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Summary

- MDR *Acinetobacter baumannii* infections represents a challenge for physicians
- Bloodstream infections are related to high rates of septic shock and mortality
- Data highlight a predominant role for colistin in definitive antibiotic regimens
- Lack of scientific data might explain the very high mortality rate observed
- This real-life clinical experience provides useful suggestions on this difficult-to-treat infection

Bloodstream infections caused by carbapenem-resistant *Acinetobacter baumannii*: clinical features, therapy and outcome from a multicenter study

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ABSTRACT

Objectives: bloodstream infections (BSI) due to multidrug-resistant (MDR) *Acinetobacter baumannii* (AB) have been increasingly observed among hospitalized patients.

Methods: prospective, observational study conducted among 12 large tertiary-care hospitals, across 7 Italian regions. From June 2017 to June 2018 all consecutive hospitalized patients with bacteremia due to MDR-AB were included and analyzed in the study.

Results: During the study period 281 episodes of BSI due to MDR-AB were observed: 98 (34.8%) episodes were classified as primary bacteremias, and 183 (65.2%) as secondary bacteremias; 177 (62.9%) of them were associated with septic shock. Overall, 14-day mortality was observed in 172 (61.2%) patients, while 30-day mortality in 207 (73.6%) patients. On multivariate analysis, previous surgery, continuous renal replacement therapy, inadequate source control of infection, and pneumonia were independently associated with higher risk of septic shock. Instead, septic shock and Charlson Comorbidity Index >3 were associated with 14-day mortality, while adequate source control of infection and combination therapy with survival. Finally, septic shock, previous surgery, and aminoglycoside-containing regimen were associated with 30-day mortality, while colistin-containing regimen with survival.

Conclusions: BSI caused by MDR-AB represents a difficult challenge for physicians, considering the high rates of septic shock and mortality associated with this infection.

Key words: bacteremia, septic shock, *Acinetobacter*, multidrug-resistant, colistin.

INTRODUCTION

In recent years, bloodstream infections (BSI) due to multidrug-resistant (MDR) gram-negative bacteria such as *Acinetobacter baumannii* (AB) have been increasingly observed among hospitalized patients admitted to the intensive care unit (ICU), surgical and medical wards [1-2-3]. MDR-AB has been defined one of the top priority pathogens by the World Health Organization [4-5]; specifically, in Italy an increased incidence of MDR-AB was observed in the last years [6].

Acinetobacter baumannii bacteria are usually resistant to carbapenems and to β-lactams, aminoglycosides, rifampin, and fluoroquinolones [7-8]. There are limited therapeutic options resulting often in inappropriate therapy and subsequent negative impact on outcome. New agents with microbiological activity against MDR-AB strains have been recently developed and they will be available in the near future [9-10-11]. Mortality rate over 60% has been reported for MDR-AB infections [12], particularly in patients with septic shock [13].

Early diagnosis and adequate administration of antimicrobials are the milestone for the management of critically ill patients with MDR-AB [14-15-16], and recent data were reported in literature comparing monotherapy with combination therapy [17]. On these basis, physicians should recognize peculiar clinical characteristics and treat MDR-AB infections appropriately in hospitalized patients [18], so the aim of the present study was to analyse clinical features, antimicrobial treatment and outcome of patients with BSI due to MDR-AB.

PATIENTS AND METHOD

Study Design and Patient Selection

Prospective, observational study conducted among 12 large tertiary-care hospitals across 7 Italian regions. From June 2017 to June 2018 all consecutive hospitalized patients with bacteremia caused by MDR-AB were included in the study. Inclusion criteria included: 1) age ≥18 years; 2) blood culture positive for MDR-AB; 3) clinical signs consistent with infection. Polymicrobial etiology was excluded; only one episode of MDR-AB infection for each patient was reported in the study period. The study was conducted according to the principles stated in the Declaration of Helsinki and has been approved by local Ethical Committees (No 4547-2017); informed consent was waived by Ethical Committees. The present study was promoted by ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva).

Patient data were collected from medical charts and from hospital computerized databases or clinical charts according to a pre-established questionnaire. The following information were reviewed: demographics; clinical and laboratory findings; comorbid conditions; microbiological data; duration of ICU and hospital stay; any MDR infection during hospitalization; treatment and procedures (e.g. non-invasive ventilation, mechanical ventilation, continuous renal replacement therapy [CRRT]) carried out during hospitalization and/or in the 30 days prior to infection; class of antibiotics received on admission and/or during admission before a positive culture of a biological sample was obtained; the simplified acute physiology score (SAPS II); sequential organ failure assessment (SOFA) and quick (q)-SOFA at time of infection; anamnestic MDR-AB colonization or during hospitalization; source of infection and its adequate control; antibiotic regimens used for MDR-AB infection; development of septic shock; all-cause 14- and 30-day mortality.

Definitions and MDR-AB Identification

Infections were defined according to the standard definitions of the European Centers for Disease Control and Prevention (eCDC) [19].

Infection was defined as the presence of at least 1 positive blood culture for MDR-AB in individuals with signs and symptoms consistent with infection [20]; concomitant isolation of MDR-AB in other sites like urine, skin swabs or biopsies, lung or abdomen were also recorded. Infection onset was defined as the date

of collection of the first positive blood culture for MDR-AB. Infection was considered of unknown origin when the source of infection was not established after routine clinical, microbiological, and radiological examination. Primary BSI was defined as BSI occurring in patients without a recognized source of infection. The central venous catheter (CVC) was considered the source of infection if one of the following condition were present: 1) a positive result of semi-quantitative (> 15 colony-forming units per catheter segment) catheter culture, whereby the same species was isolated from the catheter segment and a peripheral blood culture; 2) growth in a blood culture obtained through a catheter hub is detected by an automated system at least 2 hours earlier than a peripheral blood culture of equal volume simultaneously collected, providing that the same species was isolated [21].

