A Comparison of the Efficiency of Treatment With Imipenem/Cilastatin, Ceftazidime and Piperacillin/Tazobactam in Patients With Ventilator-Associated Pneumonia

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Abstract

Objective: To compare the efficacy of three separate antibiotics (ceftazidime, imipenem/cilastatin and piperacillin/tazobactam) as an early empiric (de-escalating) antibiotic therapy in patients with ventilator-associated pneumonia (VAP).

Materials and Methods: Forty-nine patients with VAP caused by Gram (-) organisms, were given ceftazidime (13 patients), imipenem/cilastatin (19 patients) or piperacillin/tazobactam (17 patients) as an early empiric therapy. By the end of the treatment the adequacy of the antibiotic treatment was evaluated clinically (cured, partly cured, failure), bacteriologically (eradication, persistence of the pathogen, new infection) and also as number of days free of mechanical ventilation and of application of antibiotic agents in the three groups.

Results: There were no differences as to sex, age, diagnosis, severity, complications (sepsis, septic shock, multiorgan insufficiency) or pathogens causing VAP among the three groups of patients. Treatment with imipenem/cilastatin resulted in the highest percentage of pathogen eradication, the highest number of days without mechanical ventilation and of application of antibiotics and the highest chance of favourable outcome ($p<0.05$), thus imipenem/cilastatin was found to be superior as an initial therapeutic agent to the other two antibiotics.

Conclusions: Early empiric antibiotic therapy is the prerequisite of a successful treatment in VAP. In this study, imipenem/cilastatin was found to be the antibiotic of choice as an initial antibiotic. Treatment with imipenem/cilastatin was found to lead to better clinical and microbiological results compared to ceftazidime and piperacillin/tazobactam. Treatment with this antibiotic also proved to be more cost-effective because of the shorter duration of treatment and of mechanical ventilation.

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Introduction

Pneumonia in patients on artificial pulmonary ventilation (Ventilator-Associated Pneumonia; VAP) is the most common nosocomial infection in intensive care units. The incidence of VAP can be as high as 57% depending on the population studied, the type of intensive care unit and of diagnostic criteria applied (1,2). VAP is associated with considerable mortality. Death from VAP can be 2 to 10 times higher than death from other causes in patients in intensive care (3,4). Of crucial importance for the outcome of the disease is the adequacy of the initial empiric antibacterial therapy (5,6). Following the 1996 recommendations of the American Tho-

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racic Society (7), a new, so called de-escalation therapy has been implemented lately (8,9). This therapy entails 1) prompt onset of wide-spectrum antibiotic therapy (even when the results of the direct microscopic evaluation are negative), 2) choice of an antibiotic with good penetration to the pulmonary tissue, 3) application of the antibiotic in high doses, and 4) alteration of the antibacterial therapy, if necessary, in accordance with the microbiology test results.

The de-escalation strategy defines the balance between the need for implementing an adequate initial treatment in high risk patients and the need for avoiding an unnecessary antibiotic application (10,11). The choice of the initial empiric treatment should be in compliance with the local microbiological "picture" which may be different in different countries, in different hospitals and even in separate hospital units within the same hospital. This imposes the development of local antibiotic treatment algorithms, based on clinical data, microbiological and epidemiological testing, local hospital recommendations and cost efficiency (12).

The goal of our study was to compare the effect of ceftazidime, imipenem/cilastatin and that of piperacillin/tazobactam, as an early empiric (de-escalation) antibiotic therapy regimen in patients with VAP.

Materials and Methods

The Intensive Care Unit (ICU) of the Department of Anesthesiology and Intensive Care of the Medical University of Plovdiv, Bulgaria, has 16 beds. On average 260-280 patients, including both surgical and non-surgical cases, are treated per year. Approximately 25% of our patients (60 to 70 per year) require mechanical ventilation. The most common agents of nosocomial infections are Gram (-) organisms, mainly *Pseudomonas aeruginosa* and *Acinetobacter baumanii*. Since the end of 1996 a protocol for antibiotic treatment of nosocomial pneumonia following mechanical ventilation is in effect in our ICU, based on the early empiric application of antibacterial agents which are active against these organisms.

