ERJ Express. Published on February 12, 2009 as doi: 10.1183/09031936.00149508

Feedback dose alteration significantly affects probability of pathogen eradication in nosocomial pneumonia

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Key word

Nosocomial pneumonia, optimizing antibiotic therapy, pharmacokinetic/pharmacodynamic indices

Short title

Optimizing antibiotic therapy in nosocomial pneumonia

Abstract

Background: Nosocomial pneumonia (NP) is associated with considerable morbidity and mortality. Data have shown that inadequate initial antibiotic therapy is a major risk for infection-attributed mortality. The aim of the study was to measure antibiotic concentration and MIC's in infected hospitalized patients early in therapy to determine if dose alternations, in those with low drug concentrations could affect outcomes.

Methods: Only patients treated with aminoglycosides (AG), fluoroquinolones (FQ), and beta-lactams (βL) were evaluated. MICs were determined using standard NCCLS procedures. Antibiotics were assayed using validated HPLC methods. PK/PD markers adopted were: AG peak/MIC ratio ≥8 mg/l; FQ peak/MIC /≥10 mg/l; βL peak/MIC ≥4 mg/l and $T_{>MIC}$ ≥70%. Statistical analyses were performed using the SYSTAT for Windows v. 10.2.

Results: 638 patients with NP were included in the study. In 205 patients, both drug concentration and isolate MIC were available while in other patients, used as controls, one or both parameters were lacking. For clinical outcome, the APACHE II score($p<0,0001$), the presence of combination therapy ($p=0.0014$) and whether both MIC and drug concentration(s) ($p=0,0002$) were measured significantly affected the probability of a good outcome. For microbiological outcome, the MIC (≤ 2 mg/L) for the βL ($p<0,0001$) and whether the second drug was a FQ or AG (FQ > AG) ($p=0,0177$) and whether the measurement of both MIC and drug concentration(s) were measured .($p=0,02$) affected the probability of eradication.

Conclusions: Measurement of drug concentrations and determination of pathogen MIC values with subsequent dose alteration significantly improves the probability of good clinical outcome and pathogen eradication in NP.

Introduction

Nosocomial pneumonia (NP) remains a major cause of mortality and morbidity despite advances in antimicrobial therapy and supportive care (1). The mortality attributed to an episode of NP is debated but could be as high as 30% (2). Multiple studies have shown that NP increases hospital length of stay by an average of 7 to 10 days, and, in patients with ventilator-associated pneumonia, the duration of both mechanical ventilation and ICU stay is increased (3). In the last 10 years, evidence has accumulated that initial inappropriate antibiotic treatment is an important independent risk factor for excess mortality in patients with NP. In order to address this problem of excess mortality, several strategies have been suggested (4). Optimization of antibiotic dosing regimens is one approach that might ameliorate this problem (5). Recognizing that the MIC of the pathogen being treated and the individual patient's pharmacokinetic handling of the drug being employed each has an important and independent impact on the probability of a good clinical and microbiological outcome (6-7), it becomes crucial to know the MIC of the infecting pathogen for the drug employed and obtain an accurate estimate of the drug exposure to aid in the prediction of antimicrobial activity. Unfortunately, in clinical practice, it is rare to be able to know the pharmacokinetics of a drug in a patient (8). We reasoned that measuring the drug concentrations in infected patients as well as knowing the infecting organism's MIC would allow rapid identification of patients at high risk for clinical and microbiological treatment failure. As a primary hypothesis, we wished to test whether measuring drug exposure and pathogen MIC and subsequently altering dose when the seriously infected patient was felt to be at high risk of failure would significantly alter the probability of a good clinical or microbiological outcome.