Septic shock was defined according to international definitions [22]. The severity of clinical conditions was determined by using SAPS II, SOFA and qSOFA scores calculated at the time of infection onset. Length of hospital and ICU stay were calculated as the number of days from the date of admission to the date of discharge or death.

Identification of MDR-AB strains was based accordingly with local laboratory techniques. The Vitek 2 automated system (bioMérieux, Marcy l'Etoile, France) was used for isolate identification and antimicrobial susceptibility testing. Minimum inhibitory concentrations (MICs) were established

according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints [23]. Isolated strains were classified as multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) according to Magiorakos et al [24].

Antimicrobial Treatment Evaluation and Adequate Source Control of Infection

Depending on the number of drugs used (1 or >1), treatment regimens were classified either as monotherapy or combination therapy. Initial antibiotic therapy, defined as antimicrobial chemotherapy implemented within 24 hours after the onset of infection, was assessed along with definitive antibiotic therapy, defined as antimicrobial treatment based on *in vitro* MDR-AB isolate susceptibilities. Drugs in definitive therapy must have been administered for at least 50% of the total duration of therapy (except for patients who died while on definitive therapy, who were included if they received at least 1 complete day of therapy). Time to initial definitive therapy was the period between the infection onset and initial definitive therapy.

Adequate control of source of infection was defined as the removal of any preexisting contaminated CVC as well as the drainage of intra-abdominal abscesses or other fluid collections have been performed within 24 hours after the onset of infection. Timing of CVC removal was based on medical record review and was confirmed by review of patient radiographs.

Primary Endpoint and Statistical Analysis

The primary endpoint of the study was to evaluate risk factors associated with survival or death at 30 days from BSI onset. Secondary endpoints were risk factors associated with 14-day mortality and septic shock. To detect significant differences between groups, we used Chi-square test or Fisher exact test for categorical variables, and the 2-tailed *t* test or Mann-Whitney test for continuous variables, when

appropriate. All pre-treatment variables identified at univariate analysis were tested at logistic regression analysis to identify risk factors associated with development of septic shock. In a multivariate analysis of survival, the Cox regression model was tested using a proportional hazards model analysis with backward stepwise selection and $p < 0.05$ for all variables, to determine the effects of all anamnestic, clinical and therapeutic variables on 14- and 30-day survival. Kaplan-Meier curves were used to determine survival at 14- and 30-day in patients treated either with monotherapy or combination therapy. Survival curves for time-to-event variables, constructed with the use of Kaplan–Meier estimates, were based on all available data and were compared with the use of the log-rank test. Wald confidence intervals and tests for hazard- and odds-ratios were computed based on the estimated standard errors. Possible confounding factors and interactions were weighted during analyses. Statistical significance was established at ≤ 0.05. All reported *P* values are 2-tailed. The results obtained were analyzed using a commercially available statistical software packages (SPSS, version 20.0; SPSS Inc, Chicago, Illinois).

RESULTS

During the study period, 281 BSI caused by MDR-AB strains were observed. Out of these, 98 episodes (34.8%) were classified as primary bacteremia, and 183 (65.2%) cases as secondary bacteremia; 177 (62.9%) episodes were associated with development of septic shock. Resistance rates were the following: colistin 1.4%, gentamicin 87.3%, amikacin 89.1%, and meropenem 100%. On these basis, 98.6% of AB strains were considered XDR and 1.4% PDR. Finally, 14-day mortality was observed in 172 (61.2%) patients, while 30-day mortality in 207 (73.6%) patients.

Figure 1 shows hospital wards at time of infection onset: 83% of patients were hospitalized in ICU, 9.7% in medical wards, 3.6% in surgical wards, and 1.7% in emergency department.

Table 1 shows univariate analysis comparing survivors and non-survivors at 30 days from infection onset. Differences between survivors and non-survivors were reported for age (53.9 ± 17.4 Vs 63.8 ± 15.9 years, p<0.001), male sex (81.1% Vs 64.7, p=0.009), heart failure (8.1% Vs 23.7%, p=0.003), Charlson Comorbidity Index (3.8 ± 3.5 Vs 6.4 ± 3.9 points, p=0.004), patients transferred to ICU (9.5% Vs 16.9%, p=0.001), septic shock (41.9% Vs 70.5%, p<0.001), SAPS II at time of infection onset (35.7 ± 14.1 Vs 46.6 ± 15.3 points, p<0.001), and qSOFA at time of infection onset (1.5 ± 0.9 Vs 2.1 ± 1 points, p=0.003).

As reported in **Table 2**, Cox regression analysis of factors associated with 14-day mortality in MDR-AB BSI showed that septic shock (HR 10.79, CI95% 1.12-141, p=0.04), and Charlson Comorbidity Index >3

(HR 1.44, CI95% 1.04-2, p=0.02) were associated with death, while adequate source control of infection (HR 0.22, CI95% 0.01-0.42, p=0.01) and combination therapy (HR 0.36, CI95% 0.01-0.89, p=0.03) were associated with survival. Conversely, Cox regression analysis of factors associated with 30-day mortality showed that septic shock (HR 1.54, CI95% 1.04-2.27, p=0.03), previous surgery (HR 1.63, CI95% 1.16-2.29, p=0.005), and aminoglycoside-containing regimen (HR 2.57, CI95% 1.33-4.94, p=0.005) were associated with death, while colistin-containing regimen (HR 0.41, CI95% 0.27-0.63, p<0.001) is associated with 30-day survival.

