SUPPLEMENT ARTICLE

Treatment Guidelines and Outcomes of Hospital-Acquired and Ventilator-Associated Pneumonia

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Hospital-acquired pneumonia is the second most frequent nosocomial infection and the first in terms of morbidity, mortality, and cost. In recent years, international societies and, most recently, the American Thoracic Society jointly with the Infectious Disease Society of America, have developed guidelines for the management of hospital-acquired pneumonia, health care–associated pneumonia, and ventilator-associated pneumonia. These guidelines include recommendations for risk stratification, initial and definitive antibiotic treatment, and prevention. The validation of these guidelines is important because it confirms that they can be used in clinical practice, as quality indicators, and as a standard of care. Several processes can be validated and are included in the guidelines, such as the accuracy of the prediction of microorganisms according to stratification criteria and the impact of guidelines on outcomes, including length of hospital and intensive care unit stay, duration of mechanical ventilation, complications, and in-hospital and 30-day mortality. Clinical studies have shown that the accuracy of predicting microorganisms according to risk stratification is reliable (~80% and ~90%). Three studies suggest that the implementation of guidelines, with a special emphasis on antibiotic treatment, improves several parameters of outcome. Only one study, using a before-and-after design, showed a decrease in 14-day mortality after guidelines implementation. A key issue for these studies is to modify recommendations according to local patterns of microbiology and drug resistance. In summary, implementation of guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia decreases the rate of initial inappropriate antibiotic treatment and decreased 14-day mortality in a study. More clinical studies to validate the influence of guidelines on outcome are warranted.

Hospital-acquired pneumonia (HAP) is the second most common nosocomial infection and accounts for approximately one-fourth of all infections in the intensive care unit (ICU). Ventilator-associated pneumonia (VAP) is defined as HAP in patients receiving mechanical ventilation [1]. The incidence of VAP is 10%–30% among patients who require mechanical ventilation for >48 h. This incidence depends on the type of population studied, the presence or absence of risk factors, and the type and intensity of preventive measures implemented. Although mortality rates vary from one study to another and the prognostic impact of nosocomial pneumonia is debated, it is recognized that one-third to one-half of all HAP-related deaths are directly attributable to pneumonia [2].

Over the past decade, several risk factors associated with mortality have been detected. The most consistent and evident prognostic factor throughout the literature is the accuracy of initial inadequate antibiotic treatment [2]. In fact, in a large series involving patients with HAP, Alvarez Lerma et al [3] revealed that patients who received adequate antibiotic treatment had lower mortality than did those who received inadequate therapy (16% vs 25%). In addition, in that study, the numbers of complications, cases of septic shock, and cases of gastrointestinal hemorrhage were also lower in the group of patients receiving initial adequate antibiotic treatment. The percentage of inadequate treatment has varied in the literature from 22% to 73% [2]. In ad-

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dition, the microorganisms not covered by the initial treatment in these studies were most often multidrug-resistant microorganisms, such as *Pseudomonas aeruginosa, Acinetobacter* species, and methicillin-resistant *Staphylococcus aureus* (MRSA) [2, 3]. For all the aforementioned reasons, it is very important to establish antibiotic treatment protocols that potentially may cover most of the microorganisms causing HAP or VAP.

In 1996 [4] and in 2005 (jointly with the Infectious Disease Society of America [IDSA]) [5], the American Thoracic Society (ATS) released guidelines for the management of adults with HAP. The most recent guidelines, from 2005, included patients with VAP and patients with health care–associated pneumonia.

The algorithm for stratification of patients into initial treatment groups varied in the 1996 (Figure 1) and 2005 (Figure 2) recommendations. In 1996, the guidelines recommended stratifying patients according to severity of illness (mild to moderate), presence of risk factors, and the time of onset of pneumonia (early and late onset) [4]. This algorithm was simplified in 2005 with use of only the time of onset and the presence of risk factors for multidrug-resistant microorganisms [5].

