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ERS TASK FORCE

Ventilator-associated pneumonia

European Task Force on ventilator-associated pneumonia
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CONTENTS

In the last decade, considerable investigational efforts have been made in the field of the management of ventilator-associated pneumonia (VAP). Several studies have provided important insights into the relationship of histology and bacteriology of VAP, which remain fundamental for all future research. Moreover, epidemiological research has allowed establishment of concepts for empiric initial antimicrobial treatment that are expected to improve clinical outcomes. Important contributions have also been made regarding prevention of VAP.

However, despite these advances, the majority of issues related to the management of VAP remain unresolved and are subject to controversy. This is particularly true for the diagnostic evaluation of the patient with suspected VAP. The lack of consensus regarding the best way to diagnose VAP explains in part why incidence rates vary widely from one study to another, from 5 to >50% of mechanically ventilated intensive care unit (ICU) patients.

In this review, a panel of experts in the field of VAP from four European societies has tried to provide an overview of the most important aspects under debate. In order to stimulate further research and discussion, presentation of the main topics was focussed on the breaking current knowledge. The issue of attributable mortality, which is also a matter of controversy, will not be addressed in this review. Each section of the review has been written in an attempt to answer three main questions: 1) what is not controversial, 2) what is still controversial and 3) what should be investigated? The following topics were reviewed: clinical diagnosis, bacteriological and histological aspects, aetiology, diagnostic techniques, antimicrobial treatment and prevention.

Clinical diagnosis of ventilator-associated pneumonia

What is not controversial? Clinical criteria for the diagnosis of VAP have a limited diagnostic accuracy. This is true for single criteria such as infiltrates in chest radiograph, fever or hypothermia, leukocytosis or leukopenia, and increase in the amount and/or purulence of tracheobronchial secretions, as well as for diagnostic rules incorporating some of these criteria.

FAGON *et al.* [1] found that clinical predictions about the presence or absence of definite and probable VAP were accurate in 62% and 84% of VAP patients, respectively. In another study assessing clinical criteria for VAP in surgical patients, numerous clinical parameters distinguished patients with suspected VAP from others. However, subsequent validation of this diagnosis by serial examination of clinical, microbiological and radiographic data could not identify predictors of patients truly having VAP [2]. A *post mortem* study found 69% sensitivity and 75% specificity for a diagnostic rule consisting of new and

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persistent infiltrates in chest radiograph, and two or three of the following: 1) fever ($>38.3°C$); 2) leukocytosis ($>12\times10^9$ mL^{-1}); or 3) purulent tracheobronchial secretions [3]. Thus, available evidence indicates that clinical diagnosis of VAP is associated with around 30–35% false-negative and 20–25% false-positive results.

Limited sensitivity and specificity are radiographic signs of VAP [4, 5]. In a *post mortem* study, no radiographic sign had an efficiency of >68%. Moreover, the presence of air bronchograms was the only radiographic sign that correlated with VAP, correctly predicting 64% of pneumonias [5].

The high rate of false-positive results is probably due to alternative diagnoses that may cause pulmonary infiltrates mimicking VAP such as alveolar haemorrhage, atelectasis, pulmonary infarction and the fibroproliferative phase of acute respiratory distress syndrome (ARDS) [6]. False-negative results may result from initial phases of pneumonia not detected on chest radiograph. In the presence of ARDS, false-negative results tend to increase due to diffuse areas of increased opacity obscuring the radiographic features of pneumonia [7].

The only alternative approach to the clinical diagnosis of VAP is the Clinical Pulmonary Infection Score (CPIS), which was developed by PUGIN *et al.* [8]. This score includes the following six weighted clinical and microbiological variables: temperature, white blood cell count, character and volume of tracheobronchial aspirate, Gram stain and culture of tracheobronchial aspirate, gas exchange ratio and chest radiograph infiltrates. This score proved to achieve 72% sensitivity and 85% specificity at a threshold of 6 in a *post mortem* study [9]. However, this definition is hampered because it includes microbiological criteria.

What is still controversial? The controversy about clinical diagnosis of VAP chiefly includes the role of clinical criteria in the assessment of suspected VAP. Whereas some authors have advocated an approach relying strictly on the results of invasive bronchoscopic diagnostic testing [10], others have insisted on an approach that keeps clinical and microbiological criteria in balance, not withholding antimicrobial treatment in the presence of cultures below the thresholds, but clinically suspected VAP [11].