Univariate analysis comparing patients with septic shock or not secondary to MDR-AB infection is reported in **Table 3**. In patients developing septic shock were recorded more frequently previous surgery (33.3% Vs 15.4%, p=0.001), pneumonia (61% Vs 42.3%, p=0.003), intra-abdominal source of infection (6.8% Vs 0, p=0.005), mechanical ventilation (88.5% Vs 59.3%, p<0.001), CRRT (16.4% Vs 0.9%, p=0.003), adequate source control of infection (47.5% Vs 19.2%, p<0.001), steroid therapy (48% Vs 29.8%, p=0.004), if compared with patients without septic shock. Primary bacteremia was observed more frequently in patients without septic shock (50% Vs 25.9%, p<0.001). Finally, 30-day mortality was 82.5% in patients with septic shock (p<0.001).

A logistic regression analysis about risk factors associated with development of septic shock is reported in **Table 4**: previous surgery (OR 33.9, CI95% 4.86-236.82, p<0.001), CRRT (OR 15.4, CI95% 3.77-63.09, p<0.001), no source control of infection (OR 4.21, CI95% 1.06-16.7, p=0.04), and pneumonia (OR 5.29 CI95% 1.35-20.59, p=0.016) were independently associated with higher risk of septic shock associated with BSI due to MDR-AB strain.

Characteristics of antibiotic regimens in definitive therapy used in overall population are reported in **Table 5.** Monotherapy was the choice for 46 (16.3%) patients; a combination of two antibiotics was used in 133 (47.3%) patients; the use of a colistin-containing regimen was used for 231 (82.2%) patients, and a carbapenem-containing regimen in 194 (69%) patients. Colistin was used as a monotherapy regimen in 40

cases; in combination therapy mainly with a carbapenem (73.5% of cases), and tigecycline (34.5% of cases). No differences were reported in 30-day mortality about monotherapy or combination therapy with colistin (15 [37.5%] Vs 131 [68.5%] patients, p=0.06). The colistin aerosol inhalation therapy was used in 28 (9.9%) patients; the time to initial definitive therapy was 4.4 ± 1.2 days. Comparison between characteristics of patients treated with monotherapy and combination therapy is reported in **Table 6**. Older age (67.7 ± 15.2 Vs 59.9 ± 16.8 years, p=0.004), and >2 comorbidities (54.3% Vs 21.2%, p=0.001) were reported more frequently in patients treated with monotherapy; conversely, adequate source control of infection (42.1% Vs 10.9%, p<0.001), transfer in ICU (33% Vs 19.5%, p=0.004), and higher SAPS II at time of infection (44.7 ± 15.1 Vs 39 ± 17.8 points, p=0.02) were more frequent in patients treated with combination therapy. Finally, statistically significant differences were reported for 14-day mortality (p<0.001), but not for 30-day mortality. Rates of 30-day mortality in patients treated with monotherapy (71.7%), combination therapy (74.04%), two-drug combination (70.6%), three-drug combination (78.3%), four drug combination (68.7%), colistin-containing (70.9%), and carbapenem-containing regimens (73.1%) are reported in **Figure 2**.

Finally, Kaplan-Meier analysis of 14- and 30-day survival of patients treated with monotherapy or combination therapy is reported in **Figure 3**.

DISCUSSION

In the present study we observed very high rates of 14-day (61.2%) and 30-day (73.6%) mortality; most of patients developed septic shock (62.9%) with a very high mortality (82.5%). The high mortality related to *Acinetobacter baumannii* infections was firstly reported in patients with hematologic malignancies [25]; afterwards, Freire *et al.* evaluated mortality in cancer patients with BSI caused by MDR-AB, with 7-day and 30-day mortality rates of 71.7% and 83.7%, respectively [26]. Recent studies confirmed these data with mortality over 90% in patients with septic shock [12-13]. Moreover, our data show that MDR-AB BSI remains a peculiar ICU-acquired infection, although is now more frequently observed even in medical and surgical wards.

Risk factors affecting 14- and 30-day outcome have been explored in our population. As previously reported in literature, these data confirm the weight of comorbidities and septic shock in determining higher 30-day mortality [3,13,16]. Interestingly, previous surgery was associated with 30-day mortality while adequate source control with 14-day survival. These observations emphasize the role of early source control, that remains particularly complicated in abdominal surgical patient.

Different antibiotic combinations have been studied for treatment of severe infections sustained by MDR-AB [27-28]; in this context, the role of aerosolized colistin as adjunctive treatment for treatment of severe pneumonia was also investigated [29-30-31]. In a randomized clinical trial [32], in patients with MDR-

AB infections mortality was not reduced by addition of rifampicin to colistin; further *in vitro* studies explored the synergism of some drug combinations, especially colistin plus carbapenem for treatment of MDR-AB infections [33-34], suggesting the advantage of this combination based on high in vitro synergy rates. Combination of a carbapenem plus colistin seems to be the first option for treatment of MDR-AB infections [35], even in our population. Recently, Paul and coworkers reported data from a randomised controlled trial comparing colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria [17]. Authors concluded that combination therapy was not more efficient than monotherapy, and that adding meropenem to colistin did not improve clinical failure in severe MDR-AB infections. Of importance, Dickstein and coworkers performed a subgroup analysis on patients with *Acinetobacter* infections and reported that colistin monotherapy was associated with a better outcome compared to colistin-meropenem combination therapy [36]. It is important to underline that studies comparing efficacy of monotherapy (mainly colistin) with combination regimens for *Acinetobacter baumannii* infections included a spectrum of different severe infections, like ventilator associated pneumonia, but not always associated with bacteremia. On this basis, our study confirms that comparative studies on MDR-AB therapy should include bacteremic patients. In our population, combination therapy was associated with higher survival at 14 days, but no differences were reported at 30 days if compared to monotherapy (see **Figure 3**); however, all patients (except in 1 case) treated with monotherapy died in the first 14 days from the diagnosis of BSI (see **Table 4**). In our interpretation, sepsis and septic shock are associated with a lethal cascade of events that is unlikely to be interrupted even by an appropriate initial antimicrobial treatment. In addition, most of our patients were severely ill and would probably have been unable to survive their infections independently of the administration of an adequate initial antimicrobial treatment.

