

## ANTIBIOTICS IN THE INTENSIVE CARE UNIT (II)

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### REZUMAT

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A doua parte a acestui articol discută despre una dintre cele mai importante infecții nosocomiale: pneumonia dobândită în cursul spitalizării. Pneumonia intraspitalicească este una dintre cele mai importante boli din punct de vedere al mortalității, morbidității și costurilor tratamentului și reprezintă cea mai importantă infecție din secția de terapie intensivă. Semnele clinice nespecifice întârzie diagnosticul, în special pentru că afecțiunile variate prezente la această grupă de pacienți pot imita o boală pulmonară. Creșterea numărului de tulpini rezistente și caracterul endemic al organismelor cu rezistență multiplă în multe unități de terapie intensivă ridică probleme suplimentare. Acest review va discuta câteva aspecte legate de diagnosticul și managementul pneumoniilor intraspitalicești. Investigațiile microbiologice vor beneficia de o atenție specială, deoarece cresc specificitatea diagnostică și permit o utilizare mai rațională a antibioticelor, ducând astfel la o reducere a rezistenței microbiene.

**Cuvinte cheie:** infecții nosocomiale, pneumonia dobândită în cursul spitalizării, terapie intensivă

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### ABSTRACT

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The second part of this article series will shift our focus to one of the most important nosocomial infections, to the hospital-acquired pneumonias. Hospital acquired pneumonia is one of the major diseases in terms of mortality, morbidity and treatment costs and the most important infection in the Intensive Care Unit (ICU) setting. The non-specific clinical signs hamper the diagnosis, especially because various pathologies present in this patient population may mimic or affect the lung. The rising resistance patterns and the endemicity of MDR organisms in many ICUs pose additional problems. This review will discuss some of the issues pertinent to the diagnosis and management of hospital acquired pneumonia. The microbiologic work-up will be particularly emphasized, as it enhances the specificity of the diagnosis and permits a more judicious use of antibiotics, thus minimizing the resistance problem.

**Key Words:** nosocomial infections, hospital-acquired pneumonia, Intensive Care Unit

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### HOSPITAL ACQUIRED PNEUMONIA

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**Definition:** Hospital acquired pneumonia (HAP) is an infection of the lungs that develops more than 48 hours after admission of the patient to the hospital. HAP is more often bacterial in origin, viral or fungal agents being less often reported.<sup>1,2</sup> HAP is the second

most frequent nosocomial infection and the leading cause of death from nosocomial infections. Several studies report an increased length of stay, morbidity and costs in patients with HAP.<sup>1-4</sup> In the intensive care unit, hospital acquired pneumonia is the most frequent nosocomial infection, being followed by urinary tract infections, intravascular device-related bacteremias and surgical site infections (SSI).<sup>5</sup>

In the European Prevalence of Infection in Intensive Care (EPIC) study, ventilator associated pneumonia accounted for some 45% of all infections in European Intensive Care Units (ICU).<sup>6,7</sup>

Based on the epidemiology, pneumonia is classified as follows:<sup>1,2</sup>

- Community-Associated Pneumonia: is acquired before admission to the hospital and the patient has no risk factors for healthcare-associated pneumonia.<sup>1,8</sup>

- Healthcare-Associated Pneumonia (HCAP): is already present at the time of the patient's admission

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Received for publication: Aug. 25, 2005. Revised: Sep. 23, 2005.

to the hospital and the patient presents with at least one risk factor related to healthcare, e.g. chronic dialysis, home infusion therapy, home wound therapy, residence in a nursing home or chronic care facility.

- Hospital-Associated Pneumonia (HAP): develops more than 48 hours after the patient is admitted to the hospital.<sup>1,2,9</sup>

- Ventilator-Associated Pneumonia (VAP): develops more than 48 hours after hospital admission in a patient requiring mechanical ventilation.<sup>1,2,9</sup>

The most important of these entities in the ICU is represented by VAP. VAP, which was well as HAP, may be further classified into:

- Early-onset VAP – when the onset of the infection occurs more than 48 hours after, but before the 5th day of ventilation (usually during the first 96 hours, but variably defined in literature as VAP developing within 4-7 days).<sup>1,10</sup>

- Late-onset VAP – variably defined as VAP developing more than 5-7 days after the onset of mechanical ventilation.<sup>10</sup>

It is important to differentiate these two forms of VAP because of their different etiologies, treatment options and outcomes. Early-onset VAP is more likely to be due to antibiotic-sensitive bacteria and shows a better response to the antibiotic therapy, while late-onset VAP is more often caused by multiple drug-resistant (MDR) pathogens and has a worse outcome.<sup>1</sup> Even patients with early onset HAP or VAP may be infected with MDR-organisms, especially if they received prior antibiotic treatment or have been hospitalized during the last 90 days. This subset of patients may require the same treatment as patients with late onset pneumonia.<sup>1</sup>

## **EPIDEMIOLOGY AND ECONOMICAL ASPECTS**

Most authors agree that hospital acquired pneumonia is the leading nosocomial infection both because of its high incidence and its dismal prognosis. Patients with HAP have a substantially higher mortality, morbidity and contribute significantly to higher hospital costs.<sup>11</sup>

In the United States alone, there are some 300,000 episodes of HAP (mostly VAP) each year, with an incidence of 5-10 for every 1000 hospital admissions.<sup>1</sup>