Methods

Study Design and Population We started a pharmacokinetic/pharmacodynamic (PK/PD) program involving patients with Nosocomial Pneumonia (NP). The primary endpoint of the program was to measure PK/PD parameters in patients with severe infections and to evaluate the effect on the outcome. Only patients receiving aminoglycosides (amikacin), fluoroquinolones (ciprofloxacin or levofloxacin) and beta-lactams (ceftazidime or cefotaxime) were considered in the study. APACHE II score was calculated in all patients. The sequence of procedures to adjust the dose was the following: a) isolation of the pathogen and performance of an MIC test, b) initiation of therapy according to patient's physician choice, c) PK analysis, d) adjust dose or interval using pharmacodynamic principles, e) re-determine concentrations. The adopted pharmacodynamic indices were: aminoglycoside peak/MIC ≥8 mg/l; fluoroquinolone peak/MIC/≥10 mg/l; β-lactam peak/MIC ≥4 mg/l and $T_{>MIC}$ ≥70%. The same values were used for patients receiving monotherapy or combination therapy. For the aminoglycosides and fluoroquinolones, optimising the Cmax/MIC ratio was the primary objective. While there is literature indicating that AUC/MIC ratio may be the best pharmacodynamically-linked variable for these agents, we employed the Cmax/MIC ratio for tractability of implementation. For β-lactams, we decided that the T>MIC value should exceed 70% as the primary goal of therapy. Due to the limited clinical experience with targeting dosing regimens of βLs in this way, also maintaining a Cmax/MIC ratio >4 was recommended by our Ethics Committee. Only patients treated by intravenous (i.v.) infusion were included in the study. Initial dosage was: amikacin 15 mg/kg every 24 h, cefotaxime or ceftazidime 2g every 8 h, ciprofloxacin 400 mg every 12 h, and levofloxacin 500 mg every 12 or 24 h. The sampling times used to estimate PK parameters were: aminoglycoside peak: 0.5 h post end of 30 min infusion, fluoroquinolone peak: 0.5 h post end of 60 min infusion, β-lactam sampling times were: peak - 0.5 h post end of 30 min infusion and then 5.6 h from start of infusion, which is at 70% of the 8 hour dosing interval. To estimate dose correction, each patient's data (age, sex, weight, height, serum creatinine, serum albumin), combined with his/her dosage regimen and respective plasma levels were analysed by using a Bayesian pharmacokinetic approach. Particularly , amikacin results were analysed by means of a software package Abbottbase Pharmacokinetic Systems program (PKS) (V 1.10) from Abbott Laboratories Diagnostics Division. Fluoroquinolones results were analysed by means of a software package ADAPT II, using previous PK population data (9,10)
Regarding beta-lactams ,if applicable, the dosage was changed by increasing either the number of doses (from2g-q8 to 2g-q6) and the infusion time (from 0.5 hour to 3 hours).

Inclusion and Exclusion Criteria

Data Collected Demographic variables, such as age, weight, sex were collected for all patients. APACHE II score was calculated in all patients. The presence or absence of bacteremia for all patients with nosocomial pneumonia was recorded.

Inclusion and Exclusion Criteria

Adult (> 18 years old) men and women with pneumonia acquired after 48 h in an inpatient facility were enrolled in this study. Patients had to have at least two of the following: cough; purulent sputum; auscultatory findings of pneumonia; dyspnea, tachypnea, or hypoxemia. Patients also had to have at least two of the following: fever or hypothermia, systolic BP < 90 mm Hg, pulse rate ≥120 beats/min, respiratory rate > 30 breaths/min, altered mental status, total peripheral WBC count > 10,000/μL or < 4,500/μL, or > 15% immature neutrophils (band forms), adequate sputum specimens for Gram stain and culture. Radiographic findings of pneumonia (new or progressive infiltrates, consolidation, or pleural effusion and life expectancy ≥7 days was required.

Isolation of a Pathogen from Respiratory or Blood Cultures Pathogens were obtained by culture of protected specimen brush (PSB) sampling or bronchoscopic bronchoalveolar lavage (BAL). Test patients were those in whom the blood levels of the tested antibiotics were available (patients satisfying all the above criteria but with no available antibiotic levels and/or infecting pathogens available were used as controls).