Despite the relevant association between colistin use and 30-day survival, recent EUCAST recommendations [37], based on recent observations [38] advertised about potential false susceptibility to

colistin in approximately 50% of *Acinetobacter baumannii* strains with automated systems or Etest. Therefore, the very high rates of mortality observed in our population and in published studies [13,26] might be also attributed to a reported false susceptibility to colistin in patients for whom physicians were confident in the prescribing a colistin-based regimen. In strains with a real susceptibility to colistin the use of this drug was associated with long term survival in severe infections.

Finally, interesting data observed in our population show the association between aminoglycoside-containing regimen and 30-day mortality. A possible explanation should be that in a significant proportion of patients (54%), especially septic ones (61%), pneumonia was reported as primary source of infection. As reported above, severe pneumonia remains a difficult-to-treat infection and, considering the poor lung penetration of aminoglycosides, these drugs should be probably avoided for MDR AB pneumonia [39-40].

Our study reveals some limitations that should be acknowledged. Firstly, the observational nature of the study brings about an intrinsic limitation in the analysis. Secondly, overall incidence of BSI caused by MDR-AB strains was very inhomogeneous in the involved centres. Finally, the underlying mechanisms of resistance in these strains were not routinely assessed and *in vitro* synergistic combinations were not performed, except for few cases. Further analysis about *in vitro* activity of antibiotic regimens have been avoided, considering that 91 (32.3%) of patients were treated for a previous MDR infections with similar antibiotic regimens. Moreover, antibiotic regimens with two or more drugs displaying *in vitro* activity against MDR-AB have been observed in <10% of strains. However, this real-life clinical experience from prestigious hospitals in Italy provides useful suggestions to clinicians about management of this difficult-to-treat infection**.**

In conclusion, BSI caused by MDR-AB strains represents a challenge for physicians, considering the high rates of septic shock and mortality associated with this infection. Our data showed peculiar clinical features and use of different antibiotic regimens in this setting of infection, with a predominant role for

colistin. The lack of scientific data might explain the very high mortality rate observed in this population of patients [41-42].

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Table 1. Univariate analysis comparing survivors and non-survivors at 30 days from infection onset

Variables	Survivors n= 74 (%)	Non-survivors n= 207 (%)	HR (CI 95%)	*P*
Age, mean ± SD (years)	53.9 ± 17.4	63.8 ± 15.9	2.2 (1.9-4.1)	**<0.001**
Male sex	60 (81.1)	134 (64.7)	0.42 (0.2-0.7)	**0.009**
Comorbidities				
Chronic liver disease	6 (8.1)	16 (7.7)	0.94 (0.8-1.3)	1.0
Neoplasm	11 (14.9)	33 (15.9)	1.08 (0.8-1.2)	1.0
Diabetes	19 (25.7)	57 (27.5)	1.1 (0.8-1.4)	0.87
Heart failure	6 (8.1)	49 (23.7)	3.51 (2.4-5.3)	**0.003**
Coronary artery disease	26 (35.1)	103 (49.8)	1.82 (1.4-3.4)	**0.04**
Chronic renal disease	10 (13.5)	41 (19.8)	1.58 (0.7-2.1)	0.29
COPD	23 (31.1)	59 (28.5)	0.88 (0.6-1.2)	0.76
Neurological disease	7 (9.4)	10 (4.8)	1.01 (0.8-1.2)	1.0
SOT/HSCT	2 (2.7)	9 (4.3)	2.98 (0.9-3.5)	0.2
>2 comorbidities	27 (36.4)	48 (23.1)	0.91 (0.5-1.3)	0.59
Charlson Comorbidity Index, mean ± SD	3.8 ± 3.5	6.4 ± 3.9	3.1 (2.4-4.8)	**0.004**
Previous hospitalization (90 days)	26 (35.1)	69 (33.3)	0.92 (0.6-1.5)	0.77
Previous ICU admission (90 days)	7 (9.5)	29 (14)	1.55 (0.7-1.9)	0.41
Previous surgery (30 days)	11 (14.8)	64 (30.9)	2.77 (2.1-5.2)	**0.004**
Previous antibiotic therapy (30 days)	38 (51.4)	115 (55.6)	1.18 (0.8-1-7)	0.58
Previous *Acinetobacter* spp colonization/infection	4 (5.4)	8 (3.8)	0.85 (0.6-1.2)	1.0
Acinetobacter colonization prior infection	11 (14.9)	20 (9.7)	0.61 (0.5-1-3)	0.27
Source of infection				
Primary bacteremia	32 (43.2)	66 (31.8)	0.58 (0.3-1.1)	0.06
CVC-related bacteremia	1 (1.4)	10 (4.8)	3.37 (0.8-3.9)	0.29
Pneumonia	38 (51.4)	114 (55.1)	1.16 (0.8-1.4)	0.59
Catheter-related urinary tract	0	6 (2.9)	1.23 (0.8-1.3)	0.34