In Tables 1 and 2, the potential microorganisms in the different stratification groups from both the 1996 and the 2005 guidelines are listed. An additional classification for patients receiving mechanical ventilation was proposed by Trouillet et al [6]. They divided patients into 4 categories according to the presence or absence of previous antimicrobial therapy and ⩾7 days or <7 days of mechanical ventilation (<7 days of mechanical ventilation and no antimicrobial therapy, <7 days of mechanical ventilation and antimicrobial therapy, ⩾7 days of mechanical ventilation and no antimicrobial therapy, and ⩾7 days of mechanical ventilation and antimicrobial therapy). Table 3 shows the distribution of microorganisms in relation to these variables.

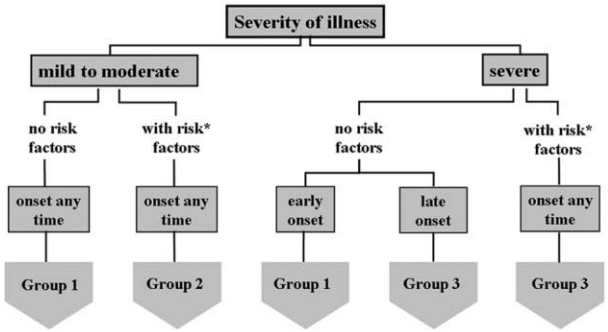

Figure 1. Algorithm for classifying patients with hospital-acquired pneumonia according to the Consensus Statement of the American Thoracic Society. Adapted with permission of the American Thoracic Society [4]. Copyright ©1996 American Thoracic Society. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventative strategies. A consensus statement. Am J Respir Crit Care Med 1996; 153:1711–1725.

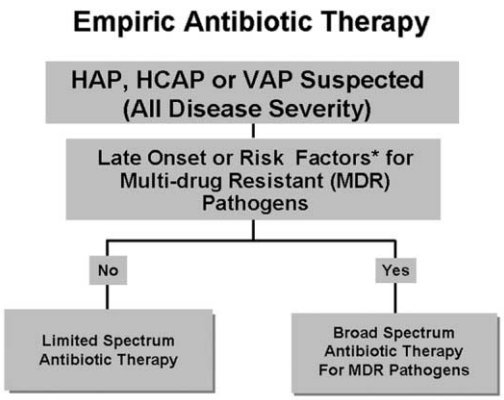

Figure 2. Algorithm for initiating empirical antibiotic therapy for hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and health care–associated pneumonia (HCAP), according to the 2005 American Thoracic Society and Infectious Diseases Society of America guideline. *****Prior antimicrobial therapy (within 90 days), hospitalization for ⩾5 days, high frequency of antibiotic resistance in the community or the hospital unit, immunosuppressive disease or therapy. Adapted with permission of the American Thoracic Society [5]. Copyright © 2005 American Thoracic Society. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated Pneumonia. Am J Respir Crit Care Med 2005; 171:388–416.

PREDICTION OF MICROORGANISMS ACCORDING TO STRATIFICATION GROUPS

Few studies have validated the accuracy of the prediction schemes for specific microorganisms. Leroy et al [7] studied 124 patients with proven HAP and assessed the microbial prediction according to the 1996 ATS guidelines [4] and to the classification of Trouillet et al [6] (Table 3). In this study, the ATS classification was able to detect episodes of HAP due to drug-resistant organisms with a negative predictive value of 100% and was more specific than the classification of Trouillet and colleagues.

In another study with similar design, Ioanas et al [8] also evaluated the 1996 ATS classification [4] and the criteria of Trouillet et al [6] in 71 patients with ICU-acquired pneumonia. The classifications of the ATS and Trouillet and colleagues showed an accuracy to predict 91% and 83% of causative microorganisms, respectively. The ATS approach failed to predict 2 microorganisms in patients classified in ATS group 2 (*P. aeruginosa* and MRSA) and 1 pathogen from a patient classified in group 3 (*Aspergillus* species). The use of the classifications of Trouillet and colleagues could properly predict the pathogen isolated in 15 (83%) of 18 patients and only failed to predict 3 pathogens: 1 MRSA in a patient in group 1, 1 MRSA in a patient in group 2, and 1 *Aspergillus* species in a patient in group 4.

