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Therapy of ventilator-associated pneumonia A patient-based approach based on the ten rules of “The Tarragona Strategy”

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Abstract Therapy of ventilator-associated pneumonia should be a patient-based approach focusing on some key features are listed here: early initial therapy should be based on broad-spectrum antibiotics. Empirical treatment may be targeted after direct staining and should be modified according to good-quality quantitative microbiological findings, but should never be withdrawn in presence of negative direct staining or delayed until microbiological results are available. Courses of therapy should be given at high doses according to pharmacodynamic and tissue penetration properties. Prolonging antibiotic treatment does not prevent recurrences. Methicillin-sensitive *Staphylococcus aureus* should be expected in comatose patients. Methicillin-resistant *Staphylococcus aureus* should not be expected in pa-

tients without previous antibiotic coverage. *Pseudomonas aeruginosa* should be covered with combination therapy. Antifungal therapy, even when *Candida spp* is isolated in significant concentrations, is not recommended for intubated nonneutropenic patients. Vancomycin, given at the standard doses and route of administration for the treatment of VAP caused by Gram-positive pathogens, is associated with poor outcomes. The choice of initial antibiotic should be based on the patient's previous antibiotic exposure and comorbidities, and local antibiotic susceptibility patterns, which should be updated regularly.

Keywords Nosocomial pneumonia · Empirical treatment · De-escalation · Ventilator-associated pneumonia · Etiology

Introduction

Development of fever, new or progressive leukocytosis, or other clinical signs of sepsis oblige the physician to exclude nosocomial infection. The combination of purulent respiratory secretions and an abnormal chest radiograph requires a diagnosis of pneumonia to be considered. The risk of nosocomial pneumonia varies between 6- and 20-fold in intubated patients. It affects between 20 and 70% of such patients [1] and accounts for at least ten episodes per 1000 intubation days. The mortality rate in patients developing ventilator-associated pneumonia (VAP) ranges from 33 to 70%. This depends on patient specific characteristics, diagnostic criteria, and

the pathogens involved; however, the *directly* attributable mortality remains controversial [2, 3, 4, 5, 6]. The VAP is associated with excess morbidity, increasing ICU and hospital stay by 6.1 and 11.5 days, respectively, and increasing patient costs by \$40,000 per episode [7].

The American Thoracic Society (ATS) guidelines [8] defined a clinical management algorithm based on severity of illness, presence of risk factors, and time of onset of hospital-acquired pneumonia. On the basis of these factors, three separate groupings were suggested: early onset; late onset in the absence of risk factors; and late onset in the presence of risk factors. Trouillet et al. [9] sought to define the epidemiological characteristics of

Table 1 The ten key points of the Tarragona strategy. *COPD* chronic obstructive pulmonary disease, *VAP* ventilator-associated pneumonia, *MSSA* methicillin-sensitive *Staphylococcus aureus*, *GCS* Glasgow Coma Score, *MRSA* methicillin-resistant *Staphylococcus aureus*. (Modified from [11])

When to start

1. Antibiotic therapy should be started immediately
- Impact of microbiological investigation on guiding and de-escalating therapy
2. Antibiotic choice can be targeted, in some cases, on direct staining
3. The antibiotic regimen must be modified in the light of microbiological findings

Dose and duration

4. Prolonging antibiotic treatment does not prevent recurrences.
- What microorganism should be covered
5. Patients with COPD or >1 week of ventilation should receive combination therapy, due to the risk of VAP due to *Pseudomonas aeruginosa*
 6. MSSA should be strongly suspected if GCS<8. MRSA is not expected in the absence of prior antibiotic administration
 7. Therapy against yeasts is not required, even in the presence of *Candida spp* colonization
 8. Vancomycin administration for MRSA-related VAP (and for other Gram-positive pneumonias) is associated with a very poor outcome

Choice of initial agent

9. Guidelines should be regularly updated and customized to local patterns
 10. The specific choice of agent should be based on the regimen to which each patient has been exposed previously
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nosocomial pneumonia in a French ICU. They classified all episodes of VAP into four groups, according to two main risk factors, namely, duration of mechanical ventilation and prior use of antibiotic therapy. They suggested a simpler treatment algorithm characterized by the use of broad-spectrum cover for fewer patients, and more restrictive administration of vancomycin than that proposed in the ATS guidelines [9]. More recently, these approaches have been challenged by more dynamic, institution-specific options based on the local flora and their resistance patterns. These new approaches should be updated over time [10].