SSTI Intra-abdominal	2 (2.7) 1 (1.4)	0 11 (5.3)	0.25 (0.1-1.1) 4.09 (0.8-4.3)	0.06 0.19
Fever	24 (32.4)	31 (14.9)	0.8 (0.5-1-8)	0.67
NIV	2 (2.7)	7 (3.3)	2.25 (0.8-2.8)	0.48
Mechanical ventilation	33 (44.5)	61 (29.4)	0.65 (0.4-1.7)	0.24
CRRT	8 (10.8)	22 (10.6)	1.01 (0.8-1.1)	0.2
ECMO	2 (2.7)	2 (0.9)	0.6 (0.4-1.8)	0.63
Inadequate source control of infection	22 (29.7)	82 (39.7)	1.51 (0.8-1.9)	0.16
Previous MDR infections during hospital stay	30 (40.5)	62 (30)	0.62 (0.4-1.3)	0.11
PCT at time of infection onset, mean ± SD	18.2 ± 49.8	33.9 ± 68.1	1.7 (0.8-1.9)	0.26
CRP at time of infection onset, mean ± SD	29.9 ± 51.3	51.1 ± 83.9	1.3 (0.7-2)	0.25
Steroid therapy	28 (37.8)	88 (42.5)	1.21 (0.8-1.8)	0.49
Transfer in ICU	7 (9.5)	35 (16.9)	7.5 (2.2-9.3)	**0.001**
Septic shock	31 (41.9)	146 (70.5)	3.32 (2.5-8.9)	**<0.001**
Length of hospitalization, mean ± SD (days)	54.2 ± 35.6	32.5 ± 27.3	0.6 (0.2-0.8)	**<0.001**
Length of ICU stay, mean ± SD (days)	42.9 ± 30.4	24.1 ± 22.7	0.5 (0.3-0.7)	**<0.001**
Length of definitive antibiotic therapy, mean ± SD (days)	15.1 ± 8.2	8.4 ± 8.3	0.63 (0.4-0.9)	**<0.001**
SAPS II at time of infection onset, mean ± SD	35.7 ± 14.1	46.6 ± 15.3	2.1 (1.8-4.2)	**<0.001**
qSOFA at time of infection onset, mean ± SD	1.5 ± 0.9	2.1 ± 1	1.2 (1.1-2.3)	**0.003**
SOFA at time of infection onset, mean ± SD	6.2 ± 3	7.2 ± 3.1	1.1 (0.8-1.4)	0.11

Legend. OR: odds ratio; SD: standard deviation; COPD: chronic obstructive pulmonary disease; SOT/HSCT: solid organ transplant/hematopoietic stem cell transplant; ICU: intensive care unit; CVC: central venous catheter; SSTI: skin and soft-tissue infection; NIV: non-invasive ventilation; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; MDR: multidrug-resistant; PCT: procalcitonin; CRP: c-reactive protein; SAPS: simplified acute physiology score; SOFA: sequential organ failure assessment.

Table 2. Cox regression analysis about risk factors associated with 14-day and 30-day mortality

14-day mortality				**30-day mortality**			
Variables	**HR**	**CI 95%**	***p***	**Variables**	**HR**	**CI 95%**	***p***
Septic shock	10.79	1.12-141	0.04	Septic shock	1.54	1.04-2.27	0.03
Adequate source control of infection	0.22	0.01-0.42	0.01	Colistin-containing regimen	0.41	0.27-0.63	<0.001
Charlson Comorbidity Index>3	1.44	1.04-2	0.02	Aminoglycoside-containing regimen	2.57	1.33-4.94	0.005
Combination therapy	0.36	0.01-0.89	0.03	Previous surgery (30 days)	1.63	1.16-2.29	0.005

Legend. HR: hazard ratio; CI: confidence interval;

Table 3. Univariate analysis comparing patients developing or not septic shock

Variables	No septic shock n= 104 (%)	Septic shock n= 177 (%)	OR	*P*
Age, mean ± SD (years)	58.6 ± 18.1	62.7 ± 15.8	2.07 (0.8-2.4)	0.46
Male sex	74 (71.2)	120 (67.8)	0.7 (0.5-1.4)	0.59
Comorbidities				
Chronic liver disease	12 (11.5)	10 (5.6)	0.45 (0.3-1.9)	0.1
Neoplasm	20 (19.2)	24 (13.6)	0.65 (0.3-1.4)	0.23
Diabetes	27 (26)	49 (27.7)	1.09 (0.6-1.5)	0.78
Heart failure	15 (14.4)	40 (22.6)	1.72 (0.8-2.2)	0.11
Coronary artery disease	33 (31.7)	96 (54.2)	2.55 (1.8-4.5)	**<0.001**
Chronic renal disease	16 (15.4)	35 (19.8)	1.35 (0.7-1.7)	0.42
COPD	32 (30.8)	50 (28.2)	0.88 (0.5-1.3)	0.68
Neurological disease	11 (10.6)	6 (3.3)	0.8 (0.5-1.5)	0.78
SOT/HSCT	5 (4.8)	6 (3.3)	0.64 (0.4-1.5)	0.34
>2 comorbidities	44 (42.3)	31 (17.5)	0.8 (0.5-1.4)	0.72
Charlson Comorbidity Index, mean SD	5.1 ± 4	5.3 ± 3.9	1.26 (0.8-1.4)	0.85
Previous hospitalization (90 days)	40 (38.5)	55 (31.1)	0.72 (0.5-1.3)	0.24
Previous ICU admission (90 days)	12 (11.5)	24 (13.6)	1.2 (0.6-1.9)	0.71
Previous surgery (30 days)	16 (15.4)	59 (33.3)	2.76 (1.5-4.6)	**0.001**
Previous antibiotic therapy (30 days)	59 (56.7)	94 (53.1)	0.86 (0.3-1.3)	0.62
Previous *Acinetobacter* spp colonization/infection	4 (3.8)	8 (4.5)	3.42 (0.9-3.9)	0.06
Acinetobacter colonization prior infection	11 (10.6)	20 (11.3)	1.07 (0.9-1.2)	1.0
Source of infection				
Primary bacteremia	52 (50)	46 (25.9)	0.33 (0.1-0.6)	**<0.001**
CVC-related bacteremia	4 (3.8)	7 (4)	1.02 (0.9-1.1)	1.0
Pneumonia	44 (42.3)	108 (61)	2.13 (1.8-2.9)	**0.003**

