Polymyxin B for Gram Negative Multidrug Resistant Bacteria in a Hispanic Population

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Objective: This study intends to determine the prevalence of multidrug resistant (MDR) infections by A. baumannii, K. pneumoniae and P. aeruginosa in a tertiary care teaching hospital intensive care unit (ICU) in San Juan, PR, estimate the mortality rate and compare the morbidity and mortality differences among those treated with and without polymyxin B.

Methods: We selected adults patients admitted to the ICU who had positive cultures from January 2012 to June 2013. Sample consisted of 25 patients with age ranges from 27-78 years, 13 women and 12 men.

Results: The median age at death was 60 years. Polymyxin B nephrotoxicity was identified on 15% of the patients. Variables related to higher survival were younger age, female sex, use of polymyxin B, and the use of daptomycin. The use of vancomycin and vasopressors were associated with worse outcome. Mortality associated to single MDR bacteria was 88% for A. baumannii, 84% for K. pneumoniae and 67% for P. aeruginosa. All patients with more than one MDR infection died in the ICU.

Conclusion: The use of polymyxin B was associated with an ICU mortality reduction. Unexpectedly we found a significantly improved survival in patients who received polymyxin B in combination with daptomycin, which awaits prospective confirmation.
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Key words: MDR, Polymyxin B, Hispanic

Infections with multidrug resistant (MDR) organisms represent a serious challenge in critically ill hospitalized patients. The incidence of MDR gram-negative bacterial (GNB) infections in the last decade has risen and there is a limited effective armamentarium to target them, creating a therapeutic challenge (1). Empiric therapy with broad-spectrum agents facilitates the emergence of resistance (2-3).

Mortality rates as high as 60% have been reported for ventilator associated pneumonia and bloodstream infections caused by GNB in studies performed in intensive care units (ICU) in the United States (4-12). Nearly two thirds of nosocomial infections are related to the GNB Acinetobacter and Pseudomonas species. Studies from different countries have ranked Acinetobacter baumannii as the most frequent nosocomial agent with the highest resistance rate to antibiotics, highlighting the worldwide scope of the problem (13-15).

There are few novel antimicrobials in the market to treat infections by MDR organisms, tigecycline, ceftolozane/tazobactam and ceftazidime/avibactam (16-24). However, clinicians have reevaluated and endorsed older therapeutic agents such as polymyxin B, a bactericidal antibiotic derived from Bacillus polymyxa to treat infections by MDR GNB, including Pseudomonas aeruginosa, Klebsiella pneumoniae, and Acinetobacter baumannii (25-28). Consequently, the use of polymyxin B has increased, despite its potential nephrotoxic and neurotoxic adverse effects, which limited its use in the past (28-30). Favorable clinical outcomes have been observed in recent studies that utilized polymyxin B in the management of nosocomial infections. However, they have failed to provide definitive conclusions on efficacy due to limitations in the methodological design and sample size of the studies (31-33).

The present study intends to: 1. Establish the frequency of A. baumannii, K. pneumonia and P. aeruginosa MDR among medically indigent Hispanic patients admitted to a tertiary care teaching hospital ICU; 2) Estimate the mortality rate among these patients 3) Compare the morbidity and mortality differences among those treated with and without polymyxin

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B. To our knowledge, no previous studies have reported this data in Puerto Rico.

Methods

A non-concurrent prospective study was performed in adult patients with positive cultures on any sites (blood, sputum, urine, cerebrospinal fluid, wounds and catheter tip) for MDR A. baumannii, K. pneumoniae or P. aeruginosa, admitted to a tertiary care teaching hospital ICU between January 1st, 2012 and June 30th, 2013. Demographic, clinical, laboratory, treatment and outcomes data were collected from the clinical records. Demographic data included: age, and sex. Clinical data included: date of admission and discharge from ICU and hospital. Risk behaviors/comorbidities recorded were alcohol use, active smoking, chronic obstructive pulmonary disease (COPD), cardiovascular diseases defined as arterial hypertension and congestive heart failure, diabetes mellitus, and immunodeficiency, defined as having HIV/AIDS, lymphoma or leukemia. Laboratories included culture and bacteria sensitivities from any site at the time of ICU entrance, creatinine levels, bilirubin, INR, WBC and hematocrit. Polymyxin B induced nephropathy was defined as the doubling of serum creatinine to a value ≥2.0 mg/dl (34-35). MDR was defined as: resistance to penicillins, cephalosporins, fluoroquinolones, carbapenems, and gentamycin or amikacin (36-38). Resistance to polymyxin B was not routinely tested for in our laboratory, therefore, it was not included.