The incidence of these infections is variable depending upon the clinical setting and on the method of reporting HAP rates.<sup>12</sup> The highest rate is encountered in intensive care units: patients in the

ICU have a 5 to 10 times higher rate of nosocomial pulmonary infections compared to those on a general ward.<sup>11</sup> In a recent systematic review, the cumulative incidence of developing VAP in patients receiving mechanical ventilation was 9.7% overall, varying between 9.1% in mixed medical-surgical ICUs and 17% in medical ICUs.<sup>13</sup> As previously stated, there are marked differences in the incidence of VAP (or HAP) depending on the denominator used, e.g. 22.8 per 1,000 ICU days, 29.6 per 1,000 ICU days at risk and 35.7 per 1,000 ventilator-days for first episode VAP based on the data from a Swiss University Hospital.<sup>12</sup> The common method of reporting VAP incidence is per 1,000 patient days, however this method does not take account of the main risk factor (ventilation), severely underestimating the true incidence of infection. The preferred method of reporting is per 1,000 ventilator days, although even this is not always ideal for comparing inter-hospital rates. Some 50 cases with VAP are diagnosed each year in the general ICU of the County Hospital Timișoara (unpublished data for 2003 and 2004).

According to the National Nosocomial Infections Surveillance System, HAP accounts for 25% of ICU infections in the US, with the vast majority of HAP episodes (90%) in the ICU occurring during mechanical ventilation. More than 50% of the antibiotics prescribed in the ICU are for VAP.<sup>1</sup>

Various crude mortality rates have been reported for patients with nosocomial pneumonia depending strongly on the case-mix and severity scores of the individual patients. Reported rates range between 54.2% in a study by Fagon in ventilated patients (1988-1990), 55% in a study by Cunnion in a surgical ICU with 95% of the patients ventilated (1987-1991) and 20.3% in non-ICU patients in a study by Leu (1982-1983).<sup>11,14</sup> HAP accounts for 15% of all hospital-associated deaths.<sup>11</sup>

The attributable mortality to VAP accounts for up to 50% of all-cause mortality,<sup>1</sup> however, other studies failed to detect an excess mortality in patients with VAP.<sup>4</sup> A recent systematic review calculated an odds-ratio for ICU-mortality of 2.03, nevertheless the results should be interpreted with caution due to significant statistical heterogeneity.<sup>13</sup>

## **ETIOLOGY OF NOSOCOMIAL PNEUMONIA**

There are significant differences in the pathogens responsible for nosocomial pneumonia between ventilated and non-ventilated patients.

VAP is a common complication in mechanically ventilated patients and is the most severe form of the hospital acquired pneumonias.

The microbial pathogens causing VAP may originate from endogenous sources like the oropharynx or the digestive tract, which they may colonize, or they may be transmitted by the ICU staff during specific maneuvers. In the latter case the pathogens originate from environmental surfaces or from other patients.<sup>10</sup>

The most common pathogens are *Pseudomonas spp.* and other resistant gram negative bacilli, *Enterobacteriaceae*, *Staphylococcus aureus* and other staphylococci, *Haemophilus influenzae* and various streptococci.<sup>10</sup>

Among 108 long-term ventilated patients in a 2001 European study, 49 (48%) developed one episode or consecutive episodes of VAP to a total number of 60 individual episodes.<sup>6</sup> The etiologic diagnosis was based on quantitative cultures from broncho-alveolar lavage (BAL) or protected-specimen brush (PSB) samples, or from tracheobronchial secretions (TBS).

The pathogens more frequently isolated were *S. aureus* in 38%, *Pseudomonas aeruginosa* in 10%, *H. influenzae* in 10% and *Klebsiella spp.* in 9% of cases.<sup>6</sup>

As previously stated, the microbial flora shows marked differences in early onset vs. that in late-onset pneumonia. In the former, the most often encountered pathogens are *Streptococcus pneumoniae*, *H. influenzae*, antibiotic sensitive enterobacteriaceae, and methicillin sensitive *S. aureus* (MSSA).<sup>10,15</sup>

In late onset pneumonia, the microbial flora is comprised mainly of *P. aeruginosa*, *Acinetobacter spp.*, MRSA and antibiotic resistant enterobacteriaceae.<sup>10,15</sup> This distinction between early and late onset pneumonia is important because the latter is due to pathogens that are intrinsically more resistant and potentially multiple drug resistant (MDR). VAP may be monomicrobial, but in up to one half of cases it is polymicrobial in origin.<sup>16</sup> Rare causes of pneumonia include various other oral and anaerobic bacteria.

Both VAP and the other forms of nosocomial pneumonia may have a non-bacterial etiology. Various causes include viruses like influenza, other respiratory viruses, cytomegalovirus, other herpes viruses, measles and many more; fungi such as *Candida spp.*, *Aspergillus spp.*, other moulds, and *Pneumocystis (carinii) jiroveci*.

