chest radiograph in addition with one to three of the following: fever or hypothermia; leucocytosis or leucopenia; and purulent tracheobronchial secretions) are outdated. It is inappropriate to ignore changes in oxygenation, the criteria for severe sepsis and/or septic shock. As regards VAP, PUGIN *et al.* [40] has suggested a scoring system, including the following six weighted clinical and microbiological variables: temperature, white blood cell count, nature and average of tracheobronchial aspirate volume, gas exchange ratio and chest radiograph infiltrates. Although this score is tedious to calculate and includes microbiological criteria it achieved a sensitivity of 72% and a specificity of 85% in a post mortem study [41]. More specific criteria for the diagnosis of VAP might significantly improve the predictive value of clinical judgment.
Furthermore the comprehension of markers of the inflammatory response associated with HAP in particular, could be of help in guiding antimicrobial treatment decisions. In addition it would be helpful if a validated scoring system could be used to guide the decision as to when an antimicrobial treatment could be safely withheld or stopped. A crucial question of any empirical antimicrobial treatment concept is whether treatment maybe withheld or whether it may even be stopped in the presence of bacterial counts below the threshold.

Firstly, it has generally been agreed that in patients exhibiting signs of severe sepsis or

| Table 3. – General framework for empirical initial antimicrobial treatment of ventilated-acquired pneumonia |
|-------------------------------------------------|---------------------------------------------------------------------------------|
| Patient                                        | Class of antimicrobial agents         | Agents and dose regimen                                                      |
| Ventilated patient                             |                                    |                                                                               |
| Early onset, no risk factors                   | Cephalosporin II                    | Cefuroxime 3×1.5 g                                                           |
| Or Cephalosporin III                           |                                    |                                                                               |
| Or Aminopenicillin/β-lactamase inhibitor       |                                    |                                                                               |
| Or Second-line quinolone                       |                                    |                                                                               |
| Or Clindamycin/aztreonam                       |                                    |                                                                               |
| Late onset, no risk factors                    | Quinolone                           | Ciprofloxacin 3×400 mg                                                       |
| Or Aminoglycoside                              |                                    |                                                                               |
| Or Plus                                        |                                    |                                                                               |
| Or Ceftazidime                                 |                                    |                                                                               |
| Or Carbapenems                                 |                                    |                                                                               |
| Plus/minus                                     |                                    |                                                                               |
| Early or late onset, risk factors              | Risk factors for *Pseudomonas aeruginosa* | Vancomycin 2×1 g                                                             |
| Refer to late onset                            |                                    |                                                                               |
| Risk factors for MRSA:                        |                                    |                                                                               |
| +Vancomycin                                    |                                    |                                                                               |
| Risk factor for *Legionella* spp. Macrolide    |                                    |                                                                               |
| Nonventilated patient                          | Refer to ventilated patients        |                                                                               |
| Early onset, no risk factors                   |                                    |                                                                               |
| Late onset, no risk factors                    |                                    |                                                                               |
| Possibly monotherapy in the absence of severe pneumonia | Refer to ventilated patient |                                                                               |

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Furthermore the comprehension of markers of the inflammatory response associated with HAP in particular, could be of help in guiding antimicrobial treatment decisions. In addition it would be helpful if a validated scoring system could be used to guide the decision as to when an antimicrobial treatment could be safely withheld or stopped. A crucial question of any empirical antimicrobial treatment concept is whether treatment maybe withheld or whether it may even be stopped in the presence of bacterial counts below the threshold.

Firstly, it has generally been agreed that in patients exhibiting signs of severe sepsis or
septic shock empirical antimicrobial treatment must be given. Secondly, it could be shown that patients with clinically suspected VAP yielding borderline colony counts ($\geq 10^2$ though $<10^3$ cfu·mL$^{-1}$ in PSB) who were left untreated had an excess mortality if they developed significant colony counts in a repeated investigation within 72 h as compared to those who did not [42]. Thus, it is argued that stable patients with suspected VAP according to judicious clinical judgment but without an established pathogen and without an alternative diagnosis, compatible with these symptoms, should continue to receive empirical antimicrobial treatment. The main reason for this attitude is that in this situation the potential short-term consequences for the individual patient, if left untreated, outweighs concerns regarding over treatment, resulting in microbial resistance. In contrast to CAP, severity assessment of VAP has not received much attention [43]. However, it is evident that valid severity criteria may be of great help in deciding when antimicrobial treatment can be safely withheld or stopped.