Catheter-related urinary tract SSTI Intra-abdominal	4 (3.8) 0 0	2 (1.1) 2 (1.1) 12 (6.8)	0.28 (0.2-1.3) 1.2 (0.8-1.4) 2.6 (2.1-4.4)	0.19 0.53 **0.005**
Fever	37 (35.5)	18 (10.1)	0.51 (0.4-1.2)	0.13
NIV	7 (8.6)	2 (3.8)	0.41 (0.2-1.3)	0.48
Mechanical ventilation	48 (59.3)	46 (88.5)	5.27 (3.1-7.2)	**<0.001**
CRRT	1 (0.9)	29 (16.4)	3.66 (2.8-5.8)	**0.003**
ECMO	1 (0.9)	3 (1.6)	4.8 (0.8-4.8)	0.3
Inadequate source control of infection	20 (19.2)	84 (47.5)	3.79 (3.1-6.4)	**<0.001**
Previous MDR infections during hospital stay	43 (41.3)	49 (27.7)	0.54 (0.2-0.7)	**0.02**
PCT at time of infection onset, mean ± SD	19.1 ± 45.2	37 ± 75.8	1.7 (0.8-2.2)	0.198
CRP at time of infection onset, mean ± SD	38.6 ± 55.9	51.2 ± 95.8	1.4 (0.8-1.7)	0.45
Steroid therapy	31 (29.8)	85 (48)	2.17 (2-5.1)	**0.004**
Transfer in ICU	23 (22.1)	19 (10.7)	0.33 (0.1-0.6)	**0.009**
Length of hospitalization, mean ± SD (days)	47.6 ± 37.8	32.7 ± 25	0.87 (0.4-0.9)	**<0.001**
Length of ICU stay, mean ± SD (days)	31.3 ± 33.2	26.2 ± 21.6	0.5 (0.3-1.3)	0.13
Length of definitive antibiotic therapy, mean ± SD (days)	11 ± 7.7	9.7 ± 9.3	0.98 (0.5-1.3)	0.2
SAPS II at time of infection onset, mean ± SD	37.4 ± 16.4	47.4 ± 14	1.9 (1.2.2.6)	**<0.001**
qSOFA at time of infection onset, mean ± SD	1.5 ± 0.9	2.45 ± 0.9	2.4 (1.9-3.2)	**<0.001**
SOFA at time of infection onset, mean ± SD	6.1 ± 2.6	8.1 ± 3.5	2.3 (1.8-3.8)	**0.004**
30-day mortality	61 (58.7)	146 (82.5)	3.32 (2.4-5.3)	**<0.001**

Legend. OR: odds ratio; SD: standard deviation; COPD: chronic obstructive pulmonary disease; SOT/HSCT: solid organ transplant/hematopoietic stem cell transplant; ICU: intensive care unit; CVC: central venous catheter; SSTI: skin and soft-tissue infection; NIV: non-invasive ventilation; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; MDR: multidrug-resistant; PCT: procalcitonin; CRP: c-reactive protein; SAPS: simplified acute physiology score; SOFA: sequential organ failure assessment.

Table 4. Logistic regression analysis about risk factors associated with development of septic shock

VARIABLES	OR	CI 95%	p
Previous surgery (30 days)	33.9	4.86-236.82	<0.001
CRRT	15.4	3.77-63.09	<0.001
Inadequate source control of infection	4.21	1.06-16.7	0.04
Pneumonia	5.29	1.35-20.59	0.016

Legend. OR: odds ratio; CI: confidence interval; CRRT: continuous renal replacement therapy; SOFA: sequential organ failure assessment.

Table 5. Antibiotic regimens as definitive therapy among overall population

ANTIBIOTIC THERAPY*	**Overall population n= 281 (%)**
Use of only 1 antibiotic as definitive therapy	46 (16.3)
Use of 2 antibiotics in combination as definitive therapy	133 (47.3)
Use of 3 antibiotics in combination as definitive therapy	74 (26.3)
Use of 4 antibiotics in combination as definitive therapy	16 (5.6)
Use of 5 antibiotics in combination as definitive therapy	1 (0.4)
Colistin-containing regimen as definitive therapy	231 (82.2)
Tigecycline-containing regimen as definitive therapy	69 (24.5)
Aminoglycoside-containing regimen as definitive therapy	16 (5.7)
Rifampin-containing regimen as definitive therapy	71 (25.2)
Ampicillin/sulbactam-containing regimen as definitive therapy	2 (0.7)
Fosfomycin-containing regimen as definitive therapy	4 (1.4)
Trimethoprim/sulfamethoxazole-containing regimen as definitive therapy	5 (1.7)
Vancomycin-containing regimen as definitive therapy	14 (4.9)
Carbapenem-containing regimen as definitive therapy	194 (69)
Use of colistin aerosol inhalation therapy	28 (9.9)
Time to initial definitive therapy, mean ± SD (days)	4.4 ± 1.2

Legend. SD: standard deviation.

*During the study period, the usual antimicrobial dosages, adopted for the most used antibiotics, were the following: for colistin, a loading dose of 9 million IU followed by 4.5 million IU every 12 h; for tigecycline, a loading dose of 150 to 200 mg followed by 100 mg every 12 h; for gentamicin, a dosage of 5 mg/kg every 24 h; for rifampin, a dosage of 10 mg/kg/day; for meropenem, a dosage of 2 g every 8 h or 1.5 g every 6 h; for fosfomycin 12-24 g/day divided every 6-8 h; for ampicillin/sulbactam 3 g every 6 h; for trimethoprim/sulfamethoxazole 15-20 mg/kg/day divided every 6 h; for vancomycin 40 mg/kg/day divided every 12 h.