The causative agents of VAP are in most cases (57% in a study by Trouillet cited by Park) multiple drug resistant.<sup>10</sup> This percentage rises still further in VAP, that develops more than seven days after initiation of mechanical ventilation.<sup>10</sup>

MDR pathogens include: *P. aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia* and MRSA.<sup>10</sup>

**Table 1.** Known and suspected microbiologic causes of VAP<sup>7</sup>

<b>Gram-positive cocci</b>	<b>Anaerobic bacteria</b>
<i>Staphylococcus aureus</i>	<b>Bacilli</b>
<i>Streptococcus pneumoniae</i>	<i>Bacteroides species</i>
Other streptococci	<i>Fusobacterium species</i>
Coagulase-negative staphylococci	<i>Prevotella species, Actinomyces species</i>
<b>Gram-positive rods</b>	<b>Cocci</b>
<i>Corynebacterium species</i> (diphtheroids)	<i>Veillonella spp.</i>
<i>Listeria monocytogenes</i>	Peptostreptococci
<i>Nocardia species</i>	<b>"Atypical bacteria"</b>
<b>Aerobic Gram-negative bacilli</b>	<i>Legionella spp.</i>
<i>Haemophilus influenzae</i>	<i>Legionella</i> -like amoebial pathogens
<b>Lactose fermenting gram negative bacilli</b>	<i>Mycoplasma pneumoniae</i>
Enterobacteriaceae/ enteric gram negative bacilli	<i>Chlamidia pneumoniae</i>
<i>Escherichia coli</i>	<b>Fungi</b>
<i>Klebsiella spp.</i>	<i>Candida spp.</i>
<i>Enterobacter spp.</i>	<i>Aspergillus spp.</i> and other moulds
<i>Proteus spp.</i>	<i>Pneumocystis (carinii) jiroveci</i>
<i>Serratia spp.</i>	<b>Miscellaneous causes</b>
<i>Citrobacter spp.</i>	<i>Mycobacterium tuberculosis</i>
<i>Hafnia alvei</i>	<i>Strongyloides stercoralis</i>
<b>Non-fermenting Gram-negative bacilli</b>	
<i>Pseudomonas aeruginosa</i>	
<i>Acinetobacter calcoaceticus</i> and <i>baumannii</i>	
<i>Stenotrophomonas maltophilia</i>	
<i>Burkholderia cepacia</i>	
<b>Gram-negative cocci</b>	
<i>Neisseria spp.</i>	
<i>Moraxella spp.</i>	

### Risk factors

In a study on 358 patients admitted in a medical ICU, six risk factors were identified as important for the development of VAP using logistic regression analysis:<sup>17</sup>

1. The duration of mechanical ventilation: the authors found a dose-response relation for the mechanical ventilation rather than a threshold value above which the risk of VAP increases dramatically. The risk of VAP is continuously present during the mechanical ventilation.

2. Cumulative pack-years of smoking provides a useful quantitative evaluation of the risk to develop VAP (more accurate than the presence or absence of COPD).<sup>17</sup>

3. High PEEP levels ( $\geq 7.5$  cm H<sub>2</sub>O) may reflect a severe respiratory failure, the presence of ARDS or possibly the mechanical effects of PEEP on local defenses.

4. Admission serum albumin level  $\leq 2.2$  g/dl reflects a poor nutritional status, which may influence the host defense. This was previously reported as a risk factor for nosocomial pneumonia, albeit not specifically for ventilated patients.

5. Absence of antimicrobial therapy as a risk factor is controversial: patients receiving antibiotics had a significantly lower risk for developing early onset pneumonia (which is caused mainly by gram-positive cocci or *H. influenzae*), but this benefit may be outweighed by the predisposition to select bacteria

with a high degree of antimicrobial resistance, which produce late onset VAP.<sup>17</sup>

6. Colonization of the airway at the time of intubation is a significant risk factor.

In the meantime, several risk factors proposed in previous studies were not significantly related to VAP in this study: age, naso-oroenteric tubes, depressed consciousness, fall-winter season, severity of illness, use of H<sub>2</sub> blockers.

Other risk factors may also be involved in the epidemiology of VAP. In a recent study (Rello 2003) percutaneous tracheotomy performed in 99 critically ill patients who needed mechanical ventilation, was associated with pneumonia in 18% of cases (median of 7 days after tracheotomy) with *P. aeruginosa* being the most frequently isolated pathogen, followed by other gram negative bacilli.<sup>18</sup>

**Pathogenesis:** the lower respiratory tract is normally sterile. To produce a pneumonia (VAP in this case), the pathogens must penetrate into these airways where they can adhere to the mucosa and produce an infection.<sup>19</sup>

Four mechanisms may allow the pathogens to reach the lower respiratory tract:

1. Aspiration of the secretions from the lower respiratory tract when these are containing microorganisms. These secretions may originate from the upper respiratory tract or they may represent infected gastric content that gains access to the oropharynx by reflux. Aspiration of oropharyngeal content and leakage of bacteria around the endotracheal tube cuff is the main route of the bacterial penetration into the airways.<sup>9</sup>

2. Direct extension of a contiguous infection: e.g. a pleural infection.

3. Inhalation of contaminated air or medical aerosols.

4. By the hematogenous route the microorganisms may be carried from a remote infected site, which may be healthcare related (central venous catheter or urinary catheter).<sup>19</sup>

The sources of pathogens in HAP and VAP are: healthcare devices, the environment (air, water), and the people (staff or other patients).<sup>9</sup>

**Epidemic VAP** represents an outbreak, which may be due to the contamination of the medical equipment such as bronchoscopes and other endoscopes. Such an outbreak should always be suspected when in two or more cases the same unusual organism was isolated. In one such outbreak, 16 episodes of hospital acquired pneumonia due to *Burkholderia cepacia* were described due to the contamination of inhaled medication

nebulizer reservoirs.<sup>19</sup>

Bronchoscopy was involved in the transmission of nosocomial infections with *P. aeruginosa*, *Mycobacterium tuberculosis* and other, nontuberculous, mycobacteria.<sup>19</sup>

Outbreaks of SARS (severe acute respiratory syndrome), influenza A, or respiratory syncytial virus were also reported. All these infections were airborne.