**Issues of particular interest**

**Monotherapy versus combination therapy**

Until only a few years ago, most intensive care specialists and infectious disease consultants used combination therapy consisting of β-lactam antibiotics and an aminoglycoside to treat nosocomial pneumonia. The rationale was that such treatment would provide a broad spectrum antimicrobial activity, which would delay the onset of bacterial resistance and work synergistically. However, arguments have arisen which lay claim to combination therapy being too expensive and in danger of exposing patients to multiple toxicities and thereby increasing the risk of antibiotic-associated complications. The addition of an aminoglycoside has particularly been associated with drug-related toxicities. Further, new broad spectrum and highly bactericidal antibiotics, including carbapenems, penicillins with β-lactamase inhibitors, and fluoroquinolones are available [44]. Therefore, a major clinical question is whether the use of a single antibiotic is sufficient for the treatment of nosocomial infections (table 4).

**Studies favouring combination therapy**

As previously described resistant microorganisms e.g. *P. aeruginosa* are a serious problem in HAP. Several studies have shown that monotherapy for pseudomonal HAP is associated with an elevated rate of clinical failures, relapses, mortality and the development of resistance in 30–50% of the patients [45–46]. Hilf et al. [47] performed a prospective clinical study of 200 patients with bacteremic *P. aeruginosa* infections. The

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<th>Table 4. – Antibiotic Therapy in Nosocomial Pneumonia: monotherapy versus combination therapy</th>
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<tr>
<td><strong>Monotherapy</strong></td>
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<tr>
<td>Lower cost</td>
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<tr>
<td>Lower risk of side effects</td>
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<tr>
<td>No antagonistic effect of antibiotics</td>
</tr>
<tr>
<td>No pharmacological interactions</td>
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<td>Equal efficacy</td>
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Adapted from Lode [44].
main results showed that the mortality rate of patients receiving combination therapy was significantly lower than for monotherapy (27 versus 47%, p<0.02) [47].

A different study investigated the effects of combination therapy versus monotherapy against *Klebsiella spp.* bacteremia in 230 patients. The results showed that the 14-day mortalities in the two groups were similar (20 and 18%). However, within the subgroup of patients who experienced hypotension within 72 h prior to, or on the day of the positive blood culture, the patients who received combination therapy experienced significantly lower mortality (24%) when compared with those on monotherapy (50%) [48]. It has to be stated here that the β-lactam agents used in these studies had less potent activity than the modern antibiotics used today. A controlled multicentre, randomised European trial of 129 patients with cancer, granulocytopenia and Gram-negative bacteremia supported a benefit of adjunctive aminoglycoside treatment [49]. Ceftazidime plus either a short course (3 days) or a long (9 days) course of treatment were compared. Clinical response rates were highest with ceftazidime plus a long (9 days) course of treatment with amikacin. In addition the benefit of the aminoglycoside was pronounced when *P. aeruginosa* was implicated, resulting in 89% response for the long course versus 38% for the short course.

**Studies favouring monotherapy.** La Force et al. [50] compared the efficacy of monotherapy and combination therapy in the management of nosocomial pneumonia. This study demonstrated that monotherapy with new antibiotics such as ceftazidime, aztreonam, cefoperazone, achieved a superior clinical success rate of 88% when compared with combination therapy which had a rate of only 76%. Furthermore the rate of superinfections was lower in the group treated with monotherapy (12 versus 18%). The effectiveness of the newer carbapenems for monotherapy of HAP was supported by a further study by Sieger et al. [51]. In this study meropenem was compared with a combination of ceftazidime/tobramycin in patients with hospital-acquired lower respiratory tract infections. The analysis of efficacy was based on the clinical and bacteriological responses at the end of treatment. A total of 121 patients were evaluated. The clinical response was found to be superior in the meropenem-treated patients (89%) compared with 72% in the combination therapy group (p=0.04). Further, bacteriological response rates were significantly higher in the meropenem group (89 versus 67%; p=0.006). However both treatment groups tolerated the antibiotics well and additional toxicity caused by the aminoglycosides was not observed.