Our group has designed an antibiotic management program for the treatment of VAP based on studies we have published over the past decade. This strategy is formulated by ten statements (Table 1) based on four key points: (a) immediate commencement of antibiotics; (b) broad-spectrum cover followed by de-escalation based on microbiology results; (c) administration of antimicrobials at high and individualized doses depending on their pharmacodynamic properties; and (d) a choice of antibiotic based on lung penetration rather than in vitro MIC or blood levels. The choice of initial agent is a dynamic process based on several key factors including prior antibiotic exposure, colonization pressure within the hospital, patient condition (e. g. , risk factors and comorbidities), and, finally, expected local sensitivity patterns. This patient-based and institution-specific approach was called “The Tarragona Strategy” in a brief preliminary report [11].

Diagnostic implications are outside the aims of this article and have been reported elsewhere [12]. Comprehensive reviews on VAP have also been recently published [13, 14]. We refer the readers to these references for background comprehensive information on the different options available for collecting and processing respiratory samples.

The present review focuses on five frequently asked questions:

1. When should antibiotics be started?
2. What is the role of microbiological tests in guiding and de-escalating therapy?
3. What is the optimal dose and duration of an antibiotic regimen?
4. Which microorganisms should be covered?
5. Which initial agent(s) should be chosen?

When to start antibiotic treatment

The timing of antibiotic commencement and the adequacy of treatment is crucial in the critically ill patient. Initial therapy is considered to be inadequate if the microbiological results indicate that the antibiotic did not cover the infecting pathogen, or if the pathogen was resistant to the antibiotic prescribed [3]. In practice this means that therapy should be targeted to the specific pathogens involved, and requires the correct choice of drug, dose, and duration. Many authors [2, 3, 4, 5, 6] have reported that inadequate initial therapy is associated with poorer outcomes with mortality rates (Fig. 1) ranging from 26 to 91% [2, 3, 4, 5, 6]. In the past decade we have learned that delays in initiation of an effective treatment in intubated patients with pneumonia are associated with increased mortality [3, 5, 6]. Severely ill patients in whom treatment is delayed may show a limited response to treatment, even if the causative pathogen is sensitive to the antibiotic prescribed [6].

Early implementation of a broad-spectrum antibiotic regimen, as soon as there is clinical suspicion of a nosocomial pneumonia, should increase the likelihood of early reduction of the bacterial burden of the pathogens responsible, thus minimizing the risks and the potential conse-

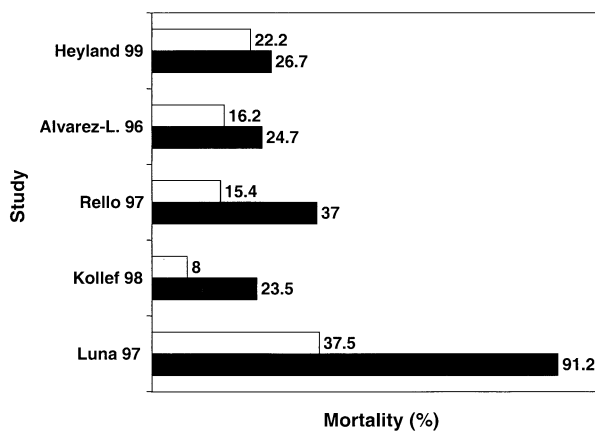


Fig. 1 Inadequate initial antibiotic therapy of ventilator-associated pneumonia is associated with a worse outcome. *White bars*: adequate antibiotic therapy; *black bars*: inadequate therapy

quences of delayed therapy [15]. Clinical information, such as patient risk factors/comorbidities and previous antibiotic exposure, can provide useful assistance in selecting the best possible initial antibiotic agent. Direct staining of respiratory secretions may also help to guide initial therapy [12]; however, a negative result should not rule out antibiotic treatment given the high incidence of false-negative results found with *P. aeruginosa* [16].

Role of microbiological tests on guiding and de-escalating therapy

Many studies have entered the debate on the optimal method of collecting specimens [17, 18]. A complete discussion is beyond the scope of this article; however, in all settings, the selection of the collection technique depends ultimately on the availability of microbiological support and expertise in the use of the specific procedure. Unfortunately, in the ICU setting, the rate of inadequate empirical antibiotic therapy for VAP is very high, ranging from 22 to 73% [2, 3, 4, 5, 6]. Empirical therapy should be modified in line with subsequent culture results to a more targeted regimen to avoid adverse effects associated with the use of certain antibiotics and the emergence of multiresistant pathogens [9].