The first approach is based on two interpretations: 1) that the diagnostic accuracy of clinical criteria is unacceptably low, leading to an unnecessary exposure to antimicrobial agents, an increased risk of selection of multiresistant micro-organisms by overtreatment and thereby to increased morbidity, mortality, and costs; and 2) that invasive diagnostic tools such as bronchoscopically retrieved protected specimen brush (PSB) and bronchoalveolar lavage (BAL) processed by quantitative culture and the determination of intracellular organisms (ICO) in BAL can overcome these limitations and allow a rapid and highly accurate microbiological diagnosis of VAP in the individual patient [10, 12]. In the algorithm proposed by the authors, patients with an ICO-count <5% in BAL, and PSB culture $<10^3$ colony forming units (cfu)·mL^{-1}, definitely remain untreated. Conversely, the opposite position has claimed: 1) that the limited diagnostic accuracy does not devalue the information obtained from clinical assessment; and 2) that according to a large body of evidence derived from several validation studies using strictly independent references, the operative performances of invasive and noninvasive microbiological testing are also associated with 30–40% false-negative and false-positive results [9, 11, 13, 14].

What should be investigated? Any approach to the management of suspected VAP has clinical assessment as a starting point. Therefore, there is a clear need for a consensus about a definition of clinically suspected VAP. Overall, the original criteria seem quite simplistic. As pointed out previously, the definition offered by the CPIS is not really applicable in clinical practice. A revised definition should take into account the following requirements: 1) the definition should include only clinical, radiographic, and laboratory criteria, but not microbiological results; these criteria should be reliable and easy to obtain (*e.g.* not include criteria such as colour or amount of tracheobronchial secretions); and 2) it should provide a scoring system resulting in stages of evidence for the presence of VAP (*e.g.* low/intermediate/high probability).

Several potentially useful criteria have not been systematically assessed as regards their ability to predict the presence of VAP. These include: 1) clinical criteria: criteria for severe sepsis (oxygenation index; oxygen tension in arterial blood (P_{a,O_2})/inspiratory oxygen fraction (F_{I,O_2}); 2) radiographic criteria: computed tomography (CT); 3) laboratory criteria: C-reactive protein (CRP), pro-inflammatory cytokines (*e.g.* interleukin (IL)-6); 4) bronchoscopic criteria: there is at least one report [15] suggesting that airway visualization is useful for the clinical diagnosis of VAP; and 5) several simple measures which may be able to provide alternative diagnoses other than VAP and thereby contribute to the negative predictive potential of clinical criteria (*e.g.* physiotherapy for the treatment of atelectasis, urine analysis).

Thus, in order to obtain a more useful clinical definition of suspected VAP, conventional and new criteria should be included in a prediction model to provide stages of evidence for the presence of VAP. This prediction model should then be validated in independent patient populations using strictly independent references.

Bacteriological and histological aspects of ventilator-associated pneumonia

What is not controversial? Polymicrobial and multifocal VAP is one of the major unresolved diagnostic issues. More than one pathogen is found in around 30–70% of VAP cases. Not only is there a scattered distribution of inflammation throughout the lung, but also of different pathogens, *e.g.* ROUBY *et al.* [16] showed that in monomicrobial bronchopneumonia, causative micro-organisms were found in all lobes in 50%, and in only one of the two lobes in 50% of cases. In polymicrobial

pneumonias, all bacteria involved in the infectious process were found in all lobes in only one third of the cases, whereas different bacteria were found in lower and upper lobes in 25% of the cases. The authors also noted partial discrepancies in the remaining 42% of polymicrobial bronchopneumonias with all bacteria found in one lobe and only some of them in the other lobe [16]. Another problem is the unequal distribution of infection in central and peripheral areas of the lung. In one study it was shown that in several cases, pneumonia was absent from peripheral lung samples while more central areas of the same segment displayed pneumonia [13].

What is controversial? A highly controversial issue is the appropriate threshold for considering lung infection to be present in quantitative cultures of lung tissue. A threshold of 10^4 cfu·g^{-1} has good specificity but only a limited sensitivity ($<30\%$) in the majority of studies [9, 14, 16–19]. Conversely, when qualitative cultures are considered, there is an improvement in sensitivity with a moderate specificity [18, 19]. However, it is important to note that some authors found different results.

The relations of histology and quantitative cultures are highly complex. Investigation in this field is hampered by several unresolved methodological problems, *e.g.* in a *post mortem* study of 25 mechanically ventilated patients, FABREGAS *et al.* [20] found that the number of lung cultures with colony counts $>10^3$ cfu·g^{-1} was reduced when patients received antibiotics. However, only 62% of species isolated in this latter group exhibited counts $>10^3$ cfu·g^{-1}. Moreover, there were no differences in the mean bacterial concentrations obtained from lung biopsies without pneumonia, focal pneumonia or confluent pneumonia, independent of prior antibiotic treatment.

Accordingly, recent animal studies in experimental VAP of minipigs (pigs with a weight of $\sim 20-30$ kg) have raised serious concerns about the validity of the quantitative culture technique. Whereas higher bacterial counts were found in the presence of pneumonia as compared to mere bronchial infection or absence of infection, it was not possible, due to large overlaps in bacterial loads, to define a threshold that would allow identification of the presence or absence of pneumonia [21, 22]. However, it remains unclear to what extent these findings in experimental VAP can be extended to the regular patients treated in the ICU.