Exclusion criteria were: 1) known or suspected meningitis, endocarditis, osteomyelitis, lung cancer, or another malignancy metastatic to the lung; 2) cystic fibrosis; 3) suspected active tuberculosis; 4) HIV + infection; 5) liver disease and total bilirubin more than five times the upper limit of normal; 6) severe neutropenia (< 500/μL); 7) pregnancy. In order to reduce the variability, patients with evidence of sepsis with hypotension and/or end-organ dysfunction, shock, vasopressors required for more than 4 h, duration of mechanical ventilation > 5 days, or severe renal impairment requiring dialysis were excluded. Also, since the analysis was confined to third generation cephalosporins, aminoglycoside and fluoroquinolones, patients with staphylococcal infections were excluded.

Microbiological Methods MICs from recovered pathogens were determined by use of standard NCCLS microtiter MIC methods (11).

Drug Measurement .Plasma concentrations of beta-lactams and fluoroquinolones were determined by use of sensitive and specific high-performance liquid chromatographic assays previous described.(12-15) The levels of serum amikacin were determined via FPIA in a Cobas Integra 400 analyzer (Roche Diagnostics), using reagents from the same manufacturer, with a limit of detection of 0.3 mg/L .

Definition of Clinical Success/Failure (primary end point) and Microbiological Success/Failure (Eradication/Persistence). Clinical success was defined as the absence or improvement of clinically significant symptoms and signs such that no additional therapy was required. Clinical failure was defined as the persistence or progression of symptoms and signs or death of the patient.

Microbiological success was defined as eradication or presumed eradication (for patients assessed as cured if no specimens were obtained) of all pathogens isolated at baseline.

The non-eradication has been defined as persistence or presumed persistence (if no sputum sample was available for a case classified as "clinical failure").

Statistical Methods. Patients with both pathogen MIC determination and drug concentration measurement were the intervention group. All other patients were the control group. Categorical variables were compared by the Pearson Chi-square or Fisher's exact test. Continuous variables were compared by Student's *t* or Mann-Whitney *U* test. For comparisons involving more than 2 groups, the Pearson Chi-square test was used for categorical variables; analysis of variance or the Kruskal-Wallis test was used for continuous variables. Breakpoints in the distribution of continuous variables were determined by Classification And Regression Tree (CART) analysis, a statistical tool to identify breakpoints within a continuous variable where the outcome of interest is distinctly

different between the resulting groups. Logistic regression was employed for analysis of dichotomous outcomes. For univariate analyses, all covariates that differed between treatment groups ($p \leq 0.2$) were considered for model entry in the multivariate analysis. The variable with the greatest log-likelihood was entered into the model first, and the likelihood ratio test was used to determine the appropriateness of model expansion. This metric was defined as twice the log-likelihood difference between the base and the expanded models evaluated against a χ^2 distribution with the appropriate number of degrees of freedom. The p-value criterion for expansion was < 0.05. SYSTAT for Windows v. 11.0 was employed for all statistical analysis. *P* values of ≤0.05 were considered statistically significant.

Results

Patient Characteristics A total of 638 patients with nosocomial pneumonia were enrolled in this study. In 205 patients, both drug concentration and infecting microrganism MIC values were available while in the other 433 patients who were used as controls, one or both parameters were lacking. Twenty-four patients in the test group and 52 in the control group were intubated for less than 5 days at the time of study entry. Table 1 shows the baseline characteristics of two groups. Median age and APACHE II score were similar in both: 67 ± 8 years (range 41-86) or 69 ± 8 (range 41-86) and 17.8 ± 5.0 (10-32) or 19.02 ± 4.6 (10-30), respectively. Ceftazidime and cefotaxime were the most frequently utilized antibiotics in the treatment of nosocomial pneumonia. Antibiotic combination therapy was utilized in 77.6% of cases in the first group and in 78.4% in the second group (Table 1).