Table 6. Comparison between patients treated with monotherapy or combination therapy

Variables	Monotherapy n=46 (%)	Combination therapy n=235 (%)	*P*
Age, mean ± SD (years)	67.7 ± 15.2	59.9 ± 16.8	**0.004**
Male sex	30 (65.2)	164 (69.8)	0.6
Comorbidities			
Chronic liver disease	8 (17.4)	14 (6)	**0.01**
Neoplasm	10 (21.7)	34 (14.5)	0.26
Diabetes	20 (43.5)	56 (23.8)	**0.01**
Heart failure	13 (28.3)	42 (17.9)	0.1
Coronary artery disease	26 (56.5)	103 (43.8)	0.14
Chronic renal disease	10 (21.7)	41 (17.4)	0.53
COPD	22 (47.8)	60 (25.5)	**0.004**
Neurological disease	5 (10.9)	12 (5.1)	1.0
SOT/HSCT	1 (2.1)	10 (4.2)	0.45
>2 comorbidities	25 (54.3)	50 (21.2)	**0.001**
Charlson Comorbidity Index, mean SD	5.5 ± 3.1	5 ± 4.3	0.64
Previous hospitalization (90 days)	22 (47.8)	73 (31.1)	**0.04**
Previous ICU admission (90 days)	5 (10.9)	31 (13.2)	0.81
Previous surgery (30 days)	10 (21.7)	65 (27.6)	0.7
Previous antibiotic therapy (30 days)	28 (60.9)	125 (53.2)	0.41
Previous *Acinetobacter* spp colonization/infection	1 (3.3)	10 (9.6)	0.29
Acinetobacter colonization prior infection	5 (10.9)	26 (11.1)	1.0
Source of infection			
Primary bacteremia	17 (37)	81 (34.4)	0.73
CVC-related bacteremia	0	11 (4.7)	0.22
Pneumonia	23 (50)	129 (54.9)	0.62
Catheter-related urinary tract	2 (4.3)	4 (1.7)	0.25
SSTI	0	2 (2.9)	1.0
Intra-abdominal	4 (8.7)	8 (3.4)	0.11
Fever	21 (45.6)	34 (14.5)	0.17

NIV	2 (4.3)	7 (2.9)	1.0
Mechanical ventilation	15 (32.6)	79 (33.6)	0.07
CRRT	7 (15.2)	23 (9.7)	1.0
ECMO	1 (2.1)	3 (1.2)	1.0
Source control of infection	5 (10.9)	99 (42.1)	**<0.001**
Previous MDR infections during hospital stay	21 (45.7)	71 (30.2)	**0.05**
PCT at time of infection onset, mean ± SD	34.2 ± 96.7	25.4 ± 51.6	0.63
CRP at time of infection onset, mean ± SD	69.4 ± 114.2	36.1 ± 57.1	0.09
Steroid therapy	18 (39.1)	98 (41.7)	0.87
Transfer in ICU	9 (19.5)	33 (14)	**0.004**
Septic shock	26 (56.5)	151 (64.3)	0.32
Length of hospitalization, mean ± SD (days)	32.6 ± 30.3	39.3 ± 31.2	0.18
Length of ICU stay, mean ± SD (days)	13.8 ± 11	30.1 ± 27.2	**<0.001**
Length of definitive antibiotic therapy, mean ± SD (days)	8.3 ±.2	10.5 ± 9.3	0.14
SAPS II at time of infection onset, mean ± SD	39 ± 17.8	44.7 ± 15.1	**0.02**
qSOFA at time of infection onset, mean ± SD	1.9 ± 1	1.8 ± 1	0.75
SOFA at time of infection onset, mean ± SD	6.5 ± 2.6	7 ± 3.2	0.51
14-day mortality	32 (69.5)	140 (59.5)	<0.001
30-day mortality	33 (71.7)	174 (74)	0.71

Legend. SD: standard deviation; COPD: chronic obstructive pulmonary disease; SOT/HSCT: solid organ transplant/hematopoietic stem cell transplant; ICU: intensive care unit; CVC: central venous catheter; SSTI: skin and soft-tissue infection; NIV: non-invasive ventilation; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; MDR: multidrug-resistant; PCT: procalcitonin; CRP: c-reactive protein; SAPS: simplified acute physiology score; SOFA: sequential organ failure assessment.

Figure 1. Wards of hospitalization at time of infection

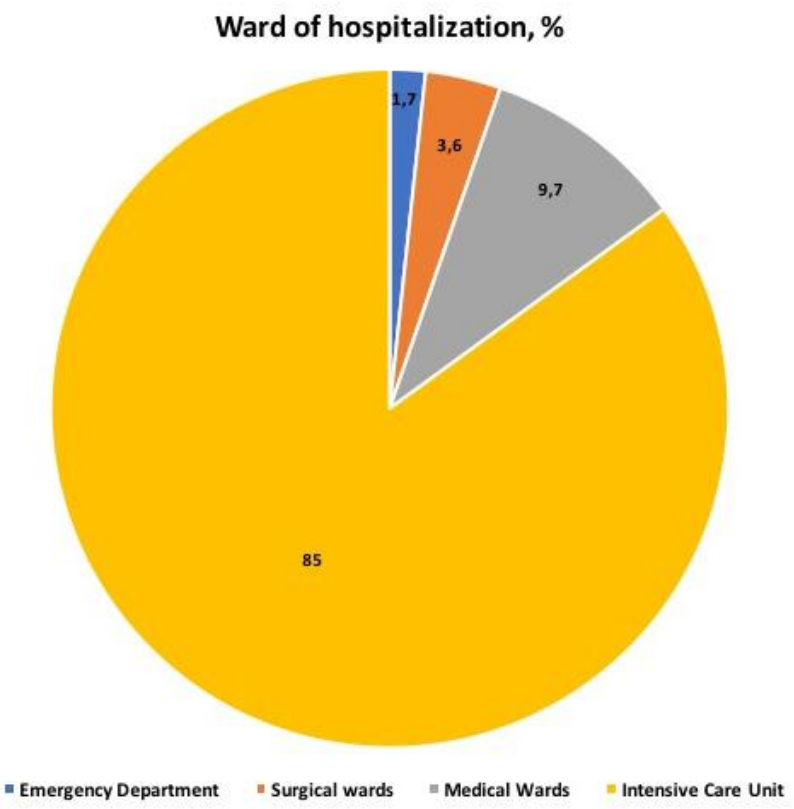


Figure 2. 30-day mortality and antibiotic regimens in definitive therapy among overall population