These findings suggest that there is no concordance between lung histology and lung culture. This could be explained in several ways. First, prior antibiotic treatment may explain both false-negatives and also false-positives. Secondly, some histological aspects could also be misinterpreted as of bacterial origin while they are nonbacterial or noninfectious. Finally, some false-positives could be explained by methodological limitations (lung tissue contamination, delay between death and sampling) or by the presence of bronchiolitis.

What has to be investigated? There are several issues that might not have been sufficiently recognized in previous studies dealing with the relation of histology and bacteriology in VAP. 1) Due to the difficulties in the conduct of such a complex issue, inclusion criteria of patients in *post mortem* studies were quite arbitrary. However, patients with underlying chronic obstructive pulmonary disease (COPD), as well as previous pneumonia episodes, could have had significant bearing on the results and should have been excluded or at least analysed separately. The same is true for other general and pulmonary conditions such as immunosuppression, ARDS *etc.* 2) Likewise, the duration of mechanical ventilation should be taken into account, adopting the concept of early and late-onset VAP. 3) The timing of *post mortem* analysis seems to be of crucial importance. In terms of clinical relevance, a study design including patients who have died from VAP that has been evaluated *in vivo* up to 72 h prior to death seems preferable to a design including any deceased patient regardless of any clinical suspicion of VAP. 4) An extremely important point is to analyse in more detail the impact of previous antimicrobial treatment on quantitative culture results. Currently available data suggest that prior antimicrobial treatment may both reduce and increase the diagnostic yield. It reduces the yield if the pathogens present are susceptible to the given antimicrobial regimen. Conversely, prolonged antimicrobial treatment may favour selection of resistant pathogens and thereby increase the yield. 5) It is essential to perform an investigation of the whole lung, or at least of multiple representative samples, including dependent and nondependent, central and peripheral lung areas.

In order to cope with these extremely demanding investigational aims, one important point is to adhere to recommendations concerning lung tissue processing as given in one of the previous consensus conferences [23].

Aetiology of ventilator-associated pneumonia

What is not controversial? In most reports, Gram-negative enteric bacilli (GNEB), *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the three leading aetiologies. However, it is important to differentiate between early and late-onset VAP. In early-onset VAP, so-called core pathogens include community pathogens such as methicillin-sensitive *S. aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, as well as GNEB. Conversely, in late-onset VAP, methicillin-resistant *S. aureus* (MRSA), *P. aeruginosa*, *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* are frequently encountered [24, 25]. These pathogens form part of the so-called potentially drug-resistant micro-organisms (PDRM) group, which has been found to be associated with increased morbidity and mortality [26].

Overall, aetiological agents may differ according to patients, units, hospitals or countries. The main epidemiological patterns may not only vary from unit to unit, but also in a given unit over the course of time. This is particularly true for their associated susceptibility patterns. Thus, reported differences can frequently be explained by local specificities. Nevertheless, comorbid conditions, length of hospital stay and

intubation, as well as exposition to antimicrobials, are the most important factors determining the aetiology [25–27]. These factors can be used for the selection of the initial empiric antimicrobial treatment.

Overall, there is a rising frequency of antimicrobial resistance in many institutions that represents a challenge to common antimicrobial treatment attitudes and policies.

What is still controversial? A very important, unresolved issue is the definition of early and late-onset pneumonia. It still remains uncertain from the literature whether the given threshold refers to the number of days in hospital or to the number of days following intubation. Likewise, the threshold of 5 days to separate early from late VAP has not been validated, and consequently, some authors have used a threshold of 7 days [26].

Recently, the criterion of the carrier state has been introduced to distinguish primary endogenous VAP due to potential pathogens imported by the patient in the admission flora, from secondary endogenous and exogenous VAP due to ICU associated bacteria [28]. Using the 48 h cut-off point, 80% of all infections were classified as ICU-acquired. According to the carrier state criterion, 60% were of primary endogenous development. The carrier state classification allowed the transfer of 49% of infections from the ICU-acquired group into the import group. A time cut-off of 9 days was found to identify ICU-acquired infections more accurately than 2 days.

Only a few studies have evaluated the aetiology of nosocomial pneumonia in nonventilated patients [29]. Nevertheless, it is very important to know whether nonventilated patients require a diagnostic and therapeutic approach different to ventilated patients or not.

Doubt persists with regard to the role of distinct pathogens, including *Legionella* spp., anaerobes, fungi and viruses, but also so-called commensals, frequently addressed as nonpotentially pathogenic micro-organisms (non-PPM). These pathogens may be more common than originally thought, but their role has not been settled due to one of the following reasons: 1) requirement of specific diagnostic techniques; 2) difficulty establishing the aetiological role of an isolated micro-organism; and 3) dependence of the incidence of pathogens on peculiar epidemiological settings.