Isolated Organisms In the first group, a total of 205 pathogens were isolated; the most frequent was *S. pneumoniae* (45 isolates), followed by *H. influenzae* (32 isolates), *P. aeruginosa* (29 isolates), *Klebsiella* spp. (25 isolates), *Enterobacter* spp. (24 isolates), *Proteus* spp. (15 isolates), *E. coli* (14 isolates), *Serratia* spp. (13 isolates). Among Gram-negative organisms, the most frequently isolated species were *P. aeruginosa* (14.1 % of all isolates). In the control group, only 142 pathogens were isolated: *S. pneumoniae* (34 isolates), *P. aeruginosa* (25 isolates), *H. influenzae* (24 isolates), *Klebsiella* spp. (18 isolates), *Enterobacter* spp. (15 isolates), *Proteus* spp. (7 isolates), *E. coli* (7 isolates), *Serratia* spp. (10 isolates) and *Citrobacter* (2 isolates). Table 2 shows the MIC range of all isolates from the test group.

Therapeutic Outcomes Success rates and overall death rate among patients in the PK/PD evaluated group as well as the LOS was significantly better than in the control group. However the duration of mechanical ventilation was not statistically different (Table 3). For clinical outcomes, the APACHE II score, combination chemotherapy and measurement of MIC and drug exposure with subsequent decision regarding drug dose/schedule alteration (or not) had a significant impact

on the probability of a good clinical outcome. The final model is shown in Table 4. The impact of the covariates on the probability of clinical outcome is displayed in Figure 1, Panels A-D.

For microbiological outcome, the MIC of the infecting pathogen for the β-lactams (whether the β-lactam MIC was $\leq$ 2 mg/l – better outcome) and whether the second drug was a fluoroquinolone or aminoglycoside (better outcomes with the fluoroquinolone) affected the probability of eradication. Adjusting dose also significantly affected eradication probability. Table 5 shows the final model for microbiological outcome, which was the secondary endpoint.

All treatments were well tolerated , no differences in side effects were found between groups

Discussion

Recently, numerous studies *in vitro* and in animal infection models have been performed to elucidate the correlation between antimicrobial therapeutic efficacy and the PK/PD indices of antimicrobials, such as the time that plasma levels remain above the MIC ($T_{>MIC}$), the ratio of the 24-h area under the plasma concentration-time curve (AUC) to the MIC (AUC_{24h}/MIC ratio), and the peak concentration in plasma (C_{max}) related to the MIC (C_{max}/MIC ratio). The general view is that $T_{>MIC}$ is the major PK/PD index that determines the in vivo efficacy of βL's including penicillins, cephalosporins, monobactams, and carbapenems, while, on the other hand, the C_{max}/MIC and AUC_{24h}/MIC ratios are the important PK/PD indices that correlate with the efficacy of AGs and FQs (6, 7, 16, 17).

In this study, we have employed the idea of knowledge of the pharmacodynamically-linked variable and a target value for this variable to test the hypothesis that outcome could be improved by identifying patients early in their infectious course that are likely undertreated (i.e. measured drug exposure, relative to the pathogen MIC is below the target value). Indeed, this is the central hypothesis of this investigation. We also wished to determine whether there was an impact in microbiological eradication. We felt that studying a specific infectious indication would allow a better test of the hypothesis and, therefore, we restricted our study to early and late nosocomial pneumonia.

Indeed, measuring drug exposure and determining the organism MIC allowed adjustment of dose in 81/205 patients. Making the judgement that therapy was adequate orrapidly adjusting dose in the first 3 days of therapy was one of the factors that had a positive impact on obtaining a good clinical outcome for these patients, relative to the group of patients where either the MIC or the drug exposure was unavailable. Figure 1, panels A-D demonstrates the impact of each of the covariates shown to have a significant impact on the probability of a good clinical outcome. The most important variable (Table 4) was the APACHE II score, which is clinically believable. As a measure of the other factors, we calculated the APACHE II score at which the probability of a good

clinical outcome fell below 90%. This APACHE II score was 22 in the group measured/adjusted and treated with monotherapy and 16 in the measured/adjusted group treated with combination therapy. For the non-measured, non-adjusted group, these values were 18 (versus 22) and 12 (versus 16), respectively.