*Legionella pneumophila*, another airborne infection, may also occur in the hospital setting.

**Endemic VAP:** the main pathogenic mechanism of endemic VAP and HAP is aspiration of the oropharyngeal organisms (gross or microaspiration), which results in colonization of the respiratory tract and afterwards may be followed by infection.<sup>9,19</sup>

The progression may be from the colonization of the trachea to tracheobronchitis and to pneumonia.<sup>9</sup> The colonization of the oropharynx may occur with the normal bacterial flora composed of viridans streptococci, *Haemophilus spp*, and anaerobes.<sup>19</sup>

In the critically ill patient the oral flora shifts to a flora composed predominantly of aerobic gram negative bacilli and *S. aureus*.

The progression to infection is favored by the mucosal decrease in IgA, increased protease production, denuded mucous membranes, and elevation of the airway pH.<sup>19</sup>

**Aspiration may be facilitated by:**

- a. Supine body position: in a study, aspiration in patients in a completely supine position (0°) was compared with that in semirecumbent position (45°), using radioactive labeled enteral feeding.<sup>9</sup>

- b. Enteral feeding itself is a risk factor for HAP because of the higher risk of aspiration of gastric contents. However, parenteral nutrition has its own weaknesses that outweigh the potential benefit of avoiding aspiration (infection of intravascular devices, microbial enteral translocation, higher costs).<sup>9</sup>

## **DIAGNOSIS OF HOSPITAL ACQUIRED PNEUMONIA**

### **The clinical approach**

The clinical diagnosis of HAP is suspected on the presence of a new or progressive lung infiltrate plus two of the following criteria: fever, purulent sputum, leukocytosis and decline in oxygenation.<sup>9</sup>

HAP is a difficult diagnosis and the clinical criteria of diagnosis have a low specificity. The accuracy of the clinical diagnosis of VAP was studied using autopsy findings, or quantitative cultures of either protected specimen brush (PSB) or bronchoalveolar

lavage (BAL). A study in which the diagnostic standard was histology plus positive microbiologic cultures of immediate postmortem lung samples, the diagnosis based on chest infiltrates plus two clinical criteria had a sensitivity of 69% and a specificity of 75%.<sup>9</sup>

Lung infiltrates may have etiologies other than pneumonia, e.g. cardiac (heart failure), ARDS and pulmonary embolism.

When fever, leukocytosis, purulent sputum and a positive culture of sputum or tracheal aspirate are present without new lung infiltrate, the diagnosis of nosocomial tracheobronchitis is considered.<sup>9</sup>

The use of a combination of symptoms and signs to diagnose HAP and VAP improves the specificity of the diagnosis.<sup>9</sup> The clinical pulmonary infection score (CPIS) is used to improve the clinical diagnosis and to help in deciding when to start antibiotherapy.<sup>20</sup>

**Table 2.** Clinical pulmonary score calculation - CPIS (from Fabregas 2002, adapted from Pugin and Singh)<sup>20</sup>

<b>Temperature</b>
≥ 36.5 and ≤ 38.4 = 0 points
≥ 38.5 and ≤ 38.9 = 1 point
≥ 39 and ≤ 36 = 2 points
<b>Blood leucocyte, mm<sup>3</sup></b>
≥ 4000 and ≤ 11000 = 0 points
< 4000 or > 11000 = 1 point + band forms ≥ 50 % = add 1 point
<b>Tracheal secretions</b>
Absence of tracheal secretions = 0 points
Presence of nonpurulent tracheal secretions = 1 point
Presence of purulent tracheal secretions = 2 points
<b>Oxygenation: PaO<sub>2</sub> / FiO<sub>2</sub>, mm Hg</b>
240 or ARDS (ARDS defined as Pa O <sub>2</sub> / FiO <sub>2</sub> lower or equal to 200, pulmonary capillary wedge pressure ≤ 18 mmHg and acute bilateral infiltrates) = 0 points
≤ 240 and no ARDS = 2 points
<b>Pulmonary radiography</b>
No infiltrate = 0 points
Diffuse or patchy infiltrate = 1 point
Localized infiltrate = 2 points
<b>Progression of pulmonary infiltrate</b>
No radiographic progression = 0 points
Radiographic progression (after CHF and ARDS excluded) = 2 points
<b>Culture of tracheal aspirate</b>
Pathogenic bacteria cultured in rare or light quantity or no growth = 0 points
Pathogenic bacteria cultured in moderate or heavy quantity = 1 point
Same pathogenic bacteria seen on Gram stain, add 1 point

CPIS was measured at baseline using the first five criteria and it was reassessed at 72 hours using all the seven criteria. A score of > 6 was considered suggestive of pneumonia. In spite of its high sensitivity, this score still lacks specificity. It is more advisable to use

this score as a diagnostic aid to decide when to start an empiric antibiotherapy given the clinical suspicion of pneumonia.<sup>20</sup>

### The bacteriological approach

The etiologic diagnosis is generally based on respiratory tract aspirates: endotracheal aspirates, BAL (bronchoalveolar lavage) and PSB (protected specimen brush).

These techniques are used to take samples from the respiratory tract and to perform quantitative cultures.