The incidence of *Legionella* spp. certainly strongly reflects the local epidemiological situation and the measures that are taken to eliminate potential sources of infection in the hospital. The demonstration of anaerobes requires appropriate transport medium and bacteriological techniques. In addition to these technical problems, the clinical significance of these micro-organisms remains unclear [30]. *Candida* spp. are frequently isolated from lower airway secretions, particularly those having received antimicrobial treatment, but the distinction between colonization and true candidal pneumonia remains difficult to ascertain since the only definite proof consists in histological demonstration of these pathogens causing pneumonia [31, 32]. Some evidence suggests that *Cytomegalovirus* (CMV) may have a role in the pathogenesis of VAP in surgical patients who require long-term mechanical ventilation [33]. However, these findings await confirmation by further investigations.

Another unresolved issue is whether micro-organisms identified in qualitative cultures of tracheobronchial secretions have the same clinical (and bacteriological) significance as compared to those cultured in significant amounts in quantitative cultures obtained by bronchoscopic techniques.

What should be investigated? The aetiology of VAP deserves future investigation, primarily in order to improve initial empiric antimicrobial treatment approaches, as well as the understanding of the mechanisms of acquisition in certain pathogens. Therefore, the following issues should be addressed: 1) a comprehensive evaluation of the definitions of early and late-onset VAP as well as of appropriate thresholds to separate these two entities; 2) epidemiological data as a function of the underlying diseases, the reasons for initiating mechanical ventilation, as well as the type and duration of prior antimicrobial treatment; 3) the exact aetiological role of different micro-organisms and preferential associations in polymicrobial VAP; and 4) a time-dependent analysis of possible preferential sequences of pathogens responsible for community-acquired, hospital-acquired and ventilator-associated infections.

Overall, because the emergence of resistance is a concern for intensive care specialists worldwide, it is imperative that investigators from different countries and regions exchange precise and updated epidemiological data on VAP. To do that, every ICU is encouraged to provide these data, thereby enabling valid comparisons of microbial and susceptibility patterns.

Diagnostic techniques for ventilator-associated pneumonia

Diagnostic techniques may be useful to establish the presence of VAP by microbiological means and detect causative pathogens of VAP.

Establishment of the presence of ventilator-associated pneumonia by microbiological means

What is not controversial? The diagnostic accuracy of several diagnostic tools has been evaluated in detail. Summarizing these investigations, the following are widely held true. 1) Blood cultures are neither sensitive nor specific. VAP is bacteraemic in only up to 20% of patients. In a recent study, sensitivity of blood culture for disclosing the pathogenic micro-organism in BAL-positive patients was 26%, and the positive predictive value to detect the pathogen was 73%. An extrapulmonary site of infection was the source of bacteraemia in 27% [34]. Nevertheless, bearing in mind these limitations, blood cultures may establish the diagnosis of VAP and the causative pathogen, and should form part of every evaluation of a patient with suspected VAP. 2) Qualitative tracheobronchial aspirates are highly sensitive (>75%) but poorly

specific (<25%) for the diagnosis of VAP [35]. Therefore, qualitative tracheobronchial aspirates cannot be used for the diagnosis of VAP. However, due to the high negative predictive value, they may be useful to exclude VAP, particularly in the patient without prior antimicrobial treatment. 3) Quantitative cultures of lower respiratory secretions retrieved by noninvasive (nonbronchoscopic) and invasive (bronchoscopic) techniques have been shown to achieve a reasonable sensitivity and specificity in most, albeit not all, studies. In general, sensitivity ranges from ~60–80% and specificity from 70–90% [9, 13, 14, 19, 35–38]. However, the validity of all reported figures of sensitivity and specificity is limited by the absence of a true gold standard. 4) Overall, nonbronchoscopic sampling with quantitative cultures may achieve comparable results to bronchoscopic sampling, particularly in surgical patients without previous lung disease. Specificity may be somewhat lower than in bronchoscopic sampling. 5) Quantitative tracheobronchial aspirates achieve a better specificity (~70%) at the cost of reduced sensitivity (~70–80%) [37, 38]. This approach is noninvasive, inexpensive, and widely available. Thus, it may be an acceptable tool for diagnosing VAP and causative pathogens. 6) Bronchoscopically retrieved PSB achieves a high specificity (up to 80–90%). It also has a good qualitative reproducibility [36, 37]. The main problem is the low volume of obtained secretions, which may lead to low sensitivity, particularly in patients with prior antimicrobial treatment. 7) Bronchoscopic BAL has the advantage to investigate the largest pulmonary area (~1%). For the same reasons, it may be more vulnerable to contamination, thereby reducing the specificity. However, summarizing current experience, it seems to achieve similar yields as compared to PSB and bear the same limitations in the presence of antimicrobial treatment [9, 13,18, 37]. 8) Nonculture techniques such as Gram stains or Giemsa stains, ICO in Giemsa stains of BAL, elastin fibres in tracheobronchial aspirates and endotoxins in BAL are additional tools that might prove useful in experienced hands. However, the sensitivity of ICO counts is particularly vulnerable to prior antimicrobial treatment, and elastin fibres and endotoxins in BAL are only of value in the detection of Gram-negative VAP [39–42]. 9) Finally, there is no doubt that a microbial investigation should always be attempted in VAP in order to adjust initial empirical antimicrobial treatment.