It may seem odd that the monotherapy group performed better than the combination therapy group. One may hypothesize antagonism or, perhaps, excess toxicity. However, the likeliest explanation arises from the pathogens being treated in each group. Of the 69 pathogens recovered from the monotherapy group, 59/69 (86%) isolates were either *Hemophilus influenza* or *Streptococcus pneumonia*, with only 9 isolates of Enterobacteriaceae and 1 *Pseudomonas aeruginosa* isolate. Among the 278 isolates from the combination therapy group, 76/278 (27%) were *Hemophilus influenza* or *Streptococcus pneumonia*, while 145/278 (52%) were Enterobacteriaceae, 53/278 (19%) were *Pseudomonas aeruginosa* and 4/278 (1.4%) were *Stenotrophomonas maltophilia*. The combination therapy group was populated by more difficult to treat nosocomial Gram-negative pathogens, which likely explains the result identified.

It is also important to note that we also analyzed the impact of measuring and not adjusting versus measuring and adjusting versus not measuring and not adjusting (data not shown). This three level categorical variable also was significant (with the same other covariates) and demonstrated that those measured and adjusted actually had the best outcomes. We may conclude that the primary hypothesis was validated and that measurement of drug exposure and early identification of the causative pathogen can identify patients at high risk for a poor clinical outcome and, perhaps most importantly, that early (first three days) therapeutic intervention can result in a better clinical outcome.

Secondarily, we also wished to examine microbiological outcome. Here (Table 5), adjustment also had a positive impact on outcome. The other covariates were having a low MIC for the β-lactam being employed (2 mg/L or less) and the use of a fluoroquinolone versus an aminoglycoside.

In this instance, it is clear that only the patients with measured drug exposure and MIC with dose/schedule alteration had a significantly higher rate of eradication. This is not overly surprising, as alteration of dose/schedule tended to place patients far away from the breakpoints, whereas a fraction of patients had values near the breakpoints, but were not dose/schedule altered.

Having a low ($\leq$ 2 mg/L) MIC for the β-lactams employed here is also quite concordant with our understanding of antimicrobial chemotherapy, as both drugs will have high target attainment rates at these lower MIC values at the doses and schedules employed. The raw eradication rate for isolates with MIC values $\leq$ 2 mg/L and greater than this value was 190/210 (90%) versus 37/70 (53%).

Somewhat surprising was the finding that use of a fluoroquinolone had a significant impact on sterilization. Aminoglycosides achieved sterilization in 41/63 instances (65%) compared with 224/255 (88%) instances. It should also be noted that aminoglycosides were never administered alone, while fluoroquinolones were administered alone in 45 patients. In 36/45 (80%) patients, the infecting pathogen was either *Hemophilus influenzae* or *Streptococcus pneumonia*, where, particularly for levofloxacin, MIC values are quite low for these pathogens and eradication would be expected. Even in combination therapy, 71/213 (33%) patients had these pathogens treated with the fluoroquinolone, whereas the aminoglycoside was employed in combination in 65 patients, of whom 51/65 (78%) were infected with *Pseudomonas aeruginosa*, Enterobacter sp, Klebsiella sp or Serratia sp. These hospital-acquired pathogens make the low eradication rate somewhat understandable.

In summary, we tested a simple hypothesis. Understanding antimicrobial pharmacodynamics allows choice of therapeutic targets. Measuring drug exposure and the pathogen MIC allows a judgement to be made as to whether dose and schedule need to be altered. We recognized the importance of making such an intervention quickly. Consequently, in this study patients had blood obtained for drug measurement early in the course, so that both pieces of information were available in the same time frame. The data demonstrated that making therapy adequate, as judged by attaining

the prospectively set therapeutic targets or altering dose and schedule early in the clinical course to hit these targets resulted in significantly better outcomes. Such interventions should be trialled again, both in pneumonia as well as in other therapeutic indications.

