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Ventilador-associated pneumonia (VAP) due to susceptible only to colistin microorganisms.

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ABSTRACT:

Acinetobacter species and *Pseudomonas aeruginosa* are common pathogens of ventilator-associated pneumonia (VAP). Presentation and outcome of VAP due to *Acinetobacter* spp. and *P. aeruginosa* susceptible to carbapenems (imipenem and/or meropenem) (Carb-S) and those susceptible only to colistin (Col-S), were compared in this retrospective study in 3 intensive care units (ICUs). Sixty one episodes of VAP caused by *Acinetobacter* spp. or *Pseudomonas aeruginosa* were studied, 30 isolates were Carb-S and 31 were Col-S.

Demographics, worsening of renal function and mortality were not different. The univariate analysis showed that later onset and previous episode of VAP, > 10 days of prior antimicrobials and previous therapy with carbapenems during the present admission were more frequent in patients with Col-S strains. On multivariate analysis, > 10 days of prior antimicrobials and previous episode of VAP remained significantly associated with Col-S VAP. Forty one percent of infections caused by Col-S isolates but no one of those due to Carb-S isolates had received prior carbapenem therapy. Col-S VAP episodes can be effectively treated using colistin without significant renal disfunction; this susceptibility pattern could be suspected in patients with previous VAP episode or prior antibiotic therapy > 10 days preceding the present VAP episode.

INTRODUCTION

The isolation of multiple drug resistant (MDR) *Acinetobacter* species and *Pseudomona aeruginosa* is an increasing phenomenon noticed in different ICUs around the world [1-3]. During the last years strains of *Acinetobacter spp.* and *P. aeruginosa* non-susceptible to nearly all classes of drugs including Carbapenems, one of the most effective antimicrobials for these pathogens [3, 4], were identified more frequently as the pathogens of ventilator-associated pneumonia (VAP) [2, 3, 5]. Here, colistin appears as an appropriate therapeutic alternative. Data available about epidemiological and clinical characteristics of VAP due to Gram-negative bacilli susceptible only to colistin (Col-S) is limited [6, 7]. The mortality rate of VAP increases when the initial antimicrobial therapy is inappropriate [8-11], so it is extremely important to identify patients "at risk", and to begin the appropriate empiric antimicrobial therapy as soon as possible.

Colistin is one of the polymyxin antibiotics, produced by *Bacillus colistinus*. It has been available since 1959 for treatment of infections caused by Gram-negative bacteria [12]. Possibly, it acts by altering the wall cell permeability producing bacterial lysis [13]. *In vitro* colistin has a broad spectrum of action against Gram-negatives, including some resistant strains to penicillins, carbapenems, aminoglycosides and fluoroquinolones. However, *Proteus mirabilis, Providencia spp, Serratia spp, Burkholderia cepacia* and *Stenotrophomonas maltophilia* are naturally non-susceptible to colistin [14]. Severe adverse effects (i.e.: nephrotoxicity and neurotoxicity) have been reported, and led to discontinue the parenteral use of this drug in the seventies [7, 14]. Acquisition of resistance to colistin is uncommon; it has been described in cystic fibrosis patients chronically treated with nebulized colistin for tracheal colonization with MDR *P. aeruginosa*. Sodium colistin methanesulphonate is the commercially available form for intravenous use [15]. Since colistin has been associated with severe adverse effects and an inappropriate initial empirical antibiotic treatment is consistently associated with increased mortality, the identification of factors

associated to *Acinetobacter spp.* and *P. aeruginosa* Col-S, compared with susceptible strains to other antibiotics, would help in choosing the initial antimicrobial therapy.

The aim of this study was to compare the epidemiological conditions and clinical presentation of patients with VAP caused by MDR *Acinetobacter spp.* or *P. aeruginosa* that preserve their susceptibility to carbapenems (Carb-S) with those Col-S, focusing on worsening serum creatinine concentration identified during therapy.