It is important to make the difference between infection and colonization because it is crucial to avoid undertreatment or overtreatment of the patients. The difference is made by the quantification of the pathogens and the threshold between colonization and infection depends on the technique and the level of suspicion.<sup>9,21</sup>

Endotracheal aspirates can and should be cultured quantitatively. With a threshold of 10<sup>6</sup> CFU/ml the sensitivity of this method ranges from 38% to 82% (mean 76 ± 9%) and the specificity is in the range 72-85% (mean 75 ± 28).<sup>9,22</sup>

BAL – bronchoalveolar lavage studies use a threshold of 10<sup>4</sup> to 10<sup>5</sup> CFU/ml. The sensitivity is 42-93% with a mean of 73 ± 18% - and a specificity of 45 – 100% with a mean of 82 ± 19% as presented by the American Thoracic Society (ATS) documents.<sup>9,23</sup>

Twelve studies used the detection of intracellular organisms as the diagnostic criterion. The diagnosis of pneumonia was confirmed if 2-5% of the recovered cells demonstrated intracellular bacteria. The American Thoracic Society guidelines (2004) report a mean sensitivity of 69 ± 20% and a specificity of 75 ± 28% if this approach is used.<sup>9</sup>

PSB – protected specimen brush studies use a threshold of 10<sup>3</sup> CFU/ml or more. The sensitivity ranges from 33% to 100% (mean 66 ± 19 %) and the specificity is 50-100% (mean 90 ± 15%).<sup>9</sup>

The BAL may be obtained bronchoscopically or not. Bronchoscopy is not always available especially in the evenings.<sup>9</sup>

Gram stains may be obtained from the bronchial samples and are useful for the beginning of the antibiotherapy: it may show the presence of gram positive cocci and/or gram negative bacilli. This approach has the advantage of allowing the selection of an optimal antibiotic treatment, particularly in the selection of empiric MRSA coverage.

Some authors demonstrated that the Gram stain, while useful for the early diagnosis of VAP, is unreliable in the empiric choice of antibiotics.

A positive culture in the absence of a specific

radiological image may represent only colonisation. On the other hand, a negative culture from the respiratory tract in an intubated patient is strong evidence against pneumonia and a different site of infection must be suspected.

The overall sensitivity of blood cultures is less than 25%. In the rare case of a positive blood culture, the organisms isolated may have a different origin even in the case of proven VAP. Blood cultures play a minor role in the microbiologic diagnosis of VAP.

## **TREATMENT OF HOSPITAL ACQUIRED PNEUMONIA (HAP AND VAP)**

Prompt antimicrobial therapy is the mainstay of a successful treatment.

To better understand the judgment behind the antibiotherapy, several points must be addressed: the choice of the drug, the appropriate dose and way of administration, duration of the treatment, drug associations, and monitoring of the therapy. Some basic knowledge about antimicrobial drugs is required to answer these questions.

### **Classification of the antimicrobial drugs**

Different classes of antibiotics can be distinguished based on their mechanism of action:<sup>25</sup>

**Cell wall-active drugs:**  $\beta$ -lactams and glycopeptides.

**Beta lactams** comprise penicillins, cephalosporins, monobactams and carbapenems. They act on the cell walls by inhibiting the cell wall synthesis through binding to special sites called penicillin-binding proteins (PBP).

**Glycopeptides:** vancomycin and teicoplanin inhibit the cell wall synthesis by binding to peptidoglycan precursor molecules.

**Protein synthesis inhibitors:** aminoglycosides, macrolides, tetracyclines, lincosamides, oxazolidinones and streptogramins act by binding irreversibly to various ribosomal subunits, thus inhibiting protein synthesis.

**DNA synthesis inhibitors:** fluoroquinolones inhibit DNA synthesis by blocking DNA gyrase and topoisomerase.

**RNA synthesis inhibitors:** rifamycins inhibit DNA dependent RNA polymerase.

**Antimetabolites:** sulfonamides inhibit folic acid synthesis.

**Miscellaneous mechanisms:** polymyxins (colistin is polymyxin E) behave as detergents on the bacterial plasma membrane thus disrupting the normal function through permeability changes.

Nitroimidazoles (metronidazol) produce direct

DNA damage.

### **Pharmacokinetics (PK) and pharmacodynamics (PD)**

The effectiveness of an antimicrobial drug is related both to its mechanism of action and to its pharmacokinetic profile. The pharmacokinetics determines the concentration of the drug in blood and at the site of infection.

The blood concentration of any intravenously given drug rises rapidly (immediately) after a single dose reaching a maximum and declining continuously thereafter. If the drug is given repeatedly at regular intervals, the drug level will achieve a steady state characterized by a maximum (peak) and a minimum (trough) level.

The concentration – time profile of the various antibiotics is compared to the minimal inhibitory concentration (MIC, necessary to inhibit bacterial growth by 90 %). Current antibiotics fall into one of two classes based on the pharmacodynamic mode of action: concentration-dependent and concentration-independent bacterial killing.

For concentration-dependent killing, the antibacterial activity of a drug may be best correlated with the ratio between  $C_{max}$  and the  $MIC_{90}$ . These drugs demonstrate enhanced killing with raising concentrations, the antibacterial effect showing a good correlation with high levels of the plasmatic or tissue drug levels. A  $C_{max}/MIC$  ratio above 10 is predictive of a favorable clinical and bacteriological response. This mechanism is time-independent.