Treatment data included antibiotics given to the patient during their stay in the ICU and those administered in hospital prior to ICU entrance. Time to start of polymyxin B after positive culture was determined. Admission date, discharge date and outcome (alive or dead) were recorded. Those with positive MDR cultures prior to ICU admission were discarded. Study embraces only positive MDR cases identified by cultures taken after ICU entrance. Subjects follow up began when the first dose of polymyxin B was given, or when the MDR culture sample was taken in those who did not receive polymyxin B. Follow up ended with the discharge alive or participant's death in the ICU. Study time period was selected to permit access to the medical records and to reflect recent bacteriologic data. The ICU was selected because of the frequency of infections by MDR bacteria and because of its clear demarcation within the hospital. Bacterial species were selected because they are the most frequently reported MDR GNB in the hospital and thus most likely to affect survival of our patients. The study was approved by the Institutional Review Board.

Statistical analysis

The Statistical Package of Social Sciences (SPSS) program was used to perform univariate, bivariate and proportional hazard analyses. Fisher's exact test and Mann-Whitney test were used to evaluate differences between polymyxin B groups in relation to demographic factors, clinical manifestations, MDR GNB infection, treatment and mortality in ICU. Cox proportional hazard analysis with relevant covariates, including variables with p values ≤ 0.05 in the bivariate analyses, was used to evaluate ICU mortality after MDR. Data was presented as percentage, median with interquartile rate, and hazard ratios with their 95% confidence interval. The p value used to determine statistical significance was ≤ 0.05.

Results

We identified 41 patients with positive cultures; 6 were excluded because they did not fulfill definition for MDR and 10 were not included because medical records were not available for evaluation. Our final sample consisted of 25 patients with age range from 27-78 years, 12 men and 13 women. Common comorbidities included: cardiovascular diseases in 48%, diabetes mellitus in 32%, COPD 12%, immunosuppression in 16% and strokes in 8%. The median for age at death was 60 years and survivor's ages were 27, 35 and 52 years. Three patients developed nephrotoxicity (15%).

Table 1 describes the clinical characteristics of the patients. It shows no significant differences between cases that received or not polymyxin B during their ICU stay other than the use of carbapenems, which is usually combined with polymyxin B.

Patients who were older, and who received vasopressors, or vancomycin prior to positive MDR culture had a higher mortality rate. Post culture treatments associated with lower mortality rate included the use of daptomycin, carbapenems and polymyxin B. However, only the use of daptomycin reached statistical significance by Fisher's exact test (Table 2).

Eight patients were infected with A. baumannii, six with K. pneumoniae and three with P. aeruginosa as single infection with mortality rates of 88%, 84% and 67%, respectively. Co-infection by MDR bacteria was observed in eight patients with mortality rates of 100%. Most common organism identified was A. baumannii, both as a single agent and in combination followed by K. pneumonia and P. aeruginosa (Figure 1). This is all cause mortality, as we did not try to separate deaths caused by the underlying disease form death caused by infection.

Sputum and blood were the most frequent sources of positive cultures. P. aeruginosa was frequently observed on catheter tip culture and K. pneumoniae on urine culture (Figure 2). Five patients did not receive polymyxin B because they died before the culture results were reported.

When evaluating the ICU survival time, we found that patients treated with polymyxin B, carbapenems, or daptomycin after positive culture had significantly longer survival time. Conversely, chronic liver disease and the use of metronidazole prior to positive MDR culture were associated with a shorter survival time (Table 3).

Cox proportional hazard analysis show that patients who were: female, younger and treated with polymyxin B, had a

Table 1. Demographic, clinical conditions and treatment in the ICU by use of polymyxin B.