This study is based on a retrospective analysis of all VAP cases caused by Gram (-) organisms admitted to the ICU between January 1997 and December 2002 (49 patients in total). All these patients had received either ceftazidime (n=13), imipenem/cilastatin (n=19) or piperacillin/tazobactam (n=17) as an early empiric therapy. The total survival rate was 61.22% (30 patients). Patients referred from another ICU with already developed VAP, patients with acquired immune deficiency (AIDS, following treatment with steroids and cytostatics) and those with neutropenia (WBC<1000 mm^3) were not included in the analysis.

A diagnosis of VAP was made in patients whose findings (appearing at least 48 hours after the start of the mechanical ventilation) were in compliance with the criteria of the Centres for Disease Control and Prevention (CDC) (13) for pneumonia and whose total points for the Clinical Pulmonary Infection Score (CPIS) (14,15) was over 7.

Microbiological tests on samples from tracheobronchial aspiration material, from mini-bronchoalveolar lavage (mini-BAL) fluid, from pleural effusion fluid and from blood were done immediately before starting the antibiotic therapy and then repeated three times a week. All organisms were identified and tested for resistance in accordance with the disc-diffusion method of Curby-Bauer and following the assessment of minimal inhibitory concentration of Septor system of Becton-Dickinson, in compliance with the criteria of the American National Committee for Clinical Laboratory Standards (NCCLS).

Patients who were diagnosed as VAP following the obtaining of samples for microbiological testing, regardless of the results of direct microscopic findings, were immediately started on a treatment regimen with one of the following antibiotics given intravenously in the indicated doses: Ceftazidime 3x2.0 g/day, imipenem/cilastatin 3x1.0 g/day or piperacillin/tazobactam 3x4.5 g/day.

The clinical effect of the treatment was evaluated as "cured" when all symptoms of the primary infection disappeared and the antibiotic treatment could be discontinued; as "partly cured" when the clinical symptoms of the infection showed a tendency toward improvement, but did not not completely resolve and the antibiotic therapy was continued as started; and "failure" in case of no effect or worsened clinical signs such as development of severe sepsis or multiorgan insufficiency. This last group required a change in the antibiotic therapy. Additional indicators for clinical efficacy were number of days with no need for mechanical ventilation (number of days out of the first 28 days following the initiation of the antibiotic therapy, when there was no need for the patient to be on mechanical ventilation) and number of days without antibiotic therapy (number of days out of the first 28 days following the initiation of the antibiotic therapy, when there was no need for the patient to be treated with antibiotics).

The bacteriological outcome, or effect at the end of the treatment was defined as "eradication" of the pathogen when the original pathogen was not isolated or there was no pathological material left to be sampled; "persistence of the pathogen" when the original pathogen was isolated from the infection site; and "new infection" when the original agent was eradicated but one or several more were isolated from the sample taken from the infection site.

The antibiotic therapy was defined as "adequate" according to the susceptibility results of the isolated organisms to the antibiotic therapy applied (i.e. according to the *in vitro* susceptibility of the isolated organism), or in patients in whom no organism was isolated, improvement of the clinical condition by the 72^{nd} hour from the start of the treatment. In case of "inadequate initial antibiotic therapy", based on the results of the microbiology test, the antibiotic regimen was changed.

The statistical processing of the collected data was done with alternative, variation and non-parametric analysis. For statistically significant differences, a level of significance of $p<0.05$ was accepted. The statistics SAS-Version 8 was used in the analyses.

Results

A total of 103 patients were found to develop VAP during the study period. Due to deviations from the accepted protocol 21 patients were excluded from the study. Another 18 patients were excluded, as they had received as an early empiric antibiotic therapy, antibiotics other than those listed in the "Materials and Methods" section. Of the remaining 64 patients, 15 were also excluded from the study due to isolation of Gram (+) organisms or of fungi as agents of infection.