Among a variety of factors, prior antimicrobial treatment is one of the most important potential confounders in the interpretation of diagnostic results. It has been shown that prior antimicrobial treatment does not reduce the diagnostic yield if current antimicrobial treatment administered for other reasons than VAP remains unchanged prior to diagnostic sampling [43]. Thus, pulmonary secretions need to be obtained before new antimicrobials are administered.

Probably the most important risk of not performing a diagnostic evaluation of suspected VAP is that another site of infection may be missed. The major benefit from a negative result of lung secretion sampling may in fact be to direct attention away from the lungs as the source of fever.

What is still controversial? Several studies using the *post mortem* approach to validate diagnostic techniques have made clear that there is no irrefutable reference standard. The use of histology is hampered by the difficulty to distinguish a recent infection from the sequelae of a previous one. On the other hand, even if all potential confounders are eliminated, there is no absolute correlation between lung histology and tissue cultures. Finally, a combination of both histology and lung tissue cultures, albeit possibly reflecting ongoing infection more confidently, may be undersensitive.

Although a microbiological diagnosis is necessary, there is no consensus about the exact role of the different microbiological tools for diagnosing VAP. There is no clear evidence which of the reported bronchoscopic techniques should be preferred. Recent studies suggest that the operating characteristics of PSB, conventional BAL, mini-BAL and protected BAL are probably very close. Moreover, blind sampling techniques seem to achieve similar performances. However, no technique is without problems. Both inherent limitations of each technique, as well as personal skill and experience, have to be taken into account in the selection of a specific diagnostic tool.

The use of bronchoscopic techniques is limited by the lack of standardized, reproducible methods and diagnostic criteria. Several issues remain unresolved. 1) Should sampling be performed in the area of radiographic affection or the segment visualized during bronchoscopy or, should multiple and bilateral samples even be obtained? 2) If PSB is used, should secretions be collected under direct vision or wedged distally? 3) If BAL is obtained, what volume of saline should be used? 4) Which is the standard transport medium? 5) Should results be expressed in colony forming units ($cfu \cdot mL^{-1}$) or by a bacterial index composed of the sum of the exponents from each quantitated isolate?

One of the most important controversies concerns the role of quantitative tracheobronchial cultures instead of bronchoscopic techniques. Most post mortem studies have found tracheobronchial cultures to be at least equally valid as bronchoscopic techniques [9, 13, 14, 19]. Conversely, the reproducibility of this technique has not been assessed. The role of each approach cannot only be assessed by comparison of operative performances, but must include the randomized assessment of clinically meaningful outcome measures.

What should be investigated? In general, there is currently little enthusiasm to repeat studies comparing operative characteristics of different diagnostic tools in VAP. Obviously, the diagnostic yields reported largely depend on peculiarities of local epidemiology, patient selection, underlying reference standards, and individual skills in sampling and work-up of samples. Nevertheless, there is still a lack of studies comparing diagnostic tools in strictly defined patient populations derived from well-characterized local epidemiological settings. Such studies might offer insights into the impact of the patient population, local incidence of VAP, microbial and susceptibility patterns, and antimicrobial treatment strategies on the diagnostic yield of different tools.

Investigational strategies have largely shifted to the evaluation of the impact of different diagnostic strategies on important clinical outcome measures [44, 45]. Up to now, four randomized studies have been published comparing outcomes with regard to the use of noninvasive *versus* invasive diagnostic tools. Whereas one study claimed an advantage in terms of morbidity and mortality for invasive diagnostic testing [46], three other studies that however, included a more limited number of patients, and where therapy was not strictly conducted according to results of samplings, could not find a corresponding difference [47–49]. Further efforts should be made to clarify the exact contribution of the results of different diagnostic techniques to defined medical outcomes.

Another field that has been poorly studied is the evaluation of patients with antimicrobial treatment failures. This population bears the following important peculiarities which make it possible that diagnostic tests may operate more favourably: 1) a high pre-test probability of VAP, particularly late-onset VAP; 2) an increased probability of drug resistant pathogens; 3) perhaps an increased risk for opportunistic pathogens; 4) the presence of noninfectious conditions which can be diagnosed by BAL (*e.g.* atelectasis, alveolar haemorrhage, hypersensitivity pneumonitis); and 5) the presence of specific tracheobronchial conditions which require a visualization of the tracheobronchial tree. Moreover, since VAP with failure to respond to initial antimicrobial treatment is likely to carry an attributable mortality, diagnostic techniques which provide a rapid and accurate diagnosis are likely to contribute to an improved outcome and, thereby, to be truly cost-effective.