Variables	Patients with polymyxin n=20	Patients without polymyxin n=5	p
Demographics			
Men (%)	55	40	0.645
Age in years (median, IQR)	58.5 (37-71.5)	61 (59-66)	0.447
Clinical conditions			
Diabetes (%)	25	60	0.283
Cardiovascular (%)	50	40	1
Lung Disease (%)	10	20	0.504
Immunosuppression (%)	15	20	1
Chronic Liver Disease (%)	0	20	0.2
Stroke (%)	10	0	1
Chronic Renal disease (%)	0	0	
Days in ICU prior to positive culture (median, IQR)	11.0 (2.25-19.5)	5.0 (1.5-10.0)	0.083
MDR			
A. baumannii (%)	55	80	0.615
K. pneumoniae (%)	50	20	0.341
P. aeruginosa (%)	30	20	1
Pre culture Treatments			
Aminoglycoside (%)	70	60	1
Aztreonam (%)	0	0	
Cefepime (%)	30	0	0.289
Cephalosporin (%)	5	0	1
Clindamycin (%)	15	20	1
Imipenem/Cilastatin (%)	45	60	0.645
Linezolid (%)	15	40	0.252
Meropenem (%)	30	20	1
Metronidazole (%)	30	40	1
Piperacillin/Tazobactam (%)	35	60	0.358
Quinolone (%)	25	60	0.283
Tigecycline (%)	0	0	
Trimethoprim/Sulfa (%)	5	20	0.367
Vancomycin (%)	90	80	0.504
Post culture Treatment			
Aminoglycoside (%)	5	0	1
Carbapenem (%)	95	20	0.002*
Cephalosporin (%)	5	0	1
Daptomycin (%)	15	0	1
Linezolid (%)	15	0	1
Metronidazole (%)	5	10	0.367
Quinolone (%)	10	0	1
Vancomycin (%)	70	20	0.121
Vasopressors (%)	85	100	1
Death at ICU (%)	85	100	1

*Fisher's ≤ 0.05 was considered statistically significant.

Table 2. Demographics, previous conditions and treatment by mortality in ICU.

Variables	Death n=22	Alive n=3	p
Demographics			
Men (%)	50	33.3	1
Age in years (median, IQR)	60 (50-72)	35 (31-43.5)	0.046*
Clinical conditions			
Diabetes (%)	31.08	33.3	1
Cardiovascular (%)	50	33.3	1
Lung Disease (%)	13.6	0	1
Immunosuppression (%)	18.2	0	1
Chronic Liver Disease (%)	4.5	0	1
Stroke (%)	9.1	0	1
Chronic Renal disease (%)	0	0	
Days in ICU prior to possitve culture (median, IQR)	7.5 (4.5-17.25)	8.0 (8.0-18)	0.151
MDR			
A. baumannii (%)	63.6	33.3	0.543
K. pneumoniae (%)	45.5	33.3	1
P. aeruginosa (%)	27.3	33.3	1
Pre culture Treatment			
Aminoglycoside (%)	72.7	33.3	0.231
Aztreonam (%)	0	0	
Cefepime (%)	18.2	66.7	0.133
Cephalosporin (%)	4.5	0	1
Clindamycin (%)	18.2	0	1
Imipenem/Cilastatin (%)	54.5	0	0.22
Linezolid (%)	22.7	0	1
Meropenem (%)	27.3	33.3	1
Metronidazole (%)	36.4	0	0.527
Piperacillin/Tazobactam (%)	45.5	0	0.25
Quinolone (%)	36.4	0	0.527
Tigecycline (%)	0	0	
Trimethoprim/Sulfa (%)	4.5	33.3	0.23
Vancomycin (%)	95.5	33.3	0.029*
Post culture treatment			
Aminoglycoside (%)	4.5	0	1
Carbapenem (%)	77.3	100	1
Cephalosporin (%)	0	33.3	0.12
Daptomycin (%)	4.5	66.7	0.029*
Linezolid (%)	9.4	33.3	0.33
Polymyxin B	77	100	1
Metronidazole (%)	4.5	33.3	0.23
Quinolone (%)	9.1	0	1
Vancomycin (%)	59.1	66.7	1
Vasopressors (%)	95.5	33.3	0.029*

*Fisher's ≤ 0.05 was considered statistically significant.

significant lower risk of dying in the ICU. Similarly, cases that were treated with daptomycin and were not on vancomycin after positive culture had lower ICU mortality risk after controlling for age, and polymyxin B use (Table 4).

Discussion

This is the first study performed in Puerto Rico evaluating the use of polymyxin B for MDR GNB. We found a higher mortality rate when compared to previous publications in similar health care settings (10,12, 39-40). However, the survival analysis found that the use of polymyxin B reduces significantly the ICU mortality after controlling for gender, age and use of other antibiotics. A previous study of 60 patients from Sao Paulo, Brazil reported clearance of MDR organisms in 93% of the patients treated with polymyxins from whom repeat specimens were obtained, supporting also its use (41).