METHODS

This retrospective study was based on the clinical and microbiological records from ICU patients from 3 different hospitals: Hospital Prof. A. Posadas, Hospital de Clínicas and Hospital HIGA Eva Perón, located in the metropolitan area of Buenos Aires, Argentina, during a 26 months period (December 2001 - January 2004). Episodes of VAP caused by Carb-S or Col-S *Acinetobacter spp.* or *P. aeruginosa*, fulfilling the further detailed inclusion criteria, were studied. In these ICUs the rate of VAP due to MDR microorganisms is about 69%, according to a previous multicenter prospective study on VAP [16]. In such previous study VAP incidence in mechanically ventilated patients was 14.8%, nearly 40% was due to *Acinetobacter spp.* or *P. aeruginosa* and one third of them were Col-S; empirical antimicrobial therapy included a carbapenem in approximately 60% of the cases, and other beta-lactams were used in most of the remaining cases. In the present study a combined therapy with an aminoglycoside, a fluoroquinolone or colistin was used in 12 cases as empiric therapy. In 16 cases colistin was used after the culture report showing Col-S *Acinetobacter spp.* or *P. aeruginosa*. In the remaining 15 the initial therapy with colisitin was empirical according to the decision of the attendant physician.

Inclusion criteria was adults > 18 years with a new or progressive preexistent radiographic infiltrate, plus at least one of the following: purulent secretions, abnormal temperature (> 38˚C or < 36˚ C) and/or abnormal leukocyte count (> 10,000 or < 4,000 WBC/ mm^3); plus the isolation of ≥ 10^4 colony forming units (cfu)/ml of MDR *Acinetobacter* spp. or *P. aeruginosa* from bronchoalveolar lavage (BAL) fluid or 10^3 cfu/ml of MDR *Acinetobacter* spp. or *P. aeruginosa* from protected specimen brush (PSB), bronchoscopically obtained. Microorganisms were considered MDRs when they were resistant to 2 or more antimicrobial classes to which they are naturally susceptible. The Carb-S *Acinetobacter* spp. *or P. aeruginosa* group includes VAPs due to MDR organisms that were consistently susceptible to imipenem and/or meropenem. The Col-S

Acinetobacter spp. or *P. aeruginosa* group includes VAPs due to MDR organisms that were susceptible to colistin but resistant to carbapenems and to all other parenteral available antibiotics. All patients initiated antimicrobial therapy empirically. Treatment was eventually modified when pathogens were identified and their antimicrobial susceptibilities were available (definitive therapy). The onset of appropriate antibiotic therapy, empiric or definitive, was taken into account to evaluate it and to determine the duration of therapy and time elapsed until the detection of adverse events. Definitive therapy of patients with VAP due to Carb-S bacteria was Imipenem, 2 grams per day (n = 11), or meropenem 3 grams per day (n = 19), and VAPs due to Col-S were treated with intravenous colistin, 5 mg/kilogram/day. Doses were corrected according to elsewhere published formulas in patients with renal failure [7].

Demographic data, APACHE II score at ICU admission, underlying diseases, etiologic agent, reasons for mechanical ventilation, previous VAP episodes, number of days spent in the hospital, in the ICU and on mechanical ventilation (before and after the diagnosis of VAP under study) were recorded. Also data on previous antimicrobial therapy during the 10 days preceding the VAP onset, reason for such antimicrobial therapy, days on antibiotics for VAP with carbapenems or colistin and the impact on renal function were taken into consideration. Since the initiation of colistin or carbapenem could happen 2 or 3 days after the day of diagnosis of VAP, when the result of cultures and antimicrobial susceptibility studies become available, serum creatinine change during follow-up was evaluated taking into account the day of onset appropriate antibiotic therapy. Serum creatinine concentration was obtained at the onset of appropriate therapy and 3, 5, 7, 10 and 14 days after. The bacterial antimicrobial susceptibility was established by disk diffusion. It was considered that antimicrobial therapy was inappropriate when the isolated microorganisms were not susceptible to the initial empiric antimicrobial therapy. Twenty eight days overall mortality after the diagnosis of VAP was evaluated.