Controversy also exists regarding sample processing and microbiological information. Direct staining of respiratory samples is a simple procedure and can give valuable information in less than an hour. Gram staining is useful for determining the quality of the respiratory sample. The presence of a high epithelial content in the respiratory sample suggests the possibility of contamination and the ongoing inflammatory process, and may help to decide whether the sample should be further processed to investigate the etiology or whether new samples should be collected [12]. Unfortunately, the use of

previous antibiotic therapy, steroids, or the presence of *Pseudomonas aeruginosa* in direct staining may yield false-negative results [19]. Moreover, up to 30% of samples of VAP caused by *Pseudomonas aeruginosa* have negative direct staining [12, 16]. The use of special transport media, such as thioglycolate, may improve the diagnostic accuracy of the Gram stain [20].

Over the past decade the technical accuracy of the various diagnostic procedures available has been extensively debated. The focus of the debate has recently shifted towards more practical issues such as the possible clinical impact of diagnostic strategies on outcome [21]. Microbiological information has been proposed [5, 20] as a useful tool for selection of initial antibiotic treatment, and for modifying empirical treatment allowing a more targeted and cost-effective therapy. The possibility of narrowing (de-escalating) the initially commenced broad-spectrum therapy based on culture results is thought to have a beneficial effect through decreasing the emergence of multiresistant pathogens; however, some studies do suggest that antibiotic duration and individual differences in the resistance mechanisms of different pathogens to specific antibiotics are the major causes for development of resistance [22].

In a study of 113 patients with VAP, the results from bronchoscopic procedures obtained within the first 12 h of development of VAP led to a change in initial empirical treatment in 38% of treated episodes [5]. In 75% of these cases, the change was due to isolation of pathogens resistant to the antibiotic administered; a second antibiotic had to be added in 7.8% of cases due to the unexpected presence of *P. aeruginosa*. Six percent of the changes were made to simplify the initial treatment. Related mortality was significantly higher if initial treatment was inadequate, although the change in therapy permitted rescue and clinical resolution in two-thirds of such episodes.

In addition, Luna et al. [6] demonstrated that a change of antimicrobial agent based on culture findings of bronchoalveolar lavage (BAL) specimens in a set of extremely ill patients did not alter final outcome; however, in some cases, the bronchoscopic technique was delayed for up to 24 h after the suspicion of VAP was first raised.

In an international consensus conference [13] on the diagnosis and treatment of VAP, all attending experts agreed that microbiological findings are useful. This strong consensus was based on two facts: firstly, the presence of intracellular bacteria and a positive Gram stain or other direct test may be of great help in selecting the initial antibiotic regimen but not in making the diagnosis of pneumonia. Secondly, quantitative microbiological findings can make it possible to change, adjust, or reduce the administration of antibiotics in some patients. The vast majority of this expert panel preferred to obtain invasive respiratory samples within 12 h of the diagnosis of VAP being suspected, and agreed that the use of broad-spectrum antibiotics for less than 48 h would not induce a significant risk of multiresistance.

Dose and duration of the antibiotic regimen

Antibiotic classes exhibit different pharmacodynamic responses that should be taken into account when deciding the optimal dose and duration that should be prescribed. For instance, frequent doses of beta-lactams would probably be more effective than higher doses given less frequently, due to their time-dependent killing effect. On the other hand, the concentration-dependent killing effect of aminoglycosides and fluoroquinolones dictates a different administration pattern. New pharmacological parameters for monitoring the killing effect of antibiotics are being implemented [23]. The Area Under the Inhibitory Concentration curve (AUC) allows comparisons between drugs of different classes, regardless of their pharmacokinetics and pharmacodynamic responses. Antibiotic dose and duration should be targeted to achieve an AUC above 125, which represents 80% of the entire AUC above the MIC, in order to prevent the emergence of resistance [23].

Tissue penetration should also be taken into account when deciding the optimal antibiotic route and form of administration. For example, a continuous infusion of vancomycin should be preferred for treatment of MRSA pneumonia since this agent exhibits concentration-dependent bactericidal activity and poor lung penetration [24]. Our protocol is based on giving 15 mg/kg vancomycin over 1 h followed by 30 mg/kg infused over 24 h by volumetric infusion pump. The dose is adjusted to maintain a plateau serum vancomycin concentration between 20 and 30 mg/l [25, 26].