Monotherapy with imipenem has also been compared with a combination of imipenem plus netilmicin for the empirical treatment of nosocomial pneumonia, nosocomial sepsis, and severe diffuse peritonitis. Monotherapy was successful in 80% of the cases and combination therapy in 86%. Emergence of *P. aeruginosa* resistant to imipenem occurred in 6% of the patients treated with monotherapy and in 9% of those treated with the combination therapy. The authors concluded that the addition of netilmicin increased nephrotoxicity and did not prevent the emergence of resistant *P. aeruginosa* strains [52].

Previously two studies were conducted to compare different regimens of monotherapy treatment. One involved a prospective multicentre study which compared the efficacy of intravenous (IV) ciprofloxacin or imipenem in the treatment of severe nosocomial pneumonia requiring mechanical ventilation [53]. Only patients with a significant growth for potentially pathogenic microorganisms in quantitative bacterial cultures were included in the study. The success rates were satisfactory, however neither the clinical success rate (ciprofloxacin 71%; imipenem 79%) nor the bacteriological response rate (ciprofloxacin 49%; imipenem 50%) were significantly different between the study arms. In the subgroup of patients with *P. aeruginosa* (35%) both study medications showed nonsignificantly different clinical (ciprofloxacin: 71%; imipenem: 67%) or bacteriological
response rates (ciprofloxacin: 50%; imipenem: 25%). Resistance by *P. aeruginosa* developed in 7% cases to ciprofloxacin and 33% cases to imipenem (*p*=0.147). In addition the mortality did not differ between both treatment arms. The authors finally concluded that treatment with both substances was equally effective. However, smaller differences between the treatment-arms of the study may have been missed due to sample-size limitations, especially as regards the development of resistance to *P. aeruginosa* [53].

A different multicentre, randomised double-blind trial compared intravenous ciprofloxacin with imipenem/cilastatin in 405 patients with severe pneumonia. A total of 79% of the patients required mechanical ventilation. The primary and secondary efficacy endpoints in this study were bacteriological and clinical responses at 3–7 days after the completion of therapy. The patients who received ciprofloxacin demonstrated a higher bacteriological eradication rate than those in the imipenem group (69 versus 59%; *p*=ns). Clinical response rates were also significantly higher in the ciprofloxacin group (69 versus 56%; *p*=0.02). Ciprofloxacin resulted more effective in the eradication of *Enterobacteriaceae* (93 versus 65%; *p*=0.009). However, when *P. aeruginosa* was recovered from initial respiratory tract cultures, only 41% responded to imipenem and 33% to ciprofloxacin. Resistance developed in 33% of the patients treated with ciprofloxacin and in 53% of the patients receiving imipenem. The authors concluded that in patients with severe pneumonia, monotherapy with ciprofloxacin was as least as effective as monotherapy with imipenem in terms of bacteriological eradication and clinical response. Although equally effective the authors suggest that monotherapy either with imipenem or ciprofloxacin can not be recommended for pneumonia when *P. aeruginosa* is suspected [46].

The majority of monotherapy studies addressed patients with an Acute Physiology, Age and Chronic Health Evaluation (APACHE) II score <20, consequently no evidence based data are available for the more severe patient population suffering from nosocomial pneumonias. In accordance to the guidelines published by the ATS all seriously ill patients should receive empirical combination therapy, targeting *P. aeruginosa* until culture results are available. Furthermore patients with an increased risk for *P. aeruginosa* e.g. those with prolonged steroid treatment, COPD or structural lung disease would benefit from combination therapy. However, more data are needed to support this as studies targeting other multiresistant Gram-negative bacteria *i.e.* *Acinetobacter spp.* or *S. maltophilia* are scarce.