Statistic analysis: data is noted in absolute numbers with or without percentages, as means ± standard deviations or as medians with 1-3 quartiles; ***t*-**test were used to compare continuous variables, whereas the χ^2 test or the Fischer exact test were used to compare categorical data and proportions. Univariate and multivariate analysis with forward stepwise logistic regression analysis with the variables that were significantly different in patients with Col-S, were applied in order to understand better the risk factors related to the development of Col-S VAP episodes. Variables were entered to the model when p was < 0.05. Adjusted odds ratios, and 95% confidence intervals (CI) were calculated. The variation of serum creatinine concentration at 3, 5, 7, 10 and 14 days compared with the day of antimicrobial therapy onset was recorded in patients receiving colistin or carbapenems by using a two way analysis of variance (ANOVA). The GB-STAT 6.5 software (Dynamic Microsystems, Inc., Silver Spring, MD) was used for statistical calculations.

RESULTS

Sixty one patients fulfilling the clinical and microbiologic criteria for MDR *Acinetobacter spp.* or *P. aeruginosa* VAP in the BAL (n=55) or in the PSB culture (n=6) were included. Thirty were due to Carb-S and 31 due to Col-S strains; demographic and clinical data the two groups are displayed in **Table 1**. More than one pathogen was isolated in 11 specimens (1.18 per patient) (**Table 2**). Among the remaining 50 cases, 36 were due to *Acinetobacter* spp. and 14 were due to *P. aeruginosa.* All the Carb-S pathogens were susceptible to imipenem and/or meropenem and to colistin. Additionally, among the 20 Carb-S *Acinetobacter spp*. isolates 9 were susceptible to ampcillin-sulbactam, 3 to piperacillin ± tazobactam, 2 to levofloxacin and 1 to amikacin**.** Among the 11 Carb-S *P. aeruginosa* isolates (2 cases with mixed etiology due to *Acinetobacter spp. + P. aeruginosa*), 6 were susceptible to piperacillin ± tazobactam, 4 to cefoperazone, 3 to ciprofloxacin, 3 to amikacin, 2 to levofloxacin and 2 to gentamicin. The 26 *Acinetobacter spp.* isolates and 11 *P. aeruginosa* Col-S isolates (7 cases with mixed etiology due to *Acinetobacter spp. + P. aeruginosa*) were resistant to all the other parenteral available antibiotics (a small number were susceptible to minocycline, not available for parenteral use). Twenty-nine patients died within 28 days after VAP onset (mortality = 47.5%), mortality for Acinetobacter spp and *P. aeruginosa* when they were the only isolated microorganism was 41.7 and 61.3%, respectively (p = 0.361). Length of stay after the VAP diagnosis in survivors was 45.8 ± 110.2 days. Sixty two percent of the admissions were due to medical and 38% to surgical reasons. Demographic and clinical data from the patients for the Carb-S and Col-S groups of patients are displayed in **table 2**.

Antimicrobial therapy

Duration of therapy in patients who survived at least 15 days were 12.0 ± 6.2 days for Carb-S group, and 12.2 ± 5.8 for Col-S group. There was no difference in mortality rate between Carb-S and Col-S groups, but hospital and ICU length of staying was significantly longer in those patients in the Col-S group (**table 1**). Initial empirical antimicrobial therapy included in most of the cases a beta-lactam active against MDR Gram-negative bacilli (carbapenem or piperacillin-tazobactam). Some patients received also an aminoglycoside or ciprofloxacin and/or colistin as part of this empirical antimicrobial therapy. In 20 patients this therapy was inappropriate, 14 in the Col-S group and 6 in the Carb-S group (p = NS). However, a significantly higher mortality rate was identified in patients who received an initial inappropriate therapy (70% versus 36.6%, p = 0.014). This difference persisted in patients who had switched to an appropriate therapy few days after starting point (**Figure 1**). The mortality rate from those VAP caused by *Acinetobacter* spp. or *P. aeruginosa,* treated with appropriate empiric antimicrobial therapy was exactly the same, 33.3% (8/24 and 3/9), respectively.

Other characteristics during the hospitalization

APACHE II score at ICU admission and mortality rate were similar in both groups (**table 1**). In this cohort, hospitalization was very long [28(23-41) days]. During the UCI stay [23 (17-34) days], patients remained on mechanical ventilation for 19 (14-28) days. Comparing both VAP groups, the following were significantly shorter in patients with Carb-S isolate in relation to those Col-S *Acinetobacter spp.* or *P. aeruginosa*: hospitalization time, time in ICU, days on mechanical ventilation and days in the ICU before the VAP onset (**table 1**). Prior antimicrobial treatment, particularly with carbapenems, and the antecedent of a previous VAP were significantly more frequent in the Col-S groups.