The optimal duration of antibiotic therapy has seldom been evaluated and recommendations mostly originate from expert panels. Most clinical trials recommend a 2-week course of therapy for uncomplicated respiratory infections. Shorter antibiotic regimens have been used by some authors to reduce antimicrobial costs, adverse effects, and the emergence of antibiotic-resistant pathogens [27]. Prolonged (>7 day) treatments have been implemented to avoid recurrent pneumonia episodes, as is commonly seen with certain pathogens; however, long courses can select resistant microorganisms and increase the risk of adverse effects as well as cost [27]. The American Thoracic Society [8] recommends a course of 7–14 days for *S. aureus* or *Haemophilus influenzae* pneumonia, and a course of 14–21 days for *P. aeruginosa*, *Acinetobacter* spp or Gram-negative necrotizing pneumonia, and for cases with multilobar involvement. Our group uses shorter courses of antibiotic therapy given at high dose, depending on their pharmacodynamic properties and tissue penetration. This means withdrawal of antibiotics 72 h after clinical resolution (defervescence and change in respiratory secretions) in our patient-based approach.

Many studies have documented persistent isolation of *Pseudomonas aeruginosa* from the respiratory airways de-

spite several days of antibiotic treatment [28, 29]. The incidence of recurrent pneumonia in intubated patients ranges from 3 to 50%, depending on the definition used. Establishing whether these are caused by a reactivation of the same strain (relapse) or by an exogenous reinfection has important clinical consequences in terms of prevention and treatment strategies. In 1997, using chromosomal fingerprinting techniques in a cohort of intubated patients with *P. aeruginosa* pneumonia [29], we suggested that most of the recurrent episodes observed were due to relapses from the same primary strain. This observation suggests that prolonging antibiotic therapy in intubated patients with *P. aeruginosa* pneumonia is probably not the right approach, and that interventions to reduce superinfections should instead be based on preventive strategies [29].

Microorganisms to be covered

The major risk factors described as determining the causative agent in nosocomial pneumonia are: the presence of risk factors for specific organisms; prior antibiotic exposure; the length of stay at the time the patient develops pneumonia; and the local pattern of environmental contamination [9, 10].

Considerable information is available on the influence of certain comorbidities or risk factors such as steroids, head trauma, lung structural disease, and immunocompromise on the spectrum of the pathogens responsible for an infectious event [28]. Previous antibiotic treatment has also been reported to influence the type of microbial flora responsible for subsequent VAP episodes [9, 10]. It is also associated with a negative impact on outcome [30]. This finding is thought to be due to selection of more lethal and antibiotic-resistant pathogens following suppression of the normal colonizing bacterial flora by the previous antibiotic regimen.

Several studies have demonstrated that both risk factors and microbiological profile vary in VAP patients depending on the duration of intubation [31, 32]. In the first 48 h after intubation, the expected pathogens should be those already colonizing the respiratory tract at the time of intubation with predictable susceptibility patterns [31]. Exceptions may be those patients with prolonged hospitalization [3] or immunocompromise [33, 34, 35]. On the other hand, VAP occurring after a week of intubation is caused by organisms existing in the hospital environment (exogenous organisms) – in this case, local ecology and previous antibiotic utilization – should be considered [32].

All these variables should be taken into account when deciding which pathogen should be expected in a specific patient admitted to the ICU. In one study [36] of patients without previous antibiotic therapy and early VAP, *Haemophilus influenzae*, methicillin-sensitive *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Entero-*

bacteriaca were shown to be the most commonly isolated pathogens.

The presence of methicillin-sensitive *Staphylococcus aureus* (MSSA) should be strongly suspected in comatose patients. Several reports have demonstrated a higher incidence of MSSA in patients with an altered level of consciousness. In a prospective study of 161 multiple trauma patients performed in the early 1990s [37], *S. aureus* was the predominant (>50%) bacterium isolated in comatose [defined as a Glasgow Coma Score (GCS) <8 patients with ventilator-associated pneumonia]. These considerations have implications for the treatment of this subgroup of patients. Drugs effective against *S. aureus* should be included in the empirical regimen for treating nosocomial pneumonia in patients in coma.