The mortality rates reported by other authors are highly variable ranging from under 10% to over 60%. Most, but not all studies report a survival advantage with the use of polymyxins (31, 34-35, 42). On the other hand, being on vancomycin at the time of positive culture or receiving vasopressors were significantly correlated with worse prognosis and is likely a marker for more severe disease or debilitation.

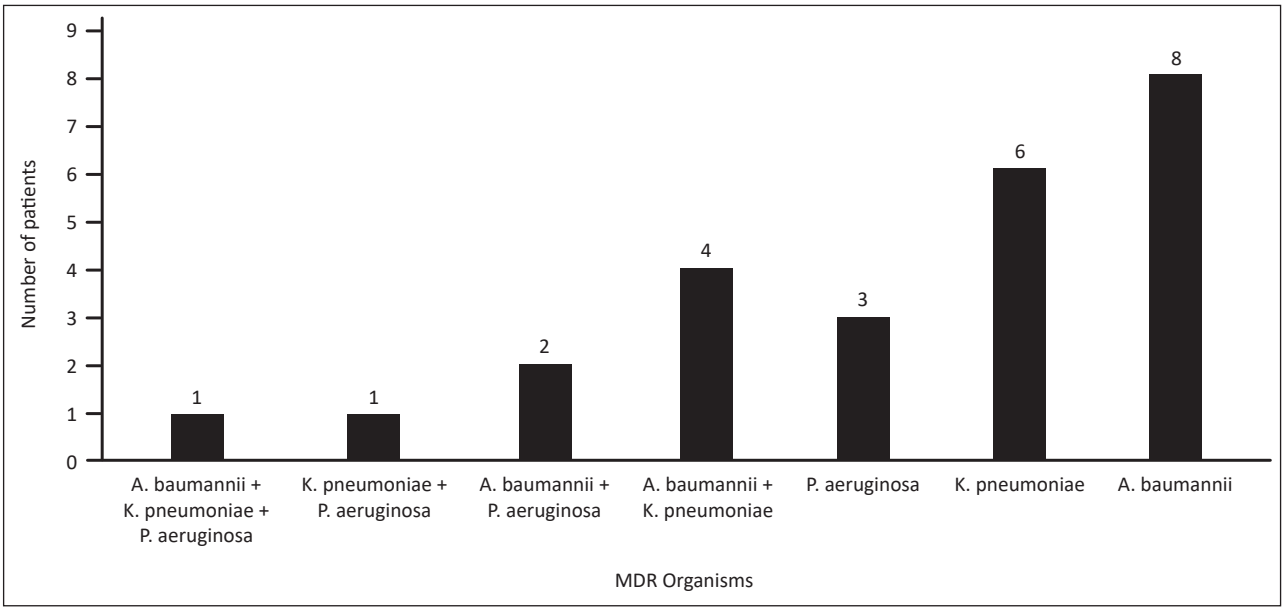

Figure 1. Frequency of MDR bacterial infections.

The study noted also that everyone above age 52 died irrespective of clinical conditions or comorbidities, and that all survivors had single organism MDR bacterial infection. These findings suggest a more severe weakness or compromised immunological response among elderly and co-infected patients treated in the ICU. Consequently, a more aggressive and timely treatment may be recommended to these high-risk groups of patients.

Nephrotoxicity rates associated to the systemic use of polymyxin B have been reported from 14% to 44% (41, 43, 44-46). A recent study from Colombia by Osorio, et al (43) reported a higher rate, however their dosing range (15,000 to 25,000 Units/kg/day) was higher and the definition of renal damage (AKIN) was more sensitive. An average dose of 1,076,000 Units per day as continuous infusion was given to our patients and even though 22 out of 25 patients received vasopressors,only 15 % of them developed kidney injury.

Daptomycin was administered to 3 patients because of concomitant soft tissue or enterococcal infection. Two of these patients survived. The combination of polymyxin B and daptomycin has shown enhanced in vitro activity against polymyxin B susceptible MDR GNB isolates described by Galani et. al. and Morris et. al. (47-48). Mechanism of action proposed was related to decreased cell surface charges. The hypothesis that the combination of polymyxin B and daptomycin improves survival awaits confirmation by prospective trials.