Detection of causative pathogens of ventilator-associated pneumonia

What is not controversial? An attempt to establish a microbiological diagnosis is desirable in every patient with suspicion of VAP. This implies both epidemiological and clinical benefits. The detection of the local epidemiology is important in order to define a general, local policy of initial antimicrobial treatment. There is clear evidence that treatment guidelines such as those provided by the American Thoracic Society (ATS) can only serve as a general framework. The selection of a distinct antimicrobial regimen has to be designed according to local microbial and resistance patterns [50]. Moreover, the detection of causative organisms may be useful in the individual patient, in order to adjust the initial empiric regimen. This is particularly true for patients who suffer a failure of initial antimicrobial treatment.

What is still controversial? Causative pathogens may be detected by noninvasive or invasive diagnostic tools using quantitative cultures [22]. However, the role of the detection of the causative pathogen in the individual patients, in terms of outcome and cost-efficiency, has not been definitively settled. There are also not enough data to support the use of one specific technique. Qualitative tracheobronchial cultures may offer some insight into the general epidemiology of the local setting and thereby provide a basis for the definition of general policies of empiric initial antimicrobial treatment. However, this has not been systematically evaluated. Finally, only a few studies have addressed the patient with failure to respond to the initial empiric antimicrobial treatment.

What should be investigated? The specific impact of the detection of causative pathogens in the individual patient on medical outcome and cost, remains a crucial issue worth addressing in future studies. This is particularly true for patients with antimicrobial treatment failures. This individual diagnostic approach should be compared with an epidemiological approach that is restricted to the record of general local trends in microbial patterns and susceptibilities.

Antimicrobial treatment of ventilator-associated pneumonia

What is not controversial? Immediate initiation of appropriate antimicrobial treatment has a significant impact on clinical outcome of patients with VAP. In a paradigmatic study, Luna *et al.* [51] illustrated that inappropriate initial empiric antimicrobial treatment was significantly associated with increased mortality. Moreover, excess mortality could not be reduced by correction of inappropriate regimens according to results of microbial investigation. On the other hand, it was also shown that antimicrobial pretreatment may favour the selection of multiresistant pathogens and, thereby, cause excess mortality [27]. Thus, any policy of empiric antimicrobial treatment must outweigh potentially associated benefits and risks.

The controversy about the indication for antimicrobial treatment in patients with suspected VAP has already been outlined. In any case, at least all patients with severe VAP (*i.e.* VAP associated with severe sepsis) must be subject to an empiric antimicrobial approach. In an attempt to provide a basis for the definition of such empiric regimen, the ATS guidelines have suggested an algorithm based on the main criteria severity, specific risk factors, and early- *versus* late-onset VAP. Several studies have confirmed the validity of the underlying concepts [26, 52, 53]. Accordingly, this approach seems to have reached wide acceptance in clinical practice. At the same time, it has become evident that the selection of specific antimicrobial regimens must not follow global recommendations, but should be based on local microbial and susceptibility patterns [50].

What is still controversial? Whereas the criterion "admission to the ICU", suggested in the ATS guidelines, can identify patients who are at risk of PDRMs, it does not seem to be a satisfactory criterion for severe VAP. Accordingly, the definition of severity needs to be validated. Another issue that might have been underestimated is the differentiation of the nonventilated from the ventilated patient. Possibly, the algorithm should start from this differentiation.

One of the most conflicting areas in the treatment of

VAP is the issue of monotherapy. The ATS guidelines have reinforced combination antimicrobial treatment for late-onset VAP and VAP with distinct risk factors (mainly those predisposing to potentially drug resistant micro-organisms) at least initially, suggesting consideration of a subsequent reduction to monotherapy whenever possible. Nevertheless, evidence for this recommendation is limited. In fact, the widely established practice of combination antimicrobial treatment is still based on one single study, which demonstrated a superiority of combination antimicrobial treatment in bacteraemic *P. aeruginosa* infections of the neutropenic patient [54]. On the contrary, there are several studies that have failed to confirm a difference between mono- and combination antimicrobial treatment [55–57]. The concepts advocated by SCHENTAG *et al.* [58] are based on the recognition that an appropriate dosage, rather than a combination regimen, represents the main requirement for success. In this view, combination regimens work simply by increasing the probability that at least one antimicrobial substance may reach appropriate microbicidal levels.

What should be investigated? The assessment of severity of VAP is a crucial part of a future revision of the ATS guidelines. Valid criteria for severity may even stimulate the controversy about the role of microbial diagnosis of VAP by allowing stratification of patients according to their risk. It should be clarified whether nonventilated patients with nosocomial pneumonia need a different treatment approach than ventilated patients. Without any doubt, new antimicrobial drugs for the treatment of VAP need to be developed urgently in view of increasing resistances in many institutions throughout the world. This is particularly true for drugs covering resistant Gram-positive pathogens.