Acknowledgments

The study was supported by a grant of Italian Ministry of Health (prot. N. 2003051858)

No Conflict of Interest for all authors

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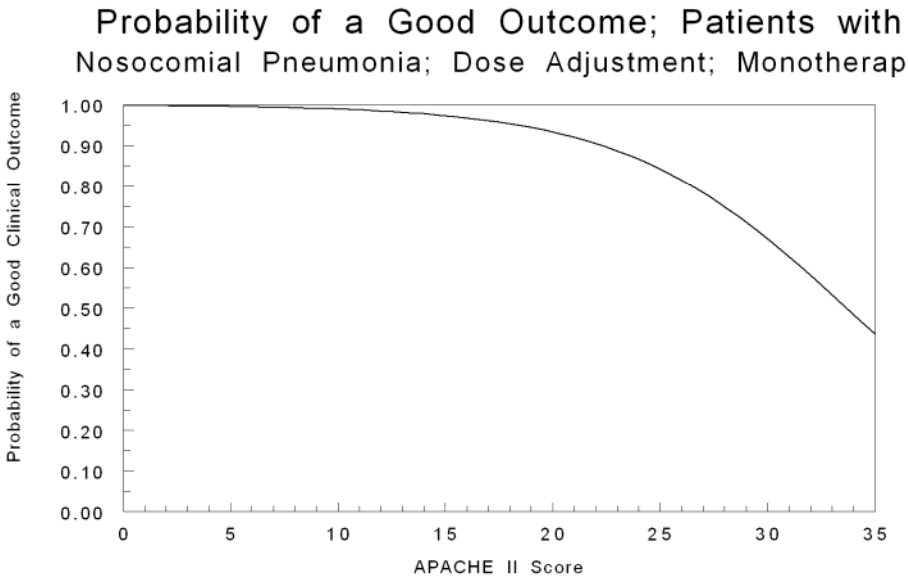
Legend of figure

Figure 1: Impact of Adjusting Therapy or use of Monotherapy versus Combination Therapy on the Probability of a good Clinical Outcome, as a Function of APACHE II Score

Figure 1

A.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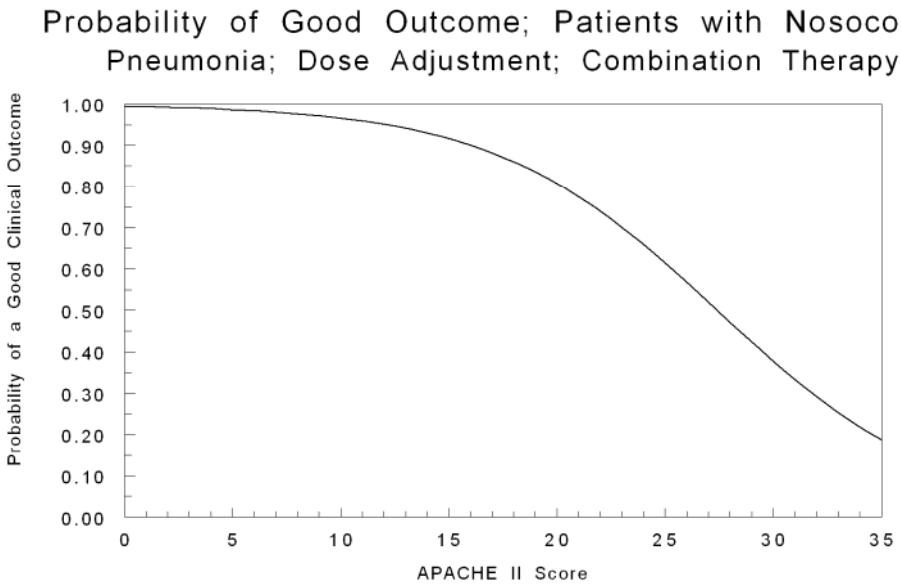
APACHE II Score