**The role of aminoglycosides**

Aminoglycosides have been used for ~30 yrs for the treatment of nosocomial pneumonia. However, few data exist on the optimisation of dosing regimens. Today the role of aminoglycosides deserves further comment as the data accumulated are controversial. While the synergistic bactericidal activity against *P. aeruginosa* of a β-lactam in combination with an aminoglycoside is clearly shown in *vitro*, there is some doubt about a synergistic advantage in *vivo* [48, 54]. Aminoglycosides are the cheapest available antibiotics active against *P. aeruginosa*. In addition to this they are bactericidal in a concentration-dependent manner and show a prolonged postantibiotic effect enhancing bacterial growth even after serum levels are below the minimal inhibitory concentration (MIC) of the target organisms [55]. Drawbacks however are the narrow therapeutic range, the poor penetration into the lung parenchyma and a decreased activity in the presence of a low pH of the infected airways. While the bronchal secretin to serum ratio of fluorquinolones is 0.8–2.0, higher than those in plasma, aminoglycosides only reach 0.2–0.6.
Kashuba et al. analysed 78 patients with nosocomial pneumonia caused by Gram-negative bacteria treated with aminoglycosides, mostly in combination with a β-lactam antibiotic. Logistic regression predicted a 90% probability for resolution of the endpoints of temperature and leukocyte count resolution by day 7 if a $C_{\text{max}}/\text{MIC}$ ratio of $\geq 10$ was achieved within the first 48 h of therapy. The results of the study emphasise early, aggressive aminoglycoside dosing immediately followed by individualised pharmacokinetic monitoring to ensure optimal $C_{\text{max}}/\text{MIC}$ ratios.

This pharmacokinetic consideration, lead to specific dosing regimens, in particular the administration of aminoglycosides once daily. Administration in this manner leads to peak concentrations that decline rapidly, thereby taking advantage of the concentration-dependent killing manner and the prolonged postantibiotic effect, minimising the toxicity.

Local application of aminoglycosides

To avoid systemic toxicity a direct instillation of aminoglycosides into the respiratory tract appears to make sense. A double-blind randomised trial including patients with endobronchial tubes or tracheostomies and documented Gram-negative bacilli infection (GNB) compared the clinical efficacy of intratracheal instillation of tobramycin ($40 \text{ mg} \cdot 8 \text{ h}^{-1}$) versus saline solution. All patients received concomitant, systemic therapy with a β-lactam antibiotic and an aminoglycoside. GNB were eradicated from sputum more frequently in the tobramycin group (68 versus 31% in the controls). However, clinical improvement was identical in both groups (81 versus 80%) [56]. Other studies have come to similar conclusions [57]. The local application of aminoglycosides appears to be an interesting option but more data are needed before this procedure can be generally recommended.

Duration of treatment

The duration of antibiotic treatment for HAP has never been defined clearly. In general, carefully controlled studies documenting duration of therapy have not been reported. In VAP, most series show a duration of $\sim 10 \text{ days}$ [46, 52]. The main arguments against a prolonged duration of treatment include the selection of resistant microorganisms, the increased risk of adverse events and elevated antibiotic costs. However, short courses may lead to treatment failure or a relapse, particularly in the presence of resistant microorganisms. The recommendations of the ATS are to adapt the duration of treatment according to the severity of the case, the time to clinical response and the responsible microorganism [8]. A short course lasting 7–10 days is recommended in the presence of $H. \text{ influenzae}$ and methicillin-sensitive $S. \text{ aureus}$. A long course of treatment is suggested when microorganisms with a high risk of treatment failure are implicated, i.e. $P. \text{ aeruginosa}$ or $Acineobacter$ spp. Furthermore, multilobar involvement, malnutrition, severe debilitation, cavitation, or necrotising pneumonia may be associated with delayed and often incomplete resolution. Therefore therapy lasting 14–21 days is recommended in these patients.