Conclusion

The usage of polymyxin B is associated with increased ICU survival. Nephrotoxicity associated to its use was lower than reported studies. Unexpectedly, we found a significantly

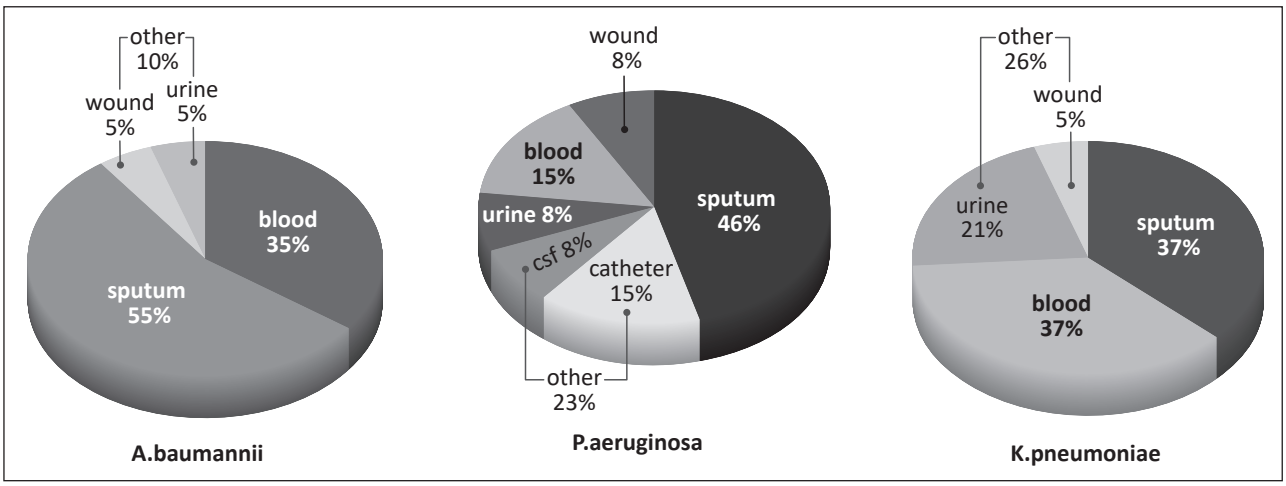

Figure 2. Organisms by culture site.

Table 3. Survival time by gender, previous conditions and treatment.

Variables	ICU survival in days, median (IQR)	p
Demographics		
Women vs. Men	6.0 (1.0-20.0) vs 6.0 (4.0-30.0)	0.68
Clinical conditions (Present vs Absent)		
Diabetes	2.0 (1.0-7.0) vs 9.0 (4.0-30)	0.773
Cardiovascular	7.0 (2.0-20.0) vs 6.0 (4.0-30.0)	0.872
Lung Disease	6.0 (2.0-42.0) vs 6.0 (3.0-30.0)	0.997
Immunosuppression	6.0 (4.0-30.0) vs 6.0 (2.0-20.0)	0.769
Chronic Liver Disease	1.0 (1.0-1.0) vs 6.0 (3.0-30.0)	0.030*
Stroke	5.0 (5.0-20) vs 6.0 (2.0-30.0)	0.835
Chronic Renal disease (%)	n/a vs 6.0 (3.0-30.0)	
MDR (Present vs Absent)		
A. baumannii	5.0 (3.0-30.0) vs 6.0 (2.0-9.0)	0.923
K. pneumoniae	6.0 (1.0-19.0) vs 5.0 (3.0-30.0)	0.237
P. aeruginosa	9.0 (1.0-30.0) vs 6.0 (3.0-30.0)	0.571
Pre culture Treatment (Used vs Not used)		
Aminoglycoside	7.0 (3.0-30.0) vs 5.0 (1.0-30.0)	0.497
Aztreonam	n/a vs 6.0 (3.0-30.0)	
Cefepime	5.0 (1.0-6.0) vs 7.0 (3.0-30.0)	0.878
Cephalosporin	9.0 (9.0-9.0) vs 6.0 (2.0-30.0)	0.922
Clindamycin	3.0 (2.0-7.0) vs 6.0 (4.0-30.0)	0.258
Imipenem/Cilastatin	6.0 (4.0-30.0) vs 6.0 (2.0-42.0)	0.874
Linezolid	4.0 (2.0-5.0) vs 7.0 (3.0-30.0)	0.327
Meropenem	3.0 (1.0-9.0) vs 7.0 (4.0-30.0)	0.499
Metronidazole	3.0 (1.0-5.0) vs 19.0 (6.0-30.0)	0.018*
Piperacillin/Tazobactam	4.0 (3.0-9.0) vs 19.0 (2.0-30.0)	0.281
Quinolone	5.0 (2.0-9.0) vs 7.0 (3.0-30.0)	0.282
Tigecycline	n/a vs 6.0 (3.0-30.0)	
Trimethoprim/Sulfa	4.0 (4.0-4.0) vs 6.0 (2.0-30.0)	0.149
Vancomycin	6.0 (3.0-30.0) vs 1.0 (1.0-1.0)	0.753
Post culture Treatment (Used vs Not used)		
Aminoglycoside	7.0 (7.0-7.0) vs 6.0 (3.0-30.0)	0.824
Carbapenem	9.0 (4.0-30.0) vs 2.0 (2.0-4.0)	0.013*
Cephalosporin	n/a vs 6.0 (3.0-30.0)	
Daptomycin	42.0 (42.0-42.0) vs 5.0 (2.0-19.0)	0.015*
Linezolid	5.0 (1.0-5.0) vs 6.0 (3.0-30.0)	0.415
Polymyxin B	9.0 (5.0-30.0) vs 2.0 (2.0-4.0)	0.002*
Metronidazole	4.0 (4.0-4.0) vs 6.0 (2.0-30.0)	0.185
Quinolone	19.0 (19.0-20.0) vs 6.0 (3.0-30.0)	0.873
Vancomycin	19.0 (4.0-30.0) vs 4.0 (2.0-6.0)	0.077
Vasopressors	5.0 (2.0-20.0) vs 7.0 (7.0-7.0)	0.061