Thirty Col-S and 25 Carb-S patients had received antimicrobials previously to VAP ($p = 0.012$). Duration of prior therapy was 9.2 ± 6.8 days [5.2 ± 2.5 for the Carb-S and 12.3 ± 4.3 for the Col-S groups ($p < 0.0001$)]. The two most common causes for prior antimicrobial treatment were community and hospital acquired respiratory tract infections. All antimicrobial therapy causes are listed in **table 3**. Forty one percent of Col-S but not one of Carb-S episodes had received prior Carbapenem therapy.

Renal function evaluation:

By the time of VAP onset of appropriate therapy the mean serum creatinine concentration was within the normal range (1.32 ± 1.19 mg/dl), there was no difference between Carb-S and Col-S groups. Comparing the value observed at onset of appropriate therapy with the levels observed 3, 5, 7 and 10 days later, there was a trend towards a reduction of serum creatinine concentration in both groups (**Figure 2**). Twelve patients had an initial serum creatinine level above the normal limit of 1.40 mg/100mL (7 in the Carb-S and 5 in the Col-S group). Three days later, there were 5 patients (2 Carb-S and 3 Col-S), and on day 5, there were 6 patients with a creatinine ≥ 1.4 mg/dL (2 Carb-S and 4 Col-S). Considering the 34 patients with normal renal function at onset of appropriate antibiotic therapy remaining in the study for at least 5 days, and taking into account the creatinine level on days 0, +3 and +5, we observed that on day +3, there were 4 patients with a creatinine value ≥ 1.4 mg/dL (two in each group) and on day +5 there were 2 patients in each group with a creatinine level ≥ 1.4mg/dL Four patients had a serum creatinine value ≥ 4.0 mg/dL (1 in the Carb-S and 3 in the Col-S group), and not one of them worsened their renal function during the antimicrobial therapy (data not shown). None of the 61 studied patients required dialysis neither at the onset nor during the follow-up of their VAP.

Multivariate analysis

A multivariate logistic regression model was applied to the categorical variables to disclose which conditions were significantly related to Col-S isolates. The forward stepwise model using the therapy with Colistin or Carbapenems as the dependent variable demonstrated that the following remained significantly associated with the Col-S condition at VAP onset: duration of prior antimicrobial therapy more than 10 days Overall ICU staying for more than 40 days also was associated to Col-S VAP (**Table 4**).

DISCUSSION

Although intravenous colistin is accepted as an antimicrobial option for specific MDR pathogens [17], the clinical experience with this antibiotic is poor, as it has been nearly discontinued due to the occurrence of serious adverse effects while other suitable alternatives were available. The development of MDR susceptible only to colistin Gram-negative infections, particularly in critically ill patients, led to renew the interest on this drug.

It has been acknowledged that VAP episodes caused by the so-called "high risk pathogens", particularly non-fermenting Gram-negative bacilli *Acinetobacter* spp. and *P. aeruginosa*, are associated with a higher mortality rate in comparison with other microorganisms. A relative risk of 2.5 has been recorded [18]. The increased incidence of nosocomial infections due to MDR pathogens has grown impressively during the last 15 years [19-23]. This microbiological data leaded a more frequent use of inappropriate antimicrobial therapy [8, 10, 24]. Imipenem and meropenem have been the more effective antimicrobials against *Acinetobacter* spp. and *P. aeruginosa* during the last 10 years. Resistance to these antimicrobials is nearly always associated with non-susceptibility to other beta-lactams, fluoroquinolones, and aminoglycosides [3, 4]. It remains unknown if bacterial resistance to carbapenems has an intrinsic higher risk of morbidity or mortality. The results of this study concerning this topic, similarly to previous publications, indicate that mortality rate was similar in patients with severe infections due to Carb-S and Col-S *Acinetobacter spp.* or *P. aeruginosa* [6, 25]. Even though we observed that inappropriate therapy was consistently associated to higher mortality, regardless of which antimicrobial was used.