In an elegant study, Singh et al. [58] randomised patients with suspected nosocomial pneumonia (58% VAP) and a Pugin score $< 6$ (i.e. low clinical probability of pneumonia) into patients who received a standard antimicrobial treatment at the discretion of the attending physician versus those who received a 3 day course with ciprofloxacin. After 3 days, patients were revaluated and antimicrobial treatment was stopped in those with a persistent Pugin score $< 6$, whereas those with a higher score received a full course of
standard antimicrobial treatment. The duration of hospitalisations and mortality were not different between both randomisation groups, however resistance and superinfection rates were higher in the control group (15 versus 39%).

In order to reduce the microbial selection pressure imposed by empirical antimicrobial treatment a reduction in treatment duration is very important. The main challenge in such a concept would be to identify the low risk groups and to treat patients with potentially drug resistant microorganisms i.e. P. aeruginosa and Acinetobacter spp. as a separate group. Because clinical criteria are unspecific and radiological resolution might last, it is not known when empirical therapy can be withheld or withdrawn safely. It can take as long as 6 days for fever and other clinical signs of pneumonia to improve under appropriate antibiotic treatment [59, 60]. In the ICU-setting some studies show that it may be safe to withdraw therapy when quantitative cultures of the lower respiratory tract are sterile or show a bacterial concentration under the threshold of infection [61, 62]. However, it must be emphasised that these studies were not designed to address the issue of withdrawing therapy. The decision to stop antibiotic therapy was made by the physician based on culture results and clinical status. The results from the study published by Singh et al. [58] shifted the perspective away from conflictive diagnostic issues. Instead a strategy was implemented which allowed, at the same time, to reduce the risk of individual undertreatment and general overtreatment with its inherent consequences.

New antibiotics

New antimicrobial drugs

In view of the growing microbial resistance rates worldwide, particularly those of Gram-positive microorganisms, the evaluation of new antimicrobial drugs becomes an emergent issue. The glycopeptides (vancomycin and teicoplanin) have been one of the last therapeutic options for infections due to multiresistant Gram-positive microorganisms, including MRSA. Despite this vancomycin has some clear disadvantages, it is only slowly bactericidal against staphylococci, furthermore it does not penetrate well into cerebrospinal fluid. Glycopeptides are potentially nephrotoxic and rapid infusion might lead to histamine release [63]. There are two promising drugs which have been investigated in nosocomial pneumonia associated with Gram-positive pathogens, these are quinopristin/dalfopristin and linezolid.

Quinopristin/dalfopristin. This is the first injectable streptogramin antibiotic. It is composed of two semisynthetic streptogramin molecules derived from Streptomyces pristinae spirali. Quinopristin/dalfopristin is active against a wide range of Gram-positive microorganisms including MRSA.

In a prospective, randomised, open-label multicentre study quinopristin/dalfopristin (7.5 mg·kg⁻¹·per 8 h) was compared to vancomycin (1 g per 12 h) in patients with nosocomial pneumonia. Aztreonam and tobramycin could be added in both groups as required. In total 208 patients were included in the study. In the bacteriologically evaluable population, cure or improvement could be achieved in 56.3% and 58.3%, respectively. Likewise, the clinical success rates for defined Gram-positive microorganisms were equivalent. Adverse effects were frequent in both groups; antimicrobial treatment was discontinued because of adverse reactions in 15.3% and 9.5% respectively. Therefore, quinopristin/dalfopristin and vancomycin were equivalent in the treatment of nosocomial pneumonia caused by Gram-positive organisms [64].
Linezolid. This is the first of a new class of antibacterial drugs, the oxazolidinones. It inhibits bacterial protein synthesis, though unlike other protein synthesis inhibitors, Linezolid acts early in translation, thereby preventing the formation of a functional initiation complex [65]. A clear advantage of this mechanism is that cross-resistance with other antibacterial drugs is not expected. Linezolid is effective against a broad range of bacteria including MRSA, glycopeptide-intermediate S. aureus, vancomycin resistant enterococci, and penicillin resistant S. pneumoniae. The drug also shows activity against certain anaerobes including Clostridium perfringens, Clostridium difficile, Peptostreptococcus spp and Bacteroides fragilis. Linezolid has only moderate in vitro activity against H. influenzae and Moraxella catarrhalis. P. aeruginosa and Enterobacteriaceae are not susceptible.