More recently, we evaluated a series of patients with HAP in the ICU and the prediction of microorganisms with use of

Table 1. Potential Microorganisms in Each Group According to the 1996 Consensus Statement of the American Thoracic Society

Core organism
Group 1
Enteric gram-negative bacilli
Escherichia coli
Enterobacter species
Klebsiella species
Proteus species
Serratia marcescens
Haemophilus influenzae
MSSA
Streptococcus pneumoniae
Group 2[a]
Anaerobes
MSSA and MRSA
Legionella species
Pseudomonas aeruginosa
Group 3
Pseudomonas aeruginosa
Acinetobacter species
MRSA

NOTE. Data are from [4]. MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *S. aureus.*

[a] Risk factors include abdominal surgery, witnessed aspiration, coma, head trauma, diabetes mellitus, renal failure, receipt of high-dose steroids, prolonged intensive care unit stay, receipt of antibiotics, and structural lung disease.

both the 1996 ATS guidelines [4] and the 2005 ATS/IDSA recommendations [5]. We found that the 1996 guidelines better predicted the microorganisms causing HAP or VAP in the ICU [9].

Specifically, 10 patients (26%) in group 1 of the 2005 classification [5] had potentially drug-resistant bacteria despite the absence of risk factors for these microorganisms according to the guidelines. Reclassifying patients according to the 1996 guidelines, these microorganisms were correctly predicted in 9 (90%) of these patients. Additional prospective studies involving larger series are needed to confirm that the 1996 ATS guidelines are more accurate in predicting microorganisms, compared with the 2005 ATS/IDSA recommendations.

ADEQUACY OF TREATMENT AND OUTCOME

Because adequacy of treatment is associated with lower mortality, the initial goal should be guideline compliance. In a previous study, the adequacy of treatment according to the 1996 ATS guidelines [4] and the recommendations of Trouillet et al [6] was 79% and 80%, respectively [8]. Microorganisms associated with inadequate treatment according to the ATS guidelines were *P. aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia,* and MRSA, whereas *P. aeruginosa* was associated with inadequate treatment according to classifications of Trouillet and colleagues.

Ibrahim et al [10] implemented a treatment protocol based on accurate diagnosis definitions, microbiological confirmation of VAP, and the administration of imipenem plus ciprofloxacin as initial empirical antibiotic treatment. Fifty-two patients with VAP were evaluated before and after protocol implementation. The adequacy of initial treatment increased from 48% before intervention to 94% after intervention. The duration of antibiotic treatment was decreased from 15 to 9 days, and the likelihood of a second episode of VAP decreased from 24% to 8%. However, mortality was not changed.

With the aim to evaluate an antibiotic treatment protocol based on local microbiology data, Soo-Hoo et al [11] studied the treatment adequacy and outcome of 56 preguideline episodes of severe HAP and 61 episodes of severe HAP treated according to guidelines. With that purpose, they implemented an antibiotic protocol for HAP based on 1996 ATS guidelines, adjusted according to local microbiological and drug-resistance patterns. After the implementation of the local protocol, the adequacy of treatment increased from 46% to 81%. The 14-day mortality decreased from 27% to 8%. There were also differences with regard to hospital and 30-day mortality in favor of the prospectively treated group, although the differences were not statistically significant.

Overall, not much evidence exists on the influence of guidelines on outcomes in patients with VAP, and this reflects the difficulties of these studies. The only published study validating the 2005 ATS/IDSA guidelines showed that adherence of empirical treatment according to the guidelines resulted in more treatment adequacy but did not influence major outcome variables, such as hospital mortality [9]. As mentioned above, performance of more studies validating guidelines is important to confirm the usefulness of these guidelines in clinical practice.