Pneumonias caused by *Pseudomonas aeruginosa* are frequent in patients with severe chronic obstructive pulmonary disease, prolonged periods of intubation (>8 days), and prior exposure to antibiotics [38]. Pneumonias caused by *P. aeruginosa* are associated with increased mortality rates and prolonged ICU stay [38, 39]. Empirical treatment in patients meeting these criteria should include combination therapy with drugs with antipseudomonal activity until a microbiological diagnosis is established.

Methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonias are common in patients with prolonged intubation periods and prior use of antibiotics. In 1994 a study comparing risk factors in a group of patients who developed VAP [40] found that all patients in whom MRSA was identified as the cause of pneumonia had received previous antibiotic therapy, compared with only 21% of patients with MSSA-related VAP. Methicillin-resistant *Staphylococcus aureus* should not be expected in patients not having received antibiotics previously. Further studies have confirmed these findings [41].

Acinetobacter baumannii is another exogenous pathogen with completely different risk factors from *Pseudomonas spp.* and other multiresistant Gram-negative bacilli [42]. As this pathogen is resistant to a wide range of antimicrobials, carbapenems play a key role (even in episodes caused by strains resistant "in vitro") in the treatment of pneumonia caused by *A. baumannii* [43].

The increasing incidence of fungal nosocomial infections and the growing proportion of immunocompromised patients being admitted to ICUs have generated a growing interest in the epidemiology, diagnosis, and treatment of these pathogens. Criteria for the diagnosis of *Candida spp* pneumonia have yet to be defined. Several studies have challenged the significance of *Candida spp* isolation in bronchoscopic samples [44, 45, 46]. For nonneutropenic intubated patients, isolation of *Candida spp*, even in high concentrations in bronchoscopy, should be classified as contamination. Antifungal therapy should not be initiated unless histological evidence of invasive candidiasis is demonstrated. This includes

intubated patients receiving steroids and/or those with AIDS [44].

The proportion of anaerobes isolated in ventilated patients ranges from 1.1 to 3.5%. It remains to be established whether this low figure is due to the low sensitivity of the diagnostic techniques for this kind of pathogen, or whether anaerobes are a rare cause of VAP [47].

Choice of initial agent

Antibiotic choice should be institution specific and patient oriented. Our group recommends the implementation of a broad-spectrum antibiotic treatment as the initial approach to the patient with suspected VAP, followed by early de-escalation depending on subsequent microbiological results.

Controversy surrounds the number of agents that should be given for the treatment of VAP. Debate on monotherapy vs combination therapy has fueled several investigations [48]. Supporters of monotherapy point to its lower cost and the lower probability of side effects. Furthermore, clear evidence of the usefulness of combination therapy for preventing bacterial resistance emergence has only been demonstrated at certain sites or for pathogens with a high mutation rate during treatment; however, the advantages of combination therapy (usually consisting of an aminoglycoside plus a carbapenem or beta-lactam), namely, synergy and the lower incidence of treatment failures, could be useful for the treatment of pathogens with a high antibiotic resistance potential such as *Pseudomonas aeruginosa* or MRSA.

In the international consensus conference on VAP [13] recently reported in "Chest," the vast majority (11 of 12) of experts present agreed that empirical combination therapy should be implemented in late-onset VAP. The same policy was supported by all experts (12 of 12) if *P. aeruginosa* was the suspected responsible pathogen. No agreement was reached, however, on specific agents that should be used.

Deciding the optimal antibiotic regimen in patients who have previously received antibiotics is a complicated task. Any new agent introduced into the therapeutic regimen must circumvent pathogen-resistance mechanisms that may have developed after the previous antibiotic exposure. Patients suspected of being infected by *Pseudomonas aeruginosa* who are receiving beta-lactams will probably exhibit resistance to these agents. Carbapenems are the drug of choice for these patients. If the patient is receiving a carbapenem, a fluoroquinolone, such as ciprofloxacin, is a reasonable option. Decreased membrane permeability appears to be the most common primary mechanism of resistance to imipenem in resistant *P. aeruginosa* strains. Unfortunately, the same mechanism may be used by ciprofloxacin-resistant strains to induce cross-resistance to carbapenems; therefore, combination

therapy with a carbapenem and a quinolone should be avoided, as should combination treatment with two beta-lactams. If a patient with VAP is receiving a quinolone, combination therapy based on a beta-lactamase inhibitor plus piperacillin may be a reasonable option [49, 50].