Thus, the effect of the applied initial empiric antibiotic therapy using three different antibiotic regimens has been evaluated in a total of 49 patients with VAP, caused by Gram (-) organisms. No significant difference was found between these three groups concerning age, sex and severity of condition (defined with APACHE II score) (Table 1).

The complications of the infection such as sepsis, septic shock and polyorgan insufficiency, are shown on Table 2. There are no significant differences between the groups here as well ($p>0.05$).

Table 3 indicates the Gram (-) organisms isolated in the initial samples of the VAP patients. The most common agent isolated was *Pseudomonas aeruginosa* in 37 cases, followed by *Acinetobacter* spp. in 26 patients. A polybacterial flora was isolated in 29 patients, the most common combination being that of *Pseudomonas aeruginosa* and *Acinetobacter* spp. in 21 cases.

The bacteriological effect, evaluated as "eradication of the pathogen", "persistence of the pathogen" and "new infection" was found to be considerably more favorable for the group treated with imipenem/cilastatin compared to ceftazidime ($p<0.05$; $\chi^2=6.97$). The comparison of these two groups using the Student-Fisher criteria showed that this difference was due to the higher rate of eradication, which was 12 (63.16%) in the group on imipenem/cilastatin and only 3 (23.08%) for ceftazidime ($p<0.01$; $t=2.59$) (Table 4).

Only in 4 patients (21.05%) from the group on imipenem/cilastatin, the initial antibiotic therapy was found to be inadequate and there was a need to change the antibiotic, while the therapy was found to be inadequate in 6 patients (35.29%) in the group on piperacillin/tazobactam and in 9 patients (69.23%) receiving ceftazidime. The differences indicating the superiority of imipenem/cilastatin to the other two antibiotics were significant ($p<0.05$; $\chi^2=8.745$).

There was no statistical difference between the distribution of patients regarding outcome. Numbers of lethal cases in the three groups were 6 (35.29%) for the piperacillin/tazobactam group, 7 (53.85%) for the ceftazidime group and 6 (31.58%) for the imipenem/cilastatin group ($\chi^2=1.281$; $p>0.05$).

The comparison of the three groups for clinical outcome (cured, partly cured, failure) also showed no significant differences ($\chi^2=2.376$; $p>0.05$) (Table 5).

Indicators related to the pharmaco-economic effect of the treatment were also analyzed (Table 6). Duration of stay in intensive care unit in all three groups was similar ($p>0.05$).

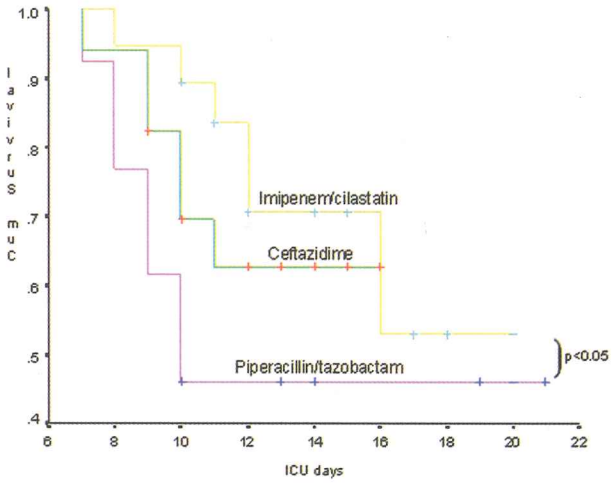

Figure 1.