The treatment of VAP due to *P. aeruginosa* remains a major challenge. In this regard, aminoglycosides bear an, as yet, uninvestigated therapeutic potential. Whereas conventional intravenous application leads to low concentrations in pulmonary secretions and is associated with considerable toxicity, both problems might be overcome by aerosolized administration of the drugs. The following problems inherent to the treatment of a parenchymal disease with aerosolized antimicrobials should be particularly addressed: 1) appropriate particle size (and nebulizer); 2) dose delivery range; 3) optimal dosage; and 4) safety.

One of the most important issues in the treatment of VAP is the assessment of monotherapy compared to combination antimicrobial treatment in patients at risk for potentially drug resistant micro-organisms, particularly *P. aeruginosa*. The calculation of the ratio of the minimal inhibitory concentration (MIC) and the area under the curve (AUC) as suggested by SCHENTAG *et al.* [58] may provide a particularly useful tool when defining the role of monotherapy. A particular problem within the complex of combination antimicrobial treatment is the issue when to add coverage for MRSA.

Very little information is available about the optimal duration of antimicrobial treatment. Although it is evident that, for example, core pathogens of early-onset VAP without risk factors need less intensive treatment than those of late-onset VAP with or without risk factors, the exact minimally effective duration of antimicrobial regimen in these different populations has never been systematically assessed. It would be particularly important to define whether quantitative cultures can help to determine the duration of antimicrobial treatment. Obviously, the economic impact of such information in terms of cost saving would be considerable.

The assessment of response to antimicrobial treatment has received very limited attention so far. However, in view of the high failure rate of antimicrobial treatment, there is a clear need for studies which help to define criteria for treatment response. Moreover, the particular role of conventional clinical and radiographic criteria as compared to systemic (*e.g.* CRP, IL-6) and local inflammatory markers (*e.g.* cytokine patterns) and microbial reinvestigation should be elucidated.

Only recently, crop rotation of antibiotics has been suggested as a tool to reduce the induction of antimicrobial resistance [59, 60]. The most intriguing issue in this regard is whether crop rotation (independently of microbiological surveillance) is superior to an antibiotic rotation approach according to documented trends of microbial resistances in the particular unit.

Prevention of ventilator-associated pneumonia

What is not controversial? Several measures to prevent VAP have been proven to be effective and are generally recommended. 1) Precautions of pathogen transmission from patient to patient including isolation [61]. The Euro-Nis study (MORO and JEPSEN [62]) described different practices that may reduce exogenous infections due to better surveillance and better staff education. 2) Hand-washing and disinfection. These are the most important measures to prevent patient to patient spread of pathogens, as well as to protect healthcare workers from potential infections [63]. 3) Change of ventilator circuit not more than once per week. Daily change of ventilator circuits was shown to be a risk factor for VAP. Although the optimal exchange interval has not been determined, a policy of circuit change once a week as compared to a 48 h interval has been shown to be safe [64]. 4) Orotracheal instead of nasotracheal intubation. Nasotracheal intubation increases the risk for sinusitis and VAP. Therefore, orotracheal intubation should be the preferred technique [65, 66]. 5) Keeping the endotracheal tube cuff pressure optimized. The pressure of the endotracheal tube cuff should be optimized in order to prevent the leakage of colonized subglottic secretions into the lower airways [67]. 6) Semi-recumbent body position. A reduction of aspiration into the lower airways, in semi-recumbent *versus* the supine body position, has been shown by scinitgraphic means [68, 69]. Moreover, the effect of semi-recumbent position on a reduction of VAP has been demonstrated [70]. 7) Avoidance of paralytic medication. Deeply sedated and relaxed patients clearly are at higher risk of aspiration and VAP [71]. Therefore, relaxation should be avoided whenever possible. 8) Avoidance of reintubation. Reintubation was clearly demonstrated to represent a risk factor for VAP [72].

Furthermore, it seems obvious that noninvasive ventilation instead of intubation should reduce the incidence of VAP. 9) Selective digestive decontamination (SDD). A recent, meta-analysis, examining 33 randomized SDD trials involving 5,727 patients, demonstrated a significant reduction in overall mortality (20%) and in the incidence of respiratory tract infections (65%) [73]. A second systematic review in critically ill surgical patients showed an even greater benefit of SDD: mortality was reduced by 30% and rates of pneumonia by 80% [74]. SDD may be used in subsets of populations such as patients with trauma, pancreatitis, major burn injury, and those undergoing major elective surgery and transplantation. Some centres with experience are using SDD in all mechanically ventilated patients.