ELEMENTS TO BE TAKEN INTO ACCOUNT TO VALIDATE GUIDELINES ON HAP AND VAP

Guidelines implementation. One of the most difficult problems with regard to guidelines is local implementation. A good example is the experience of Soo-Hoo et al [11]. To implement guidelines, the guidelines were first drafted and completed over several months. Then, a combined committee composed of members of the pulmonary and infectious diseases services and the pharmacy met, and the guidelines were discussed and confirmed. The guidelines underwent pilot testing for several months and, then, were posted and distributed to each group of house staff rotating through the medical ICU. Guidelines were distributed twice every 4 weeks. The guidelines were reviewed regularly by each group of stakeholders and were also

Table 2. Initial Empirical Antimicrobial Treatment for Patients with Hospital-Acquired, Ventilator-Associated, or Health Care–Associated Pneumonia, according to the 2005 American Thoracic Society and Infectious Disease Society of America Guidelines

Potential pathogen	Recommended antibiotic treatment
No risk factors for MDR, early onset, and any disease severity	Ceftriaxone; levofloxacin, moxifloxacin, ciprofloxacin; ampicillin-sulbactam; or ertapenem
Streptococcus pneumoniae	…
Haemophilus influenzae	…
MSSA	…
Antibiotic-susceptible, enteric gram-negative bacilli	…
Escherichia coli	…
Klebsiella pneumoniae	…
Enterobacter species	…
Proteus species	…
Serratia marcescens	…
Late onset disease or risk factors for MDR pathogens and all disease severity	Combination antibiotic therapy: antipseudomonal cephalosporin (cefepime or ceftazidime), antipseudomonal carbapenem (imipenem or meropenem), or β-lactam or β-lactamase inhibitor (piperacilin-tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) plus linezolid or vancomycin (if risk factors present)
Pseudomonas aeruginosa	…
K. pneumoniae (ESBL)	…
Acinetobacter species	…
Legionella pneumophila	…
MRSA	…

NOTE. Data are from [5]. ESBL, extended-spectrum β-lactamase; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *S. aureus.*

available on the internet. The guidelines were also reviewed regularly by one of the staff physicians during daily rounds or by one of the members of the pharmacy or infectious diseases service. During the first few months after the introduction of the guidelines, regular conference sessions were held with house staff rotating through the medical ICU to reinforce the guidelines. In summary, implementation of local guidelines is a difficult task and a key element to performing studies with a before and after design.

Delay of initial antibiotic treatment. Delay of initial antibiotic treatment may influence the results of any studies to validate guidelines. In retrospective studies, it is very difficult to know the timing of initial antibiotic treatment; however, in prospective studies, the period from initial diagnosis to treatment needs to be standardized. For example, in a study by Iregui et al [12], 107 patients were divided into 2 groups: one group received antibiotic therapy >24 h after diagnosis, and the other group received antibiotic therapy ⩽24 h after diagnosis. A delay of >24 h was an independent risk factor of mortality (odds ratio, 7.68). The most common reason for delayed antibiotic administration was a delay in writing medical orders (78.5% of patients). The results of this study are a clear example of how outcomes in patients with VAP may be modified by other factors, in addition to adherence to antibiotic recommendations in guidelines.

Dosages of antibiotics. Dosages and intervals of administration of antibiotics may be associated with outcomes in patients. In particular, dosages and intervals of administration are important for treatment of infection due to multidrug-resistant microorganisms. A classic study by Paladino et al [13] showed better survival among patients with VAP caused by *P. aeruginosa* when the area under the curve to minimum inhibitor concentration ratios for ciprofloxacin were optimized. The ATS/IDSA guidelines [5] recommend dosages and intervals of administration based on pharmacokinetic and pharmacodynamic information. Optimization of dosages and avoidance of comparisons of patients with different dosage or administration intervals are important in studies of validation.

Local adaptation of guidelines. The patterns of microbial agents and their drug-resistance patterns vary from hospital to hospital and from unit to unit in a hospital. The variability of microorganisms and resistance to antibiotics was confirmed by Rello et al [14] in a study comparing 4 different ICUs in Barcelona, Madrid, Seville, and Paris. Different incidences of multidrug-resistant pathogens were found in the 4 units.