Table 1. Patient characteristics in the groups receiving different antibiotics

	Piperacillin/tazobactam (n=17)	Ceftazidime (n=13)	Imipenem/cilastatin (n=19)	p
Age (years), (mean±SD)	51.59±14.80	50.54±18.34	54.00±16.57	>0.05
Sex, M/F	10/7	8/5	11.8	>0.05
APACHE II scale, (mean±SD)	19.00±2.65	19.77±3.79	18.32±2.50	>0.05

Table 2. Frequency of complications in the three groups

	Piperacillin/tazobactam (n=17)	Ceftazidime (n=13)	Imipenem/cilastatin (n=19)	p
Sepsis	14 (82.35%)	12 (92.31%)	14 (73.68%)	>0.05
Septic shock	3 (17.65%)	3 (23.08%)	2 (10.53%)	>0.05
Polyorgan insufficiency	10 (58.82%)	8 (61.54%)	11 (57.89%)	>0.05

Table 3. Isolated Gram (-) pathogens in the three groups			
	Piperacillin/tazobactam (n=17)	Ceftazidime (n=13)	Imipenem/cilastatin (n=19)
Acinetobacter spp.	1	0	3
Escherichia coli	1	1	1
Klebsiella pneumoniae + *Acinetobacter* spp.	1	0	0
Klebsiella pneumoniae + *Serratia marcescens*	0	0	1
Proteus mirabilis + *Escherichia coli*	1	1	1
Pseudomonas aeruginosa	5	4	4
Pseudomonas aeruginosa + *Acinetobacter* spp.	7	6	8
Pseudomonas aeruginosa + *Serratia marcescens*	1	1	1

Table 4. Bacteriological effects of the applied treatment in the three groups				
	Piperacillin/tazobactam (n=17)	Ceftazidime (n=13)	Imipenem/cilastatin (n=19)	p
Eradication	6 (35.29%)	3 (23.08%)	12 (63.16%)	<0.05
Persistence	6 (35.29%)	6 (46.15%)	3 (15.79%)	>0.05
New infection	5 (29.41%)	4 (30.77%)	4 (21.05%)	>0.05

Table 5. Clinical effects of the treatment				
	Piperacillin/tazobactam (n=17)	Ceftazidime (n=13)	Imipenem/cilastatin (n=19)	p
Cured	5 (29.41%)	2 (15.38%)	7 (36.84%)	>0.05
Partly cured	6 (35.29%)	4 (30.77%)	6 (31.58%)	>0.05
Failure	6 (35.29%)	7 (53.85%)	6 (31.58%)	>0.05

Table 6. Days of stay in ICU, days free of antibiotics and of mechanical ventilation in the three groups				
	Piperacillin/ tazobactam (n=17)	Ceftazidime (n=13)	Imipenem/cilastatin (n=19)	p
Duration of stay in ICU [days], (mean±SD)	11.53 (2.45)	12.15 (4.88)	13.21 (3.10)	>0.05
Days free of AB, (mean±SD)	14.64 (2.69)	11.50 (4.93)	15.77 (2.49)	<0.05
Days free of mechanical ventilation, (mean±SD)	18.36 (2.29)	16.17 (4.83)	20.46 (2.63)	<0.05

The analysis of the other two indicators showed that patients on imipenem/cilastatin had the highest number of days free from antibiotic application (average 15.77±2.49, F=3.78, $p<0.05$) and the highest number of days free from mechanical ventilation (average 20.46±2.63, F=4.25, $p<0.05$).

The effect of the antibiotic therapy on the survival of the patients was assessed using the Kaplan-Meier analysis. The survival analysis presented in Figure 1 and the additional analysis done (Breslow statistics) showed that treatment with imipenem/cilastatin compared to piperacillin/tazobactam led to a higher survival rate ($p<0.05$).

Discussion

Inadequate therapy is an independent variable for increased mortality in patients with VAP (16,17). The early application of an adequate antibiotic is of crucial importance for the outcome. The antibacterial therapy has to be effective on the most probable agents causing VAP, based on the results of microbiological monitoring in intensive care units. In patients with VAP who received early adequate therapy started before the microbiological test results are available, the probability to survive is twice higher compared to inadequate therapy or its delay till the results of the microbiological tests are available (3,18-21).