Trouillet et al. identified several factors related to the acquisition of VAP due to MDR microorganisms, including: duration of mechanical ventilation > 7 days, prior antimicrobial therapy and use of broad spectrum antibiotics [21]. Similarly, Rios et al. identified hospitalization

prior to the VAP onset during > 5 days and use of prior antimicrobial therapy as risk predictors of VAP caused by MRD pathogens [22].

Reports about colistin-related toxicity pointed out a variable incidence and established that their adverse effects are transient [6, 26, 27]. Conway et al considered that the first reports of adverse events could be erroneously attributed to colistin due to the complexity of the clinical background observed in those patients [28]. Aminoglycosides and glycopeptidic antimicrobials are commonly used in the critically ill patients; these highly effective antibiotics also may produce nephrotoxicity in a large number of patients [29, 30]. The knowledge about the pharmacokinetics and pharmacodynamics of intravenously colistin is limited. Montero et al.**,** in an experimental mice comparative model about the efficacy of different antibiotics against pneumonia caused by MDR *Acinetobacter spp*. reported that, disregarding its *in vitro* microbiological activity according its MICs, the results were discouraging about the use of colistin to treat *Acinetobacter spp.* Pneumonia [31]. These results would require careful interpretation and any extrapolation to humans should be very cautious.

Several studies on efficacy and/or safety of parenteral colistin for critically ill patients with VAP or other severe infections due to MDR *Acinetobacter spp.* or *P. aeruginosa* were published during the last years [6, 25, 32, 33]. Garnacho-Montero et al. compared 21 carbapenem resistant strains of *Acinetobacter spp.* VAP episodes treated with colistin and 14 carbapenem susceptible VAP episodes treated with Imipenem**,** and found no differences related to efficacy, nephrotoxicity or neurotoxicity [6]. Linden et al. studied 23 critically ill patients infected with MDR *P. aeruginosa* treated with colistin, including 18 who had pneumonia; 14 of these 23 patients had a favorable clinical response [33]. In that study, bacteremia was the only factor associated with therapeutic failure. Kasiakou et al. studied 54 episodes of severe infections in cystic fibrosis patients due to MDR Gram-negative bacteria treated with combination therapy which included parenteral colistin

[32]. They reported that 8% of the patients worsened their renal function during therapy, while 67% improved or cured, showing colistin's safety and effectiveness. Finally, Reina et al. in a study on 185 critically ill patients with *Acinetobacter spp.* or *P. aeruginosa* infections (55 of them were treated with colistin while 105 received a carbapenem) concluded that colistin was as safe and as effective as other antibiotics. But the authors did not find association among inappropriate antimicrobial therapy, more common in the colistin group, and poorer outcome [25].

Regarding renal function, we thoroughly examined serum creatinine concentration and have found no significant adverse effects attributable to colistin in this cohort. Considering patients with normal renal function at onset of appropriate antibiotic therapy, few of them showed a mild and transient elevation of serum creatinine levels. About half of the patients that had an abnormal initial serum creatinine concentration reduced their levels during colistin therapy.

Multivariate analysis demonstrated that previous VAP episodes and prior antimicrobial therapy for more than 10 days are risk factors for VAP due to Col-S *P. aeruginosa* or *Acinetobacter spp*; this group also showed a longer staying in the ICU.

Delay in the initiation of antimicrobial therapy increases the VAP mortality rate [29, 34]. We found a higher mortality rate in patients who did not receive appropriate therapy or received it with delay, comparing with those that received appropriate therapy. We believe that in patients with high risk of harboring MDR non-fermenting Gram-negatives admitted to ICUs with similar epidemiological conditions to patients included in this study, it could be suitable to begin the empiric initial antimicrobial therapy using colistin. In fact, the current ATS-IDSA guidelines for hospital acquired, ventilator associated and health care associated pneumonia recommend considering Colistin as a therapy for patients with VAP attributed to carbapenem-resistant *Acinetobacter* spp [17].