*Kaplan Meier ≤ 0.05 was considered statistically significant.

Table 4. Mortality risk after ICU admission by Cox proportional hazard.

	Mortality Hazard Ratio	95% CI	p
Sex	0.27	0.00-0.78	0.016
Age	0.96	0.92-1.00	0.049
Polymyxin B	0.09	0.02-0.50	0.006
Vancomycin	0.27	0.08-0.93	0.039
Daptomycin	0.28	0.00-0.30	0.003

CI= confidence interval

improved survival in patients who received polymyxin B in combination with daptomycin. Further studies are required to confirm these findings.

Limitations

There are several limitations to our findings. First: Only 25 of 35 medical records were available for review. Second: The study could not adjust for severity of illness because data required to calculate severity scores was not documented for every patient. Third: The study includes a single site group and its findings may not apply to other ICU's. Fourth: Because polymyxin B was given only after obtaining the MDR bacteria culture results, those cases that died before the availability of the culture results could introduce a bias in the mortality evaluation. Fifth: The study reports general deaths from any cause, not necessarily related to the infectious process in this critically ill group. Sixth: The study setting is a teaching hospital part of a public tertiary health care setting that mainly provides services to medically indigent patients. Access to care and quality of care differences could also be related to this worse ICU outcome scenario (49-51).

Resumen

Objetivo: Este estudio tiene como propósito determinar la prevalencia de infecciones por A. baumannii, K. pneumoniae y P. aeruginosa multiresistentes en la unidad de cuidado intensivo (UCI) de un hospital terciario académico en San Juan, PR, estimar la tasa de mortalidad y comparar las diferencias de morbilidad y mortalidad de aquellos pacientes tratados o no tratados con polimixina B. Métodos: Se seleccionaron pacientes adultos admitidos a la UCI con cultivos positivos entre enero 2012 y junio 2013. La muestra consiste de 25 pacientes con edades de 27 a 78 años, 13 mujeres y 12 hombres. Resultados: La mediana de edad al momento de morir fué de 60 años. La nefrotoxicidad por polimixina B fué de 15%. Las variables asociadas a una mayor sobrevida fueron: menor edad, sexo femenino, el uso de polimixina B y el uso de daptomicina. El uso de vancomicina y vasopresores fueron associados a un peor pronóstico. La mortalidad asociada a cada bacteria multi-resistente fué 88% para A. baumannii, 84% para K. pneumoniae y 67% para P. aeruginosa. Todos los pacientes infectados con más de una bacteria multiresistente fallecieron en la UCI. Conclusión: El uso de polimixina B se asoció a una reducción en la mortalidad en la UCI. Inesperadamente se encontró un aumento en sobrevida en aquellos pacientes que recibieron polimixina B en combinación con daptomicina. Este hallazgo requiere de estudios prospectivos para confirmar los resultados.

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