The objective of the protocol that has been implemented in our ICU several years ago, based on de-escalation strategy, is to initiate adequate antibiotic therapy, mainly against Gram (-) organisms, at an early stage. If we compare the total mor-

tality in our series (approximately 38%) with the results of other authors (17,19,22-26), who reported mortality rates ranging from 25% to 47% in patients who received adequate initial antibacterial therapy, we can come to the conclusion that we have chosen an optimal approach to treat our patients. The patients in our series who received different antibiotic regimens were essentially similar in severity of their clinical condition. The primary reason for admission to ICU was development of complications and isolation of VAP causing agents. This relative homogeneity shows that possible differences between the groups have to be related only to the antibiotic treatment applied. Indeed, significant differences were found among the groups of patients treated with imipenem/cilastatin, piperacillin/tazobactam and ceftazidime.

Although no statistically significant differences were found in final outcome among the three groups, mortality in the group treated with imipenem/cilastatin was 31.58%, while this figure was 53.85% in the group on ceftazidime. As to the clinical effects of the treatment, 36.84% of the patients treated with imipenem/cilastatin were evaluated as "cured", while this figure was only 15.38% in those treated with ceftazidime, although the differences were not of statistical significance. On the other hand, the survival analyses showed a reliable higher probability of survival in patients treated with imipenem/cilastatin, compared to piperacillin/tazobactam. We consider these results to show the superiority of imipenem/cilastatin compared to the other two antibiotics as far as clinical effect is concerned.

Evaluation of the effect of the antibiotic on the causative organism, again showed imipenem/cilastatin to have the highest efficiency.

In the group on imipenem/cilastatin the frequency of patients receiving adequate initial therapy was the highest (79%), while the need to change the initial therapy was the lowest. This is probably the reason for better clinical and bacteriological results.

Although no pharmaco-economic analysis was performed in this study, the significantly shorter duration of application of antibiotic therapy and of mechanical ventilation in the imipenem/cilastatin group, indicate the superiority of this antibiotic also with regard to financial and human resources issues.

Our survey has several serious limitations. The patients with Gram (+) agents have been excluded. The ground for this decision was the relatively low rate of these infections in our ICU, which for the time being does not make necessary the application of glycopeptide antibiotics, as early empiric therapy. Based on the literature (27-29), the prevalence of Gram (+) agents in VAP, and especially MRSA, is on the increase in the last two decades. In accordance with the applied protocol, in case the results of the microbiological monitoring show an increase in the incidence of Gram (+) pathogens over 20%, the initial antibiotic therapy will be supplemented with vancomycin at a dose of 2x1.0 g. If the incidence rate remains below 20%, we consider the early inclusion of glycopeptides to be unjustified.

In conclusion, the results of this study show that early empiric antibiotic therapy based on the principles of the de-escalating strategy is successful. In our patients, imipenem/ cilastatin was found to be the most successful initial antibiotic regimen. Compared to ceftazidime and piperacillin/tazobactam, imipenem/cilastatin was found as the most adequate antibiotic therapy, yielding the best clinical and bacteriological results. With this antibiotic, duration of antibiotic application and of mechanical ventilation were shorter, indicating a higher degree of cost-effectiveness.