This study has several limitations. It is a retrospective study on a relatively reduced number of patients that were recruited at 3 different institutions, thus many factors were not controlled and may have biases inherent to this kind of studies. The analysis of Acinetobacter and *P. aeruginosa* together could be inappropriate as these are different microorganisms and could have different response to therapy. A prospective randomized study with more patients could be necessary to analyze more exactly the factors associated with the development of Col-S *Acinetobacter* spp. or *P. aeruginosa* VAP and to confirm the findings of the present study. The results of this study are limited by the high incidence of MDR pathogens in the participating institutions and the local ICU practice as evidenced by a high rate of carbapenem use as empiric therapy for VAP (24 of Carb-S patients received empirically carbapenems while 12 of Col-S patients had received previous carbapenem therapy also). Carbapenems often represent the last line of beta-lactam therapy due to their greater resilience against common resistance mechanisms (e.g., beta-lactamases).

Colistin should not be always recommended as first-line therapy. Physicians should know their own ecology and should only consider to use colistin as an option when there are risk factors for Col-S isolates and as a consequence there is no other choice (i.e. highly-selected patients with a previous VAP episode and prior use of antimicrobial therapy - especially carbapenems - for >10 days).

Summarizing, patients with MDR Col-S *P. aeruginosa* or *Acinetobacter spp.* VAP are characterized because they usually present some of the following: previous VAP episodes, prior broad spectrum antimicrobial therapy for more than 10 days (particularly carbapenems) and delayed onset of VAP from the ICU admission. Under these conditions, in ICUs with the ecologic characteristics here described, colistin could be a suitable antibiotic for initial empiric antimicrobial therapy.

Table 1: Demographical and clinical characteristics from patients with VAP due to MDR *Acinetobacter spp* or *Pseudomonas aeruginosa* carbapenem susceptible (Carb-S) and susceptile only to colistin (Col-S).

	Carb-S (n=30)	**Col-S (n=31)**	**P**
Age (years)	61.3 ± 17.8	55.3 ± 19.5	0.142
APACHE II	18.2 ± 6.9	20.1 ± 8.4	0.548
Creatinine 10 days after VAP onset (mg/dL)	1.21 ± 0.89	1.32 ± 1.29	0.754
Overall hospitalization, days	23 (17-28)	37 (25-70)	< 0.001
Overall ICU staying, days	21 (16-23)	30 (19-64)	< 0.001
Days on mechanical ventilation	16 (10-22)	24 (14-55)	< 0.001
Appropriate empiric antibiotic therapy	24/30	17/31	0.056
Overall Mortality	13 (45.1%)	16 (51.6%)	0.696
Characteristics present at VAP onset			
Creatinine by the time of VAP diagnosis (mg/dL)	1.31 ± 0.92	1.42 ± 1.45	0.749
Days on mechanical ventilation at VAP onset	7 (5-10)	16 (12-34)	< 0.001
Days elapsed from admission and diagnosis of VAP	6 (1-9)	15 (10.5-28.5)	< 0.001
Days on prior antibiotics at the VAP onset	5.0 ± 3.1	13.3 ± 7.1	< 0.001
Previous episode of VAP	4 (12.5%)	16 (51.6%)	0.004
Prior antimicrobial therapy	22 (73.3%)	30 (96.8%)	0.026
Prior use of carbapenems	0 (0%)	13 (41.9%)	< 0.001

Table 2: Microorganisms isolated in respiratory specimens obtained by BAL (N = 55) or PSB (N = 6).

	Overall	**Carb-S** (n=30)	**Col-S** (n=31)
Acinetobacter baumannii	46	20	26
Pseudomonas aeruginosa	24	13	11
Staphylococcus aureus	1	1	-
Klebsiella pneumoniae	1	1	-
Microorganisms per VAP episode	1.18	1.17	1.19

Table 3: Reasons for antimicrobial therapy in 52 patients receiving prior antibiotics.

	Carb-S, n=21	Col-S, n=31	p
Nosocomial Pneumonia Including VAP	1	15	0.001
Community-Acquired Pneumonia	5	7	1.000
Intrabdominal Infection	3	5	1.000
Other Lower Respiratory Tract Infections	4	1	0.145
Acute Exacerbation of COPD	4	0	0.022
Bacteremia or Sepsis	1	2	1.000
Miscellanea	3	1	0.291

Table 4: Categorical variables significantly associated with Col-S VAP in univariate and multivariate analysis.