The typical antibiotics to show such a pharmacodynamic (PD) profile (concentration dependent killing) are the aminoglycosides and fluoroquinolones.<sup>25</sup> The activity of these two classes can be characterized by still another PD measure, which will be detailed briefly in the next paragraph.

The curve that expresses the correlation between drug concentration and time delimits a zone known as area under the curve (AUC). The ratio between this area and the minimal inhibitory concentration (AUC/MIC) expresses the effectiveness of an antimicrobial: a value exceeding 125 predicts a favorable clinical and bacteriological response (concentration dependent killing).<sup>25</sup>

On the other hand, the bacterial killing can be concentration-independent. The antibacterial activity correlates best with the length of exposure to drug concentrations above the MIC. The maximal effect is achieved at concentrations 4-5 times above the MIC. Raising the concentration further does not bring any additional benefit.

This kind of effect is seen for most cell-wall active antibiotics: if the concentration exceeds MIC for more than 40% of the dosing interval inhibition of bacterial growth is likely and if this exceeds 60-70 % of the interval a maximal response is obtained.<sup>25</sup>

- The post-antibiotic effect is characterized by an extended period of inhibition of the bacterial growth, which persists after the drug concentration has decreased below the MIC. This is characteristic for aminoglycosides and fluoroquinolones and together with the concentration effect allows for once daily dosage.

- The antibiotics which have a time dependent effect and have little or no postantibiotic effect must be administered in small frequent doses or in a continuous intravenous infusion.

**Penetration into the lungs** of the antimicrobial agent is of main importance in determining the effectiveness of a particular treatment in pneumonia.

Vancomycine, aminoglycosides and  $\beta$ -lactams penetrate into the lung tissues by diffusion. On the other hand, macrolides and fluoroquinolones are concentrated in the lung lining fluid, alveolar macrophages and leukocytes.

The lung concentration of an antibiotic is difficult to measure in individual patients. Methods used in experimental settings include determining antibiotic concentration in the bronchoalveolar lavage fluid and through microdialysis. This latter design was successfully applied to patients who had thoracic surgery. All these methods are useful only for research and not in the routine clinical practice.<sup>25</sup>

For drugs with poor lung penetration, an interesting approach is to deliver the drug directly through the airways. This mode of administration is well established in cystic fibrosis patients where colistin or high levels of tobramycin are administered for MDR *P. aeruginosa*.

**Microbial resistance** is unfortunately particularly prominent in the ICU setting and as such, it poses serious problems in the treatment of nosocomial infections and especially VAP.

Currently, MDR bacteria are involved in the etiology of pneumonia in most ICUs, as already discussed. The choice of an antibiotic has to consider the presence of these resistant pathogens, especially because most evidence points to a worse outcome if the initial antibiotic therapy is inadequate. Multiple studies show lower mortality rates when antibiotherapy is adequate from the beginning, compared to the cases when the initial antibiotherapy did not cover the pathogen and the treatment was changed only after the

arrival of the culture results.<sup>25-27</sup>

“Appropriate” antibiotherapy is defined as treatment with a drug against which the pathogen is susceptible, while “adequate” antibiotherapy means that the appropriate drug is chosen and given in optimal dosages, by the correct route for a correct duration of time and in a good association.<sup>9,26</sup>

For adequate antibiotherapy, it is necessary to choose the right drug from the beginning, although the pathogen is still unknown. The antimicrobial drug or drugs must therefore be chosen to cover the most likely pathogen/s involved in a probabilistic manner.<sup>28</sup> This implies a very good knowledge of the local pathogenic flora and resistance patterns.

In most ICUs throughout Europe and North America the major pathogens implicated in VAP are various nonfermentative or fermentative gram negative bacilli and in a variable but constant percentage staphylococci and enterococci.<sup>8,11,28</sup>

The choice of the antibiotic treatment, also called “empiric therapy” is based on the local microbiologic data from the specific medical care facility (ICU in the case of VAP).<sup>25,29</sup> The chosen therapy must cover all likely pathogens in order to minimize the chance of inadequate initial therapy and should be instituted promptly.

Before the beginning of the antimicrobial therapy it is essential to harvest either bronchial aspirate samples or BAL fluid or a PSB for further microbiologic work-up. The initial treatment should be adapted based on the results of the cultures, which, in most cases, should be available within 72 hours.<sup>29</sup>

This strategy will also give the opportunity to switch from an initial broad spectrum antibiotic to a narrow spectrum drug when targeting a susceptible microbial agent, thus preventing development of resistance and reducing the costs without jeopardizing patient safety.<sup>9,25,29</sup> Therefore this strategy is also known as “de-escalation therapy”.<sup>30</sup>

#### **Selecting the initial antimicrobial therapy for VAP**

The selection of the antimicrobial therapy is based on the likelihood of an infection with MDR pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter spp*, *Stenotrophomonas maltophilia*, and methicillin-resistant *Staphylococcus aureus* (MRSA). This risk is related both to the length of hospital stay prior to the onset of nosocomial pneumonia and to other risk factors for MDR pathogens, like previous antibiotic therapy.<sup>25</sup>

In early onset VAP without further risk factors for MDR pathogens, the most likely pathogens have a resistance phenotype more closely resembling

community-acquired agents, which are sensitive to most antibiotics. Empiric treatment may be started with a single antibiotic, e.g. a non-pseudomonal 3<sup>rd</sup> generation cephalosporin or a fluoroquinolone or Ampicillin/Sulbactam or Ertapenem.