Another subject of controversy is the treatment of MRSA pneumonia. This pathogen is the second most frequently isolated pathogen from patients who die of pneumonia. The treatment options for this pathogen are limited. Vancomycin has been the standard therapy for bloodstream infections due to MRSA for many years, but several studies [41, 51] have demonstrated its poor effectiveness in the treatment of nosocomial pneumonias caused by this pathogen. Gonzalez et al. [51], in an observational study, reported a high mortality rate among patients treated with vancomycin for pneumonia caused by either MRSA (50%) or MSSA (47%), in contrast with pneumonia caused by MSSA treated with cloxacillin (0%). In intubated patients with pneumonia caused by MSSA treated with cloxacillin, we reported [40] a mortality rate was 2.6%, compared with a 54.5% mortality in VAP caused by MRSA and treated by intermittent administration of vancomycin with serum level monitoring. Moreover, 2 patients developed VAP due to MRSA even though they were receiving treatment with vancomycin. In addition, post-mortem cultures performed in three of these patients showed persistence of MRSA. No difference in virulence patterns between MSSA and MRSA have been documented. The reason for these findings may be due to vancomycin's poor penetration into the alveolar space.

Lamer et al. [52] studied 14 critically ill ventilated patients receiving vancomycin for at least 5 days and reported a mean lung epithelial lining fluid (ELF) concentration of 4.5 mcg/ml (range 0.4–8.1 mcg/ml). The mean plasma concentration at the time of sampling was 24 mcg/ml (range 9.0–37.4 mcg/ml); thus, the plasma:ELF ratio of drug penetration was 6.1. In this study population, 36% of patients had an ELF concentration <4 mg/kg. Unfortunately, no information is presently available on teicoplanin.

These observations have important clinical implications for the treatment of patients with pneumonia due to Gram-positive cocci. Conventional dosing and continuous-infusion vancomycin therapy may have similar outcomes in patients with bloodstream infections [26]; however, vancomycin should not be considered as a first-line therapy for Gram-positive lung infection in critically ill patients. Optimal therapy with vancomycin depends on maintaining a concentration above that needed for antibacterial activity and is therefore determined by the trough concentration. Administering vancomycin as a continuous infusion and maintaining constant concentration in serum of four to five times the MIC for the infecting organism may be the ideal way to deliver this antibiotic for serious infection. Moreover, patients with pneumonia caused by MRSA should receive combination

therapy with this drug plus another agent to which the MRSA is sensitive [11]. Our personal experience of therapy in patients with Gram-positive pneumonia has been reported elsewhere [53].

Many efforts have been made to reduce the still unacceptably high rate (Fig. 1) of inappropriate initial therapy of VAP and the associated excess mortality [2, 3, 4, 5, 6]. In the past decade clinical guidelines have been developed giving general recommendations for empirical treatment of VAP in an attempt to standardize this initial approach by basing it on specified clinical factors [8, 9].

In a multicenter retrospective study [10], the microbiological causes of VAP episodes documented by Trouillet et al. [9] were compared with data obtained from three different sites. This study [10] demonstrated that the distribution patterns of the causative organism varied across sites, particularly in the case of VAP caused by *A. baumannii*. These differences may have been due to disparities in patient demographics or comorbidities, strategies for pneumonia prophylaxis, and, in particular, to local resistance patterns. These data suggest the need for wide variations in antimicrobial prescription practices based on such patterns. Namias et al. [54] reported significant variations in sensitivities between different ICUs within the same institution.

All experts attending the international conference on VAP mentioned previously [13] agreed that pathogens responsible for VAP in their ICU were substantially different from those described in the United States and from one another. Agreement was also reached that the choice of antimicrobial drug should vary depending on the suspected pathogen, underlying condition, risk factors, and local epidemiology.

Conclusion

Our antibiotic management program aims to answer simple questions that all physicians ask themselves when treating a patient with VAP. The approach is patient based and could be summarized in a short set of rules: "Hit hard" with a high dose of broad-spectrum antibiotic as soon as VAP is suspected. "Get to the point": use antibiotics according to their pharmacodynamic responses in order to obtain effective lung tissue concentrations. "Focus, focus, focus": de-escalate, when possible, according to microbiological findings and do not prolong antibiotic therapy unnecessarily. "Listen to your hospital": tailor the antibiotic policy according to regularly updated information of the type and susceptibility patterns of local pathogens. Finally, "Look at your patient": individualize the initial antibiotic administration on the basis of the patient's comorbidities, intubation period, and previous antibiotic exposure.

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