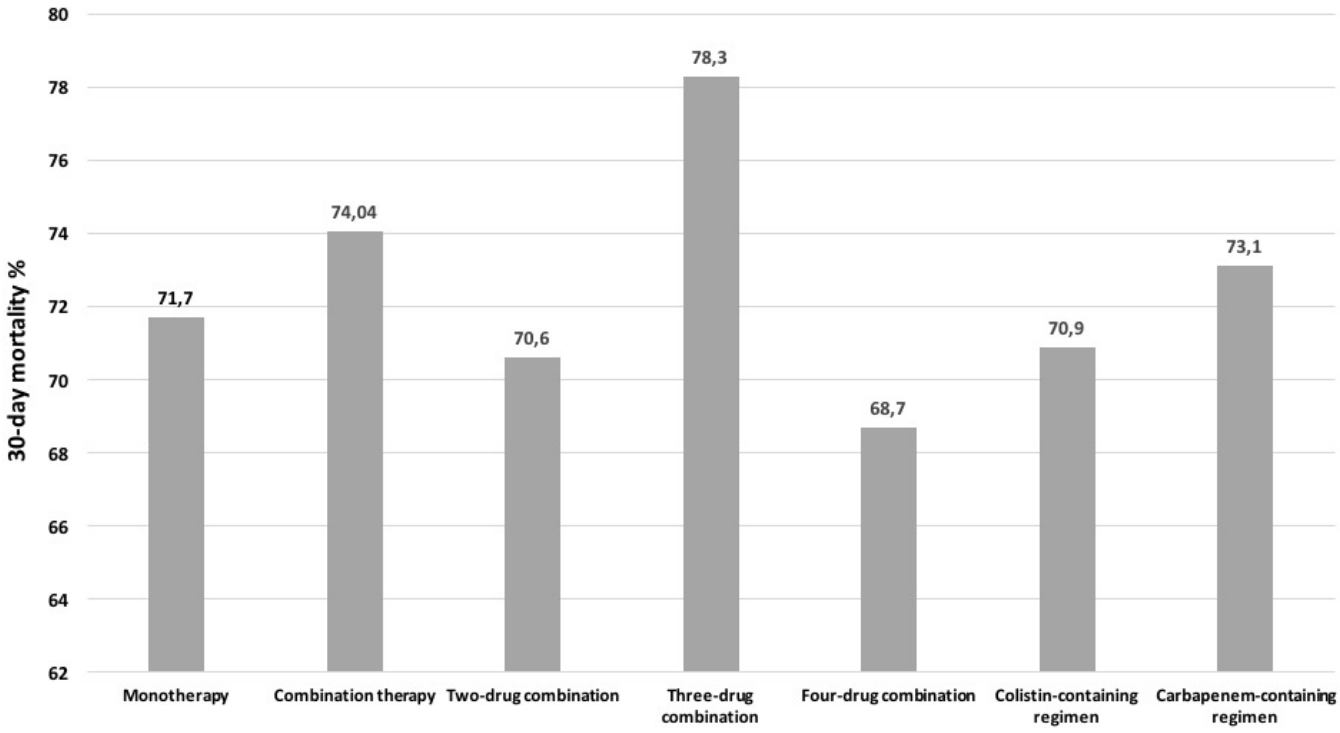
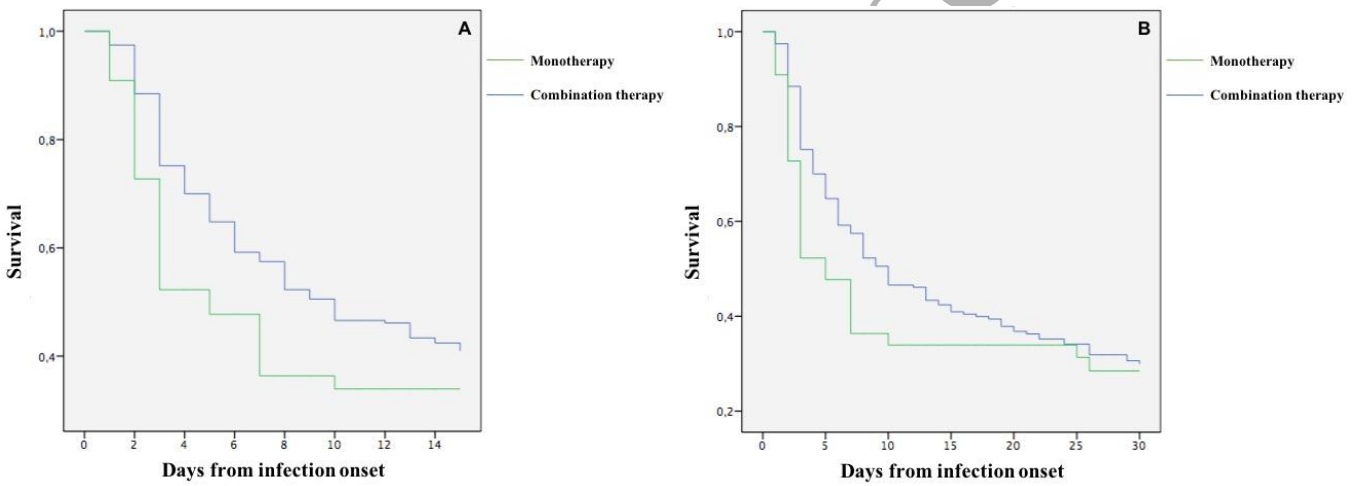


Figure 3. Kaplan-Meier curves about 14-day (**A**) and 30-day (**B**) survival of patients treated with monotherapy (green line*) or combination therapy (blue line**).



*p=0.003
**p=0.82

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