B.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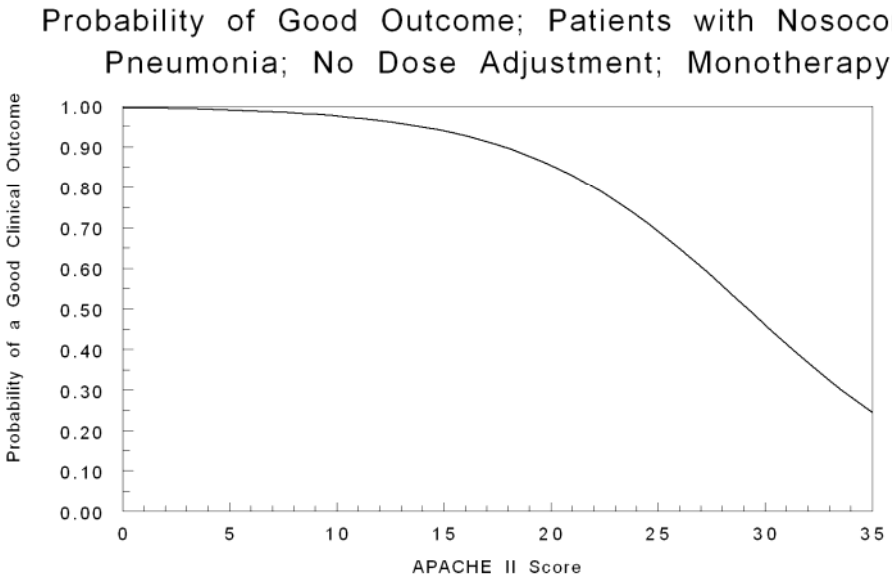
APACHE II Score

C.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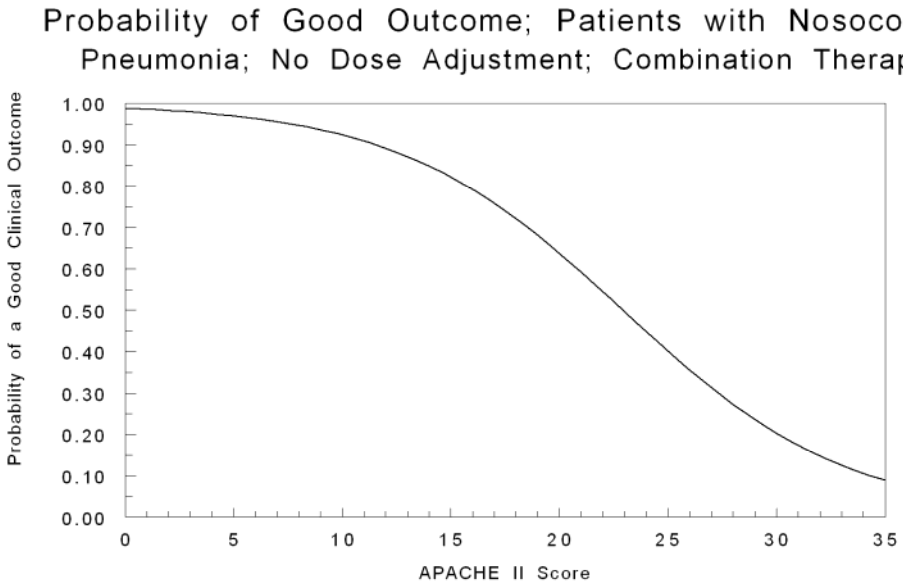
APACHE II Score