**Table 3.** Antimicrobial treatment of Ventilator Associated Pneumonia (from David Park)<sup>25</sup>

Potential pathogens	Recommended Antibiotic Therapy
<i>Streptococcus pneumoniae</i>	Ceftriaxone or
<i>Haemophilus influenzae</i>	Levofloxacin, Moxifloxacin, Ciprofloxacin or
MSSA	Ampicillin/Sulbactam or
Gram negative bacilli, sensitive to antibiotics	Ertapenem
<i>Escherichia coli</i>	
<i>Klebsiella pneumoniae</i>	
Enterobacter species	
Proteus species	
<i>Serratia marcescens</i>	

### Potential pathogens and initial empiric antimicrobial therapy for early onset VAP in a patient without risk factors for MDR pathogens

The choice of the antimicrobial agent depends on the local resistance pattern, costs, availability and history of allergy.

In late onset VAP or in the presence of risk factors for MDR pathogens, the treatment should be started with a broad-spectrum combination therapy. A study by Trouillet (quoted by Park) demonstrated that imipenem with amikacin and vancomycin had the best coverage of all pathogens in late onset VAP.<sup>25,31</sup> The recommended therapy should include an antipseudomonal cell wall active agent, e.g. a carbapenem, cephalosporin or  $\beta$ -lactam –  $\beta$ -lactamase inhibitor plus an antipseudomonal aminoglycoside or quinolone.

Antistaphylococcal antibiotics such as linezolid or vancomycin must be included if the local rate of MRSA is high. If legionellosis is likely, a fluoroquinolone or a macrolide must be prescribed (instead of e.g. the aminoglycoside).

One point deserves special emphasis: *P. aeruginosa* should always be covered due to its propensity for fulminant disease and intrinsic resistance to many antibacterial agents. This is also one of the reasons, the ATS guidelines recommend combination therapy.<sup>9</sup> Despite these recommendations, there is currently no strong support for such a strategy. A recent meta-analysis found no benefit for  $\beta$ -lactam – aminoglycoside combinations (with the possible exception in neutropenic patients).<sup>32</sup> This combination did not offer any survival benefit while contributing to an increased rate of adverse events. Neither did the subgroup of patients with *P. aeruginosa* infections profit from, nor did the combination prevent the

emergence of resistance. Considering the poor penetration of aminoglycosides in the lung (bronchial secretion-to-serum drug-concentration ratios of 0.2 to 0.6 – especially deleterious for a concentration-dependent bacterial killing), the modified volumes of distribution and pharmacokinetic properties in critically ill patients, the adverse events and the rising resistance (< 70% of isolates susceptible in high-risk regions), aminoglycosides cannot be recommended for routine therapy.<sup>33-35</sup> A possible exception is the use of inhalational tobramycin as adjunctive therapy for MDR organisms, because the concentration achieved is several fold higher than after a usual dosing regimen.

Fluoroquinolones were equally effective as carbapenems in a recent meta-analysis for treatment of nosocomial pneumonia, a result further confirmed by a recent subgroup analysis from a randomised trial.<sup>36,37</sup> Despite their favorable pharmacokinetic profile and excellent penetration in lung tissue (bronchial secretion-to-serum drug-concentration ratios of 0.8-2), the recent increase in drug resistance and, even of greater concern the rise in first-step mutations (40% of fluoroquinolone-susceptible *E. coli* harboured a first-stage mutation) and subsequent risk for clinical failure, raises some important questions.<sup>33,36</sup> The poor probability of achieving bactericidal targets in a recent Monte-Carlo simulation (43%-55% depending on model of HAP) combined with the risk for collateral damage seriously impedes the routine use of fluoroquinolones.<sup>39,40</sup>

For a thorough discussion see also the first part in this article series.<sup>40</sup>

**Table 4.** Antimicrobial treatment of Ventilator Associated Pneumonia (from David Park)<sup>25</sup>

Potential pathogens	Recommended Antibiotic Therapy
Multidrug resistant pathogens	Antipseudomonal cephalosporin (cefepim or ceftazidim) or
<i>Pseudomonas aeruginosa</i>	Antipseudomonal carbapenem (imipenem or meropenem) or
<i>Acinetobacter species</i>	$\beta$ -lactam/ $\beta$ -lactamase inhibitor (piperacilin/tazobactam)
<i>Stenotrophomonas maltophilia</i>	plus
Enteric bacilli producing ESBL	Antipseudomonal fluoroquinolones
MRSA	(ciprofloxacin or levofloxacin) or
<i>Legionella pneumophylla</i>	Aminoglycoside (amikacin, gentamicin, tobramycin) plus linezolid or vancomycin

### Potential pathogens and recommended initial antimicrobial treatment for late onset Ventilator Associated Pneumonia or in the presence of risk factors.<sup>25</sup> Dosages, administration schedule and duration of treatment.