What is still controversial? Measures which require further evaluation to determine the appropriate indication include the following. 1) Preventive antimicrobial treatment after intubation. Pathways of aspiration are particularly relevant for patients with depressed consciousness. The rate of early-onset VAP could be significantly reduced in patients with structural coma when prophylactic cefuroxime (1.5 g twice within 24 h) was administered [75]. However, patients receiving antimicrobial treatment at the same time are at increased risk of colonization with PDRMs and late-onset VAP [53]. Since late-onset VAP has a more significant bearing on outcome than early-onset VAP, preventive antimicrobial treatment may be hazardous. 2) Continuous suctioning of subglottic secretions. Subglottic secretion drainage has been shown to reduce the rate of VAP in two studies [76, 77], without reducing length of ICU stay and mortality. The tubes needed for this type of suctioning are expensive and difficult to handle. The cost-benefit relation is not settled. Moreover, the benefit seems to be restricted to early-onset VAP. 3) Early enteral nutrition. Enteral nutrition has been shown to reduce intestinal atrophy and permeability and to improve the local immune response in animal studies. Moreover, it could be shown to have protective effects in mechanically ventilated patients [78]. However, the nasogastric tube may lead to an increased rate of sinusitis and oropharyngeal colonization [79]. 4) Heat and moist exchangers (HME) instead of heated humidification. In randomized studies, the incidence of VAP using HME was comparable to heated humidifiers. Whether the reduction of condensed fluid in the expiration circuit or the bacterial filtration properties account for this effect remains unclear. Heated humidification using a heated wire reduces the amount of condensation as well. The bacterial filtration properties of hydrophobic filters are superior to hygroscopic filters; on the other hand, their humidifying capacity is reduced [80–83]. 5) Closed instead of open suctioning. Closed suctioning systems have found their way into many ICUs. Nevertheless, there is only limited evidence that closed suctioning is able to reduce the incidence of VAP. On the other hand, it is clearly more expensive. It is also not clear how often closed suction catheters have to be changed. In one study, a once weekly change was found to be equal to the once daily change endorsed by the Food and Drug Administration as regards the rate of VAP [84–87]. In a recent randomized study [88], the use of a closed suctioning system was followed by a decreased incidence of VAP. 6) Avoidance of in-line nebulizers. The potential hazards of in-line nebulizers are well known. Nevertheless, the impact of nebulizers on VAP has not been assessed systematically [89]. 7) Stress ulcer prophylaxis. In contrast to previous reports, a more recent study could not demonstrate an increased risk for VAP using H2-antagonists [90]. A recent meta analysis has shown that H_2 blockers increase the risk of pulmonary infections in critically ill patients [91].

What should be investigated? 1) Noninvasive ventilation. Noninvasive ventilation via nose or facemask has been shown to be an effective alternative in patients with cardiogenic pulmonary oedema and COPD. It has also been successfully used for weaning. Its role in pneumonia and ARDS is less clear. Since the avoidance of intubation certainly has a dramatic impact on the risk of VAP, it appears that the indications for and standards of noninvasive ventilation should be established with high priority [92]. 2) SDD. Concerns about the possible occurrence of antimicrobial resistance are suggested by available data, but cannot, at the same time, be definitely confirmed. Whether new trials are needed, and how they should be designed to answer the question of the potential for antibiotic resistance following widespread use of the treatment, are now the main issues to be settled [93]. 3) Continuous suctioning of subglottic secretions. The role of continuous suctioning should be further evaluated. Possibly, shortcomings in handling may be overcome by improved devices. 4) Enteral nutrition. Large studies are necessary to assess the best way to apply enteral nutrition (type of feeding tube, continuous *versus* intermittent application, prokinetic medication, distal enteral feeding) and its influence on VAP. 5) HME *versus* heated humidification. A standard of strategies in humidification should be established taking into account the cost-benefit relation. 6) Nebulizers. The risk of nebulizers and optimal cleaning measures should be carefully determined. The alternative applications of metered dose inhalers through aerosol port or nebulizing chamber are additional scientific targets in this field. 7) Closed instead of open suctioning. The role of closed suctioning should be studied, particularly taking into account the cost-benefit ratio. 8) Endotracheal tube properties. Measures to improve pressure control of the cuff and to reduce colonization of the endotracheal tube, particularly in the biofilm, should be determined. 9) Stress ulcer prophylaxis. The available studies suffer from a failure to stratify for early- and late-onset VAP. However, since the gastric reservoir seems to be of importance only in late-onset VAP, the impact of stress ulcer prophylaxis should be restricted to this type of VAP.

Conclusions

Many controversies remain regarding the epidemiology, diagnosis, prognosis and therapy of ventilator-associated pneumonia. In particular, the proportion of ventilator-associated pneumonia that could be pre-

vented when improving quality of care is an important issue. To answer those difficult questions, a better understanding is needed of the precise natural history of ventilator-associated pneumonia at a local and cellular level, and the steps between colonization and infection. This will be important in relation to implementation of the best cost-beneficial, preventive measures. It is hoped that this document will be an important step forward.

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