D.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APACHE II Score

Table 1: Characteristics of the patients at the baseline

Characteristic		Evaluated patients	Controls
N – (Male/female)	NS	205 (117/88)	433(247/186)
Age yr – mean ± DS – range	NS	67 ± 8 (41 - 86)	69 ± 8 (41 – 86)
Diagnosis			
Nosocomial pneumonia no. (%)	p << 0.001	172 (83.9)	415 (95.84)
Nosocomial pneumonia with bacteremia no. (%)		33 (16.1)	18 (4.16)
APACHE II score - mean ± SD – range	NS	17.8 ± 5.0 (10-32)	19.02 ± 4.6 (10-30)
Antibiotics			
Ceftazidime no. (%)		90 (24.7)	224 (28.35)
Cefotaxime no. (%)		90 (24.7)	140 (17.73)
Levofloxacin no. (%)		87 (23.9)	208 (26.32)
Ciprofloxacin no. (%)		56 (15.4)	147 (18.6)
Amikacin no. (%)		41 (11.3)	71 (9.0)
Total		364 (100)	790 (100)
Antibiotic combination therapy no. (%)	NS	159 (77.6)	261 (78.4)

Table 2: Pathogens recovered from 205 patients with Nosocomial Pneumonia and their MIC Values

	MIC, range mg/l									
	S. pneumoniae	***H. influenzae***	***P.aeruginosa***	***Klebsiella* spp.**	***Enterobacter* spp.**	***Proteus* spp.**	***E. coli***	***Serratia* spp.**	***Citrobacter* spp.**	***Stenotrophomonas* spp.**
	45 isolates	32 isolates	29 isolates	25 isolates	24 isolates	15 isolates	14 isolates	13 isolates	4 isolates	4 isolates
Ceftazidime	1-2	0.03-1	1-16	0.12-8	0.03-2	0.03-2	0.06-1	0.06-4	-	2-8
Cefotaxime	0.03-1	-	8-32	0.06-4	0.03-1	0.03-2	0.03-2	0.03-4	0.03-2	0.12
Levofloxacin	0.03-2	0.01-0.06	0.5-2	0.03-2	0.03-1	0.03-1	0.06-2	0.12-2	0.03	0.5-2
Ciprofloxacin	2-8	0.03-0.06	0.5-2	0.03-2	0.03-1	0.5-1	0.03-1	0.5-1	0.03-1	-
Amikacin	-	1	0.5-2	0.03-4	0.03-2	0.12-1	1	0.12-4	-	-

Table 3- Treatment success rates and mean LOS

	Evaluated patients N° 205	*Controls N°433*	*P*
Cure/failure (% of failure)	168/37 (18,04)	293/140 (32,33)	<0.001
Mortality or AMA (%)	21 (10,24)	102 (23,55)	<0.001
LOS± SD	12.35± 3.62	14.86± 3.94	0.0076
Duration of mechanical ventilation, (n)days ± SD	*(n25)* 4.28± 1.3	*(n52)* 5.39± 1.8	0.09

AMA= patients left hospital against medical advice-

Table 4: Final Model Parameters for Clinical Outcome for Patients with Nosocomial Pneumonia (n=638)

Parameter	Estimate	p-value	Odds Ratio	95% Confidence Interval
Constant	4.425	<0.0001	----------	----------
Mono-Therapy	1.208	0.0014	3.349	1.592-7.043
Adjustment	0.8661	0.0002	2.238	1.514-3.735
APACHE II Score	-0.1930	<0.0001	0.8245	0.7874-0.8633

APACHE II score is a continuous covariate. Monotherapy and Adjustment are two-level categorical covariates. Adjustment includes patients who had MIC determined and drug exposure measured and were determined to be adequately treated or who had their doses/schedules adjusted.

Table 5: Final Model for Microbiological Outcome for Patients with Nosocomial Pneumonia (n=272)

Parameter	Estimate	p-value	Odds Ratio	95% Confidence Interval
Constant	2.375	<0.0001	----------	----------
Amikacin	-0.8968	0.0177	0.4079	0.1944-0.8556
B-lactam MIC > 2	-2.266	<0.0001	0.1037	0.0502-0.2143
Measure/ No Adjustment	-0.255	0.5375 (NS)	0.7751	0.3450-1.7452
Measure/ Adjust	1.1276	0.0207	3.088	1.188-8.029

All covariates are categorical with 2 levels, except for adjust, Measure, which has 3 levels: Measure/No Adjustment; Measure/Adjustment; No Measure/No Adjustment.