	Univariate analysis		**Multivariate analysis**	
	OR (95% CI)	**p**	**Beta coef (95% CI)**	**p**
Total days on mechanical ventilation > 30 days	17.7 (1.7–179.4)	0.016		
Overall hospitalization > 50 days	17.7 (1.7 – 179.4)	0.001		
Overall ICU staying > 40 days	20.5 (2.0 – 205.5)	<0.001	31.6 (31.5-495.9)	0.014
Characteristics present at VAP onset				
Duration of prior antimicrobial therapy > 10 days	31.5 (2.9 – 340.4)	<0.001	13.2 (2.2-78.7)	0.005
Time from admission to diagnosis of VAP > 16 days	27.1 (2.7 – 269.5)	<0.001		
Previous episode of VAP	27.7 (2.8 – 273.5)	<0.001	6.0 (1.0-35.7)	0.047
Prior use of carbapenems	21.7 (2.2 - 212.9)	<0.001		

Legends for figures:

Figure 1: Mortality rates in the overall population of 61 patients related to empirically prescribed antimicrobial therapy appropriateness at the time of VAP diagnosis, accounting the therapeutic measure taken previous to knowledge of involved microorganisms and their antimicrobial susceptibility. Appropriate antimicrobial therapy was administered more commonly to patients with Carb-S than Col-S pneumonia.

Figure 2: mean serum creatinine concentration evolution in both Carb-S and Col-S groups from the onset to 14 days after the initial appropriate antimicrobial therapy (carbapenem or colistin). There was no difference in the serum creatinine concentration between the two groups compared (two-way ANOVA).