References

1. Rello J, Paiva JA, Baraibar J, et al. International conference for the development of consensus on the diagnosis and treatment of the ventilator-associated pneumonia. Chest 2001(3);120:955-70.
2. Kollef M. Ventilator-associated pneumonia. JAMA 1993;270:1965-70.
3. Torres A, Aznar R, Gatell JM, et al. Incidence, risk and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. Am Rev Respir Dis 1990;142:523-8.
4. Heyland DK, Cook DJ, Griffith L, et al. The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient: the Canadian Critical Trials Group. Am J Respir Crit Care 1999; 159:1249-56.
5. Kollef MH, Sherman G, Ward S, et al. Inadequate antimicrobial treatment of infections: A risk factor for mortality among critically ill patients. Chest 1999;115:462-74.
6. Alvarez-Lerma F, for the ICU-Acquired Pneumonia Group: Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. Intensive Care Med 1996;22:387-94.
7. American Thoracic Society. Hospital-acquired pneumonia in adults: diagnosis, assessment, initial severity, and prevention. A consensus statement. Am J Respir Crit Care Med 1996;153:1711-25.
8. Bodi M, Ardanuy C, Olona M, Castander D, Diaz E, Rello J. Therapy of ventilator-associated pneumonia: the Tarragona strategy. Clin Microbiol Infect 2001 Jan;7(1):32-3.
9. Rello J, Diaz E. Optimal use of antibiotics for intubation-associated pneumonia. Intensive Care Med 2001;27:337-9.
10. Ibrahim EH, Ward S, Sherman G, et al. Experience with clinical guidelines for the treatment of ventilator-associated pneumonia. Crit Care Med 2001;29:1109-15.
11. Kollef MH. Optimizing antibiotic therapy in the intensive care unit setting. Critical Care 2001;5:189-95.
12. Hubmayr RD, Burchardi H, Elliot M, et al. Statement of the 4th International Consensus Conference in Critical Care on ICU-Acquired Pneumonia. Intensive Care Med 2002;28:1521-36.
13. Garner JS, Jarvis WR, Emori TG, et al. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988;16:128-40.
14. Garrard CS, Peacock SJ. Ventilator-associated Pseudomonas aeruginosa pneumonia: the clinical and microbiological response to antibiotic therapy. Clinical Intensive Care 2000;11(6):319-26.
15. Luna CM, Blanzaco D, Niederman MS, et al. Resolution of ventilator-associated pneumonia: Prospective evaluation of the Clinical Pulmonary Infection Score as an early clinical predictor of outcome. Crit Care Med 2003;31(3):676-82.
16. Koleff M. Appropriate empirical antibacterial therapy for nosocomial infections. Getting it right the first time. Drugs 2003;63(20):2157-68.
17. Sanchez-Nieto J-M, Torres A, Garcia-Cordoba F, et al. Impact of invasive and noninvasive quantitative culture sampling on outcome of ventilator-associated pneumonia: a pilot study. Am J Respir Crit Care Med 1998;157:371-6.
18. Celis R, Torres A, Gatell JM, et al. Nosocomial pneumonia: a multivariate analysis of risk and prognosis. Chest 1988;93:318-24.
19. Luna CM, Vujacich P, Niederman MS, et al. Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. Chest 1997;111:676-85.
20. Fiel S. Guidelines and critical pathways for severe hospital-acquired pneumonia. Chest 2001;119:412S-8S.

21. Iregui M, Ward S, Sherman G, et al. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest 2002;122:262-8.
22. Rello J, Gallego M, Mariscal D, et al. The value of routine microbial investigation in ventilator-associated pneumonia. Am J Respir Crit Care Med 1997;156:196-200.
23. Alvarez-Lerma F. Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. ICU-Acquired Pneumonia Study Group. Intensive Care Med 1996;22:387-94.
24. Kollef MH, Bock KR, Richards RD, Hearns ML. The safety and diagnostic accuracy of minibronchoalveolar lavage in patients with suspected ventilator-associated pneumonia. Ann Intern Med 1995;122:743-8.
25. Ruiz M, Torres A, Ewig S, et al. Noninvasive versus invasive microbial investigation in ventilator-associated pneumonia: evaluation of outcome. Am J Respir Crit Care Med 2000;162:119-25.
26. Dupont H, Mentec H, Sollet JP, Bleichner G. Impact of appropriateness of initial antibiotic therapy on the outcome of ventilator-associated pneumonia. Intensive Care Med 2001;27:355-62.
27. Spencer RC. Predominant pathogens found in the European Prevalence of Infection in Intensive Care Study. Eur J Clin Microbiol Infect Dis 1996;15:281-5.
28. Chastre J, Fagon J-V. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002;165:867-903.
29. National Nosocomial Infections Surveillance (NNIS) report, data summary from October 1986-April 1997, issued May 1997: a report from the NNIS System. Am J Infect Control 1997;25:477-87.