The recommended dosages are: Ceftriaxone 1-2 g/24 h, Cefepime 1-2 g/24 h, Ceftazidime 2g/8h,

Ertapenem 1g/24h, Imipenem 500mg/6h or 1 g/8h or 2 g/24h in a continuous intravenous infusion (automatic syringe pump), Meropenem 1 g/8h, Ampicillin/Sulbactam 3 g/6h, Piperacilin/Tazobactam 4.5 g/6h, Gentamicin 7 mg/kg bw, Tobramycin 7 mg/kg bw, Amikacin 20 mg/kg bw, Moxifloxacin 400 mg/24 h, Ciprofloxacin 400mg/8h, Levofloxacin 750 mg/24h, Vancomycin 15 mg/kg bw/12h, Linezolid 600 mg/12h, Azithromycin 500mg/24h, Minocycline 100 mg/12h, Colistin 2.5-5 mg/kg bw/d in divided doses (from David Park).<sup>25</sup>

The optimal duration of antimicrobial treatment for VAP is still a subject of debate. In a randomized, double blind (until day 8) study in 51 French ICUs a total of 401 patients were treated for 8 or 15 days. The clinical effectiveness was comparable for the two groups in patients without infection with non-fermentative organisms. The shortening of the treatment to 8 days may help to reduce the emergence of MDR bacteria.<sup>42</sup>

**Specific aspects linked to "problem pathogens":** MRSA, highly resistant gram-negative bacilli and *Legionella pneumophylla*.<sup>25</sup>

*Methicillin-resistant Staphylococcus aureus* (MRSA) is frequently isolated in the ICUs being a common cause of VAP. Such patients have generally a poor outcome, as the MRSA is often resistant to other antimicrobial agents, too. Vancomycine is the traditional agent of choice against MRSA but its penetration into the lungs is poor. Consistent with this is the adverse outcome even with adequate empiric treatment.<sup>43</sup>

Linezolid is a relatively new drug belonging to a new class of drugs – the oxazolidinones. It is bacteriostatic rather than bactericidal but has a better penetration into the lungs.<sup>25</sup> Two randomized trials showed a better chance of bacterial eradication, clinical cure and hospital survival in the subgroup with MRSA VAP treated with linezolid. The absolute mortality benefit was 22%, corresponding to a number to treat of 5 patients to save one more life.<sup>44,45</sup> Linezolid is consequently the drug of choice for MRSA VAP.<sup>25</sup>

Tigecycline, which has a large spectrum of activity (both gram positive, gram negative and anaerobic pathogens), is still under evaluation for the management of VAP. Two new glycopeptides are currently in study: oritavancin and dalbavancin.

**Highly resistant gram-negative bacilli:** *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. The resistance rate is substantial for these pathogens. Imipenem and sulbactam may have the highest activity as monotherapy, unless the local level of resistance to carbapenems is very high. If this is the case, various

combinations have been proposed. Rifampin has the best *in vivo* efficacy, especially when combined with imipenem and tobramycin, although reliable clinical data is lacking.<sup>25</sup>

Colistin showed the same therapeutic effect for carbapenem-resistant *Acinetobacter* VAP as imipenem for carbapenem sensitive *Acinetobacter* VAP. The toxicity was not significantly different.<sup>46</sup> The intrabronchial administration of colistin for MDR gram-negative strains can be also considered.<sup>47</sup>

**Legionnaire's disease:** must be considered in institutions where there is a risk for *Legionella* infection. Fluoroquinolones or macrolides must be used. Rifampicine may also be used if the the new fluoroquinolones or macrolides are not available.<sup>48</sup>

## PROTOCOL FOR DIAGNOSING VAP

**Clinical suspicion of VAP:** Intubated patient with clinical signs of sepsis, fever, leucocytosis, purulent sputum and unexplained infiltrates on the plain chest radiograph. CPIS score  $\geq 6$ .<sup>32</sup>

**Gram stain:** tracheal aspirate, BAL, PSB. Look for the presence of intracellular bacteria (2-5%).

**Cultures from: tracheal aspirate, BAL, PSB**

- Cultures from the pulmonary secretions should always be obtained before the antibiotic administration.<sup>25</sup>

- The results of the quantitative cultures harvested by bronchoscopic techniques may enable a more effective treatment and increase the confidence of the staff.<sup>50</sup>

Rello et al found that 43% of patients required a change in the initial treatment based on the bronchoscopic evaluation because 27% of patients were receiving ineffective antibiotic therapy, 9% where receiving less than optimal therapy and 7% had unnecessary antibiotic therapy.<sup>50,51</sup>

## TREATMENT PROTOCOL FOR VAP

**Empiric antibiotherapy:** must be started during the first hour after the clinical diagnosis of suspicion.

**Early onset VAP (more than 48 hours, less than 5 days):**

1. Ertapenem 1g/day intravenously or
2. Ceftriaxone 2g/24 once a day i.v.
3. Levofloxacin 750 mg i.v. once a day or Moxifloxacin 400mg once a day

When the results of the cultures and the antibiogram are available the treatment may be adapted to the results or the initial medication may be

continued if the clinical course is favourable.

#### **Late onset VAP (more than 5 days):**

1. Imipenem 500mg/6 hours + Amikacin 20 mg/once a day + Vancomycin 15 mg/kg bw every 12 hours  
or

2. Ceftazidime 2g every 8 hours (or Cefepime 2g/8h) + Amikacin 20mg/kg bw once a day (or Gentamicin 7mg/kg bw once a day) + Vancomycin 15 mg/kg bw every 12 hours or Linezolid 2 x 600 mg/day.

3. Piperaciline/Tazobactam 4.5g/6h + Ciprofloxacin 400 mg/8h (or Levofloxacin 750 mg once a day) or aminoglycoside + Vancomycin 15 mg/kg bw every 12 h.

This treatment is to be continued until the results of the microbiological cultures are available.

The treatment should be continued by de-escalating it to the specific antibiotic indicated by the antibiogram.

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