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EDITORIAL

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# Antibiotic prescribing for ventilator-associated pneumonia: get it right from the beginning but be able to rapidly deescalate

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Ventilator-associated pneumonia (VAP) is the most frequent ICU-acquired infection among patients receiving mechanical ventilation (MV) [1, 2]. While controversy continues regarding the mortality due to this process, multiple studies have documented that VAP increases both ICU length of stay and MV duration [1, 3, 4, 5]. VAP also contributes significantly to costs in the ICU. For example, two recent analyses suggest that VAP adds some $40,000 in costs per case [3, 5]. Approximately 50% of antibiotics prescribed in ICUs are administered for respiratory tract infections [6].

Despite an enormous amount of research and many official statements the diagnosis and treatment of VAP remain controversial. All experts interested in this field, however, agree that the major goals of any management strategy are early, appropriate antibiotics in adequate doses of patients with true VAP while avoiding excessive antibiotics and the emergence of multidrug-resistant strains [1, 2]. Failure to initiate prompt appropriate and adequate therapy (the causal organism is sensitive to the therapeutic agent, the dose is optimal, and the correct route of administration is used) has been a consistent factor associated with increased mortality [7, 8, 9]. Since pathogens associated with inappropriate initial empirical antimicrobial therapy are usually antibiotic-resistant micro-organisms such as *Pseudomonas aeruginosa*, *Acinetobacter* species, *Klebsiella pneumoniae*, *Enterobacter* species, and methicillin-resistant *Staphylococcus aureus* (MRSA), patients at risk of infection with these organisms should initially receive a combination of agents that can provide a very broad spectrum of coverage [10].

Until now there has been a wide consensus in the literature that early-onset VAP in patients having not received prior antimicrobial therapy is caused mainly by relatively easy-to-treat micro-organisms such as *Streptococcus pneumoniae*, enteric Gram-negative bacilli, and methicillin-susceptible *S. aureus*, whereas late-onset VAP cases are most commonly due to potentially multiresistant bacteria, such as *P. aeruginosa*, *A. baumannii*, and MRSA. This view is now somewhat challenged by Giantsou and colleagues [11] in a new study published in *Intensive Care Medicine*. These investigators reexamined the possible effect of time of infection occurrence on pathogens in a large series of 408 patients with VAP, using strict microbiological criteria to define pneumonia. At their institution early onset (<7 days of MV) and late onset (≥7 days of MV) were caused mainly by potentially multiresistant bacteria, most commonly *P. aeruginosa* and MRSA. Because in that study the physicians in charge of the patients generally selected initial antibiotics based on the timing of infection occurrence, therapy was inadequate in a large proportion of early-onset VAP patients. Such findings are in accordance with those of other studies at other institutions that have reported that early- and late-onset VAP is associated with similar pathogens, usually multiresistant pathogens [12, 13]. Rightly, however, the authors prudently concluded that such findings, rather than providing information generally applicable to all ICUs, only emphasize the need to tailor initial therapy to local patterns of antimicrobial susceptibilities. Having a current and frequently updated knowledge of local bacteriological patterns can increase the likelihood that appropriate initial antibiotic treatment will be prescribed [1, 2, 14].

Based on this, should we reconsider our guidelines for selecting initial antimicrobial therapy in patients with a clinical suspicion of VAP? The answer is probably "no," for two reasons. First, hopefully not all ICUs in the world are confronted with the same extremely high rate of multiresistant pathogens as the one observed in that institution. Second, the time of infection onset is only one of the key variables associated with multiresistant pathogens. Most published decision trees for selecting initial therapy in patients with VAP integrate not only the timing of infection occurrence but also other specific risk factors for multiresistant micro-organisms, such as a previous contact with the health-care system and/or a recent prolonged antibiotic therapy [1, 2]. VAP, which is usually defined as infection occurring more than 48 h after hospital admission in a patient requiring MV, is in fact an entity that should be viewed as a subcategory of healthcare-associated pneumonia (HCAP). This point has very important therapeutic implications since early-onset VAP can occur in patients with previous contact with the healthcare system and thus may need therapy for multidrug-resistant bacterial pathogens. HCAP includes any patient hospitalized in an acute care hospital for 2 or more days within 90 days of the infection, resided in a nursing home or long-term care facility, receiving recent antibiotic therapy, chemotherapy, or wound care within the previous 30 days of the current infection, or attended a hospital or hemodialysis clinic [2, 15]. As underlined by several studies, the micro-organisms responsible for infection in such settings are exactly the same as those observed in late-onset infection. This type of information should therefore be taken into account for selecting initial antimicrobial treatment [2]. Interestingly, in the study by Giantsou et al. 99% of VAP episodes caused by *P. aeruginosa* and/or MRSA had been treated with antibiotics before the onset of infection. Only patients with early-onset infection and no specific risk factors, such as prolonged duration of hospitalization, admission from a healthcare-related facility, and recent antibiotic therapy, can be treated with a narrow-spectrum drug such as a nonpseudomonal third-generation cephalosporin [2].