Figure 1

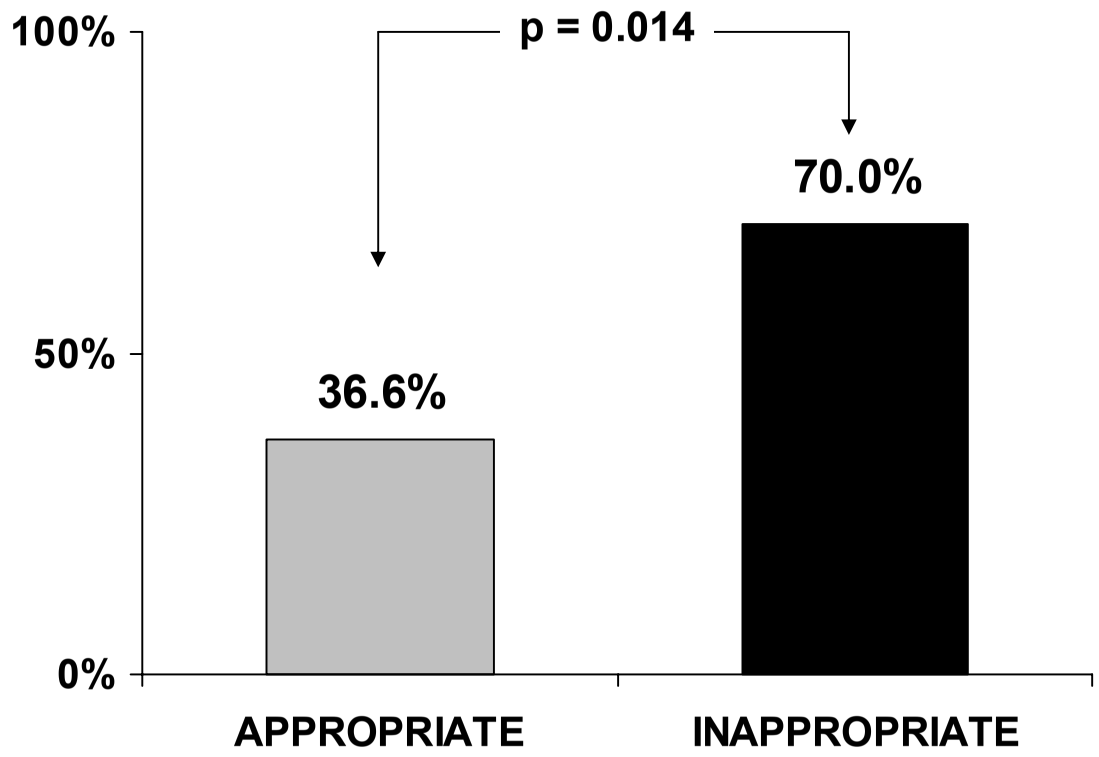
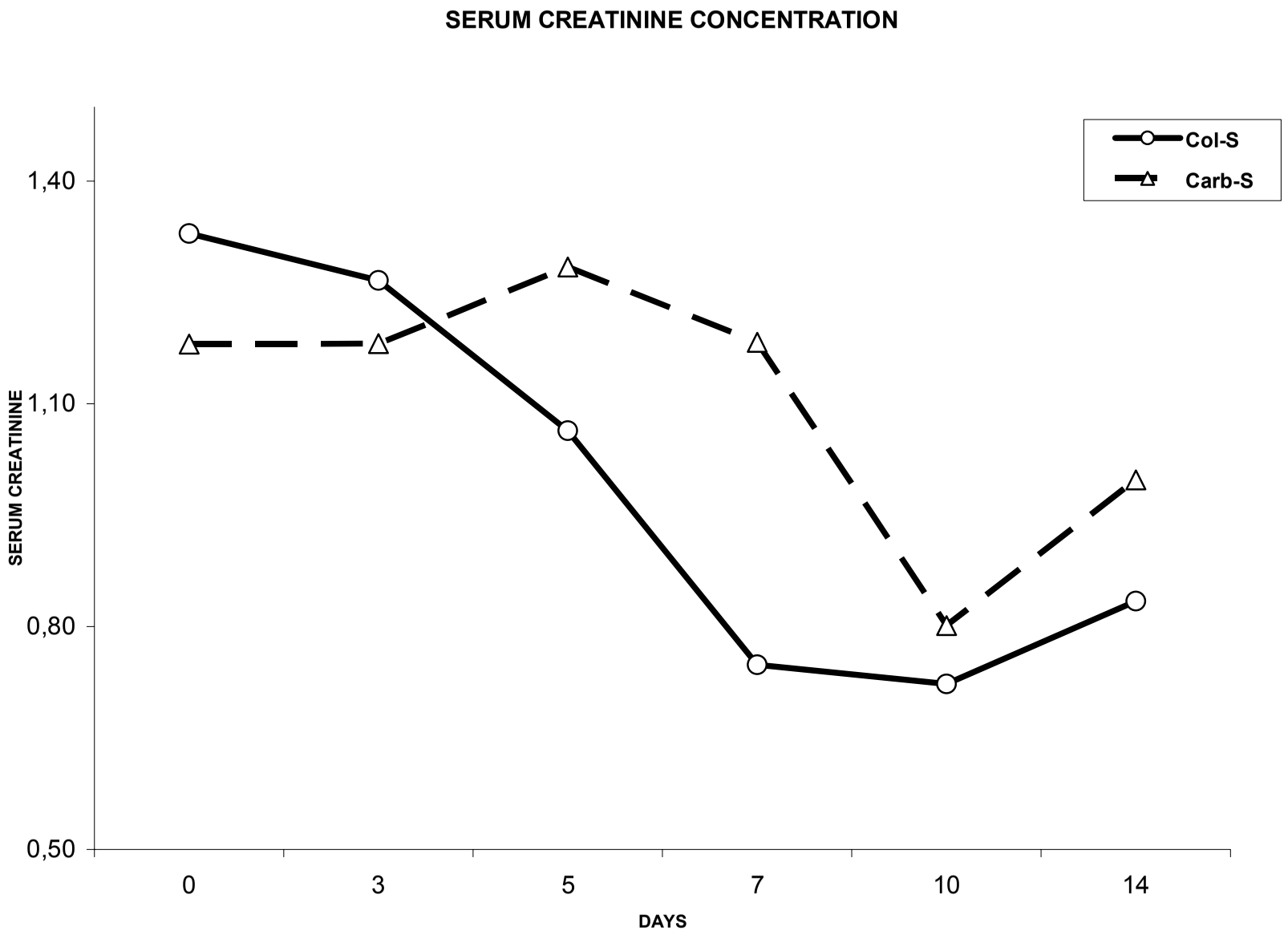


Figure 2


SERUM CREATININE CONCENTRATION
Col-S
Carb-S
1,40
1,10
0,80
0,50
SERUM CREATININE
0
3
5
7
10
14
DAYS

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