In a randomised, double-blind, multicentre study, Linezolid, (600 mg b.i.d.) was compared with vancomycin (1 g b.i.d.) in patients with nosocomial pneumonia in terms of efficacy, safety and tolerability. Clinical and microbiological success rates were equivalent for both groups (66.4 versus 68.1% and 67.9 versus 71.8%, respectively). This was also true for patients with pneumonia due to MRSA. Resistance to either treatment was not detected. However, concomitant surveillance cultures for appearance of vancomycin-resistant enterococci in stool could demonstrate the emergence of 4% vancomycin-resistant enterococci in patients treated with vancomycin, whereas no such resistance could be demonstrated in the group treated with linezolid [66].

Conclusion

Antimicrobial treatment exhibits a specific selection pressure. As a consequence past antimicrobial treatment policies lead to specific, locally differing microbial and resistance patterns. It is evident that recommendations for initial empirical antimicrobial treatment must be flexible enough to get modified according to local findings [1, 25, 39]. The change of microbial patterns and rates of microbial resistance must be recognised at the local level in order to modify general antimicrobial treatment policies [39]. Data obtained by surveillance cultures based on local epidemiological studies provide valuable information on potential pathogens and their susceptibility patterns. Regular updates of data on potential pathogens of HAP indicating trends in microbial and resistance patterns are mandatory. Investigation of each case of treatment failure is highly recommended. These data are particularly useful in order to identify patient related risk factors and microorganisms typically associated with treatment failure in the individual setting. The distribution of pathogens responsible for the majority of antimicrobial treatment failures is widely divergent and depends on local peculiarities [36, 67].

In the meantime, it is the physicians bias to judge the condition of the patient in view of all available clinical, laboratory, and radiographical information in order to increase the pretest probability for the presence or absence of HAP as much as possible.

Summary

In view of the emerging antibiotic resistance of microorganisms responsible for nosocomial pneumonia the choice of the appropriate antibiotic is a crucial issue. Although better treatment options, like new broad spectrum antibiotics are available, antimicrobial resistance is increasing worldwide. Therefore the clinician depends on guidelines to choose the appropriate antibiotic substance, as early antibiotic treatment
is crucial for favourable outcome and the initial antimicrobial therapy for hospital acquired pneumonia (HAP) must always be empirical. The following aspects should be considered: 1) severity of the pneumonia; 2) time point of occurrence; and 3) specific risk factors. Further to this the selection of antimicrobial agents has to consider local microbial and resistance patterns. As regards the aetiology of HAP in general a high rate of Gram-negative bacteria like Gram-negative rods (mostly Escherichia coli, Klebsiella spp., Enterobacter spp., Serratia spp. Proteus spp.), as well as potentially multiresistant pathogens like Pseudomonas aeruginosa, Acinetobacter spp. and Stenotrophomonas spp. have been repeatedly reported and are responsible for 55–85% of HAP cases. Gram-positive bacteria as Staphylococcus aureus have increasingly gained importance being involved in 20–30% of HAP events. Two promising drugs have been investigated in nosocomial pneumonia due to Gram-positive pathogens, quinopristin/dalfopristin and linezolid. Linezolid offers some clear advantages compared to glycopeptides that have been one of the last therapeutic options for infections due to multiresistant Gram-positive microorganisms, including methicillin-resistant S. aureus.

Some aspects of antibiotic treatment are still under controversial discussion as the duration of antibiotic treatment, the status of aminoglycosides or the role of monotherapy. However any antimicrobial treatment regimen exhibits a specific selection pressure. As a consequence past antimicrobial treatment policies lead to specific, locally differing microbial and resistance patterns. Therefore it is evident that recommendations for initial empirical antimicrobial treatment must be flexible enough to get modified according to local findings.

Keywords: Antibiotic resistance, antibiotic treatment, duration of treatment, monotherapy, nosocomial pneumonia, ventilator-associated pneumonia.

References