The need to ensure patients with true bacterial infection immediately receive an appropriate antibiotic regimen should not lead to indiscriminate use of antibiotics in the ICU. For many patients with VAP, including those with late-onset infection, therapy can often be narrowed once the results of respiratory tract and blood cultures become available, either because an anticipated organism (such as *P. aeruginosa*, *Acinetobacter* species, and MRSA) was not recovered, or because the isolated organism is sensitive to a less broad-spectrum antibiotics than used in the initial regimen. For example, vancomycin and linezolid should be stopped if no MRSA is identified unless the patient is allergic to $\beta$-lactams and has developed an infection caused by a Gram-positive micro-organism. Very broad-spectrum agents such as carbapenems, piperacillin-tazobactam, and cefepime should also be restricted to patients with infection caused by pathogens susceptible only to these agents. Similarly, in the absence of an infection caused by a nonfermenting Gram-negative bacillus or extended-spectrum $\beta$-lactamase-producing Enterobacteriaceae, the $\beta$-lactam should be changed to a nonantipseudomonal antibiotic such as ceftriaxone or cefotaxime. However, clinicians must be aware that emergence of stable derepressed resistant mutants may lead to treatment failure when third-generation cephalosporins are chosen in the case of infections caused by *Enterobacter*, *Citrobacter*, *Morganella morganii*, or *Serratia* species, even if the isolate appears susceptible on initial testing. Because fluoroquinolones may particularly lead to selection of multidrug-resistant strains, their use should be carefully restricted to cases in which no other agent can be selected [16].

The commonly cited reason to use combination therapy is to achieve synergy in the therapy of *P. aeruginosa* or other difficult-to-treat Gram-negative bacilli. However, synergy has been clearly documented to be valuable only in vitro and in patients with neutropenia [17] or bacteremic infection [18], which is uncommon in VAP [1]. A recent meta-analysis evaluated all prospective randomized trials of $\beta$-lactam monotherapy compared to $\beta$-lactam-aminoglycoside combination regimens in patients with sepsis, of which at least 1,200 of the reported 7,586 patients had either HCAP or VAP [19]. This evaluation found that the clinical failure rate was similar with combination therapy, and that there was no advantage in the therapy of *P. aeruginosa* infections over monotherapy. In addition, combination therapy did not prevent the emergence of resistance during therapy, but did lead to a significantly higher rate of nephrotoxicity. Based on these data therapy could be switched to monotherapy in most patients after 3 or 5 days, provided that initial therapy is appropriate, clinical course appears favorable, and microbiological data do not prove to a very difficult-to-treat micro-organism with a very high in vitro minimal inhibitory concentration as with some nonfermenting Gram-negative bacilli [2].

Because unnecessary prolongation of antimicrobial therapy in patients with true bacterial infection may lead to the selection of multidrug-resistant micro-organisms without improving clinical outcome, efforts to reduce the duration of therapy for nosocomial infections are also warranted. An 8-day regimen can probably be standard for patients with VAP [20, 21]. Possible exceptions to this recommendation include immunosuppressed patients, those whose initial antimicrobial treatment was not appropriate for the causative micro-organism(s), and patients who had no improvement in clinical signs of infection.

The rapid emergence and dissemination of antimicrobial-resistant micro-organisms in hospitals worldwide is a problem of crisis dimensions. The root causes of this problem are multifactorial, but the core issues are clear.

The emergence of antimicrobial resistance is highly correlated with selective pressure that results from inappropriate use of antimicrobial agents. Appropriate antimicrobial stewardship includes not only the limitation of use of initially inappropriate agents in patients with VAP but also improving our ability to avoid administering unnecessary broad-spectrum antibiotics. Either we will be able to implement such a policy, or we and our patients will face an uncontrollable surge of very difficult-to-treat pathogens.

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