Beardsley et al [15] implemented nosocomial pneumonia

Table 3. Numbers and Percentages of Microorganisms Responsible for 135 Episodes of Ventilator-Associated Pneumonia Classified According to the Duration of Mechanical Ventilation (MV) and Prior Antibiotic Therapy (ATB)

Organisms	Group 1 (n = 22) MV <7 days, ATB = no	Group 2 (n = 12) MN <7 days, ATB = yes	Group 3 (n=17) MV ⩾7 days, ATB = no	Group 4 (n= 84) MV ⩾7 days, ATB = yes
Total number of bacteria	41	20	32	152
Multidrug-resistant bacteria	0[a]	6 (30)	4 (13)[b]	89 (59)
Pseudomonas aeruginosa	0	4 (20)	2 (6)	33 (22)
Acinetobacter baumannii	0	1 (5)	1 (3)	20 (13)
Stenotrophomonas maltophilia	0	0	0	6 (4)
MRSA	0	1 (5)	1 (3)	30 (20)
Other bacteria	41 (100)	14 (70)	28 (88)	63 (42)
Enterobacteriaceae	10 (25)	4 (20)	7 (22)	23 (15)
Haemophilus species	8 (20)	2 (10)	1 (3)	4 (3)
MSSA	6	0	7 (22)	7 (5)
Streptococcus pneumoniae	3	0	0	0
Other streptococci	7	5 (25)	7 (22)	14 (9)
Neisseria species	5	2 (10)	4 (13)	3 (2)
Other pathogens	2	1 (5)	2 (6)	12 (8)

NOTE. Data are no. or no. (%) of patients. MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *S. aureus.* Adapted with permission of the American Thoracic Society [6]. Copyright ©1998 American Thoracic Society. Trouillet JL, Chastre J, Vuagnat A, Joly-Guillou ML, Combaux D, Dombret MC, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med 1998;157:531–539.

[a] P<.02, compared with groups 2, 3, and 4.

[b] P<.0001, compared with group 4.

guidelines and stratified the groups according to the onset period: early-to-late onset (⩽10 days) and late-to-late onset (>10 days). With this strategy, the initial treatment adequacy was >90%. Furthermore, the addition of ciprofloxacin to β-lactams did not improve treatment adequacy, but the addition of an amingolycoside did.

HAP versus ICU-acquired pneumonia. Although nosocomial pneumonia acquired in units other than the ICU and ICU-acquired pneumonia are considered together in guideline recommendations, microorganisms and mortality are probably different. Unfortunately, there are few studies on the epidemiology of nosocomial pneumonia outside the ICU. Sopena et al [16] performed a multicenter study involving 165 patients with nosocomial pneumonia acquired in units other than the ICU. The overall mortality was 26%. Of interest, *Streptococcus pneumoniae* was one of the most frequent microorganisms and, in several cases, it was independent of the time to onset of nosocomial pneumonia. In our opinion, when validating guidelines, ICU and non-ICU patients should be investigated separately.

Early microbiological resistance testing. Early microbiological results may help to implement early antibiotic modifications. In addition, rapid tests to detect microbiological resistance (eg, MRSA) may provide quick detection of drug-resistant organisms and consequently lead to changes in antibiotics. For example, Bouza et al [17] randomized patients with VAP to have respiratory samples studied with a rapid E-test to detect microbiological resistance. Although there were no differences in mortality, the median duration of mechanical ventilation was lower in the group that had the E-test performed than in the group that did not have the test performed. The findings of this study are important for the design of future validation studies.

CONCLUSIONS

Validation of guidelines for HAP are important to confirm the reliability of these guidelines in clinical practice and their impact on outcome parameters. Overall, implementation of guidelines is followed by an increase in initially adequate antibiotic treatment. In addition, only a few studies have shown that the prediction of microorganisms by HAP guidelines is reliable. Studies of validation are not easy and have to take into account different variables potentially related with outcome in patients with HAP.

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