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Original Research

Mortality in Patients With Septic Shock by Multidrug Resistant Bacteria: Risk Factors and Impact of Sepsis Treatments

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Stefano Busani, MD[1], Giulia Serafini, MD[1], Elena Mantovani, MD[1], Claudia Venturelli, MD[2], Maddalena Giannella, MD[3], Pierluigi Viale, MD[3], Cristina Mussini, MD[4], Andrea Cossarizza, MD, PhD[5], and Massimo Girardis, MD[1]

Abstract

Background: Patients with septic shock by multidrug resistant (MDR) microorganism maybe considered a specific population of critical patients at very high risk of death in whom the effects of standard sepsis treatment has never been assessed. The objective of this retrospective analysis was to evaluate the risk factors for 30-day mortality and the impact of sepsis management in patients with septic shock caused by MDR bacteria. **Methods:** Patients with septic shock by MDR bacteria admitted to the mixed intensive care unit (ICU) of Modena University Hospital during a 6-year period were studied. The clinical and microbiological characteristics and sepsis treatments provided were analyzed and compared between survivors (S) and nonsurvivors (NS) at 30 days after septic shock appearance. **Results:** Ninety-four patients were studied. All therapeutic interventions applied to patients during their ICU stay did not show statistical significance between S and NS groups, except for administration of immunoglobulin M (IgM) preparation which were provided more frequently in S group ($P < .05$). At the multivariate adjusted analysis, preexisting cancer (odds ratio [OR] = 2.965) and *Acinetobacter baumannii* infections (OR = 3.197) were independently correlated with an increased risk of 30-day mortality, whereas treatment with IgM preparation was protective (OR = 0.283). **Conclusions:** This retrospective study showed that in patients with septic shock caused by MDR bacteria, history of cancer and infection sustained by *A baumannii* increase the risk of mortality and that standard sepsis treatments do not seem to provide any protective effect. Adjunctive therapy with IgM preparation seems to be beneficial, but further appropriate studies are needed to confirm the results observed.

Keywords

septic shock, multidrug resistant bacteria, sepsis bundle treatment, host immune response

Introduction

Along with the improvement in social and health conditions, there has been a worldwide spread of multidrug resistant (MDR) bacteria due to a sharp increase in the level of care and in the use of antibiotics. Risk factors for the development of MDR bacterial infections are represented by colonization with resistant bacteria, prior infection with MDR, previous exposure to broad-spectrum antibiotics and/or an antimicrobial prophylaxis with quinolones, very advanced underlying disease, prolonged hospitalization, use of medical devices, need for dialysis, and cancer.[1-3]

A consistent number of clinical experiences reported an increased risk of mortality in patients with infections by MDR bacteria compared to those with non-MDR infections.[4-6] The true reasons for this increased risk are still unclear. The more frequent exposure to an initial inappropriate empiric antibiotic therapy may play a pivotal role.[7] However, other factors such

[1] Cattedra e Struttura di Anestesia e Rianimazione, Azienda Ospedaliero-Universitaria Policlinico, Modena, Italy
[2] Dipartimento Interaziendale Integrato di Medicina di Laboratorio e Anatomia Patologica, Struttura Complessa di Microbiologia e Virologia, Azienda Ospedaliero-Universitaria Policlinico, Modena, Italy
[3] Clinica di Malattie Infettive, Dipartimento di scienze mediche e chirurgiche, Università di Bologna, Bologna, Italy
[4] Dipartimento Attività Integrata di Medicine, Medicina d'Urgenza e Specialità Mediche, Malattie infettive, Università di Modena e Reggio Emilia, Modena, Italy
[5] Dipartimento di Chirurgia, Medicina, Odontoiatria e Scienze Morfologiche, Università di Modena e Reggio Emilia, Modena, Italy

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Corresponding Author:
Massimo Girardis, Cattedra di Anestesia e Rianimazione, Azienda Ospedaliera Universitaria di Modena, L.go del Pozzo, 71, 41100 Modena, Italy.
Email: girardis.massimo@unimo.it

as origin of infection, patients' comorbidities, and impairment of inflammatory immune response may also contribute to the increased mortality. Infections with MDR bacteria occur generally in patients with serious preexisting chronic or acute diseases. In addition, in critically ill patients, colonization or infections with nosocomial bacteria (eg, *Acinetobacter* subspecies), together with viral reactivation, have been indicated as a sensible marker for immune dysfunction occurring in a late phase of sepsis and closely related to morbidity and mortality.[8,9]

Therefore, patients with severe sepsis or septic shock by MDR microorganisms may be considered as a specific population of critically ill patients at very high risk of death in whom the effects of standard sepsis treatment have never been assessed. Moreover, beyond the use of an initial appropriate empirical antibiotic therapy, this population may benefit from other supportive strategies different from those used in other populations with severe sepsis or septic shock, as for instance patients with community-acquired infections, without significant comorbidities and impairment of immune system.[10]

In this retrospective cohort including adult patients with septic shock caused by MDR infections admitted to our intensive care unit (ICU) over a 6-year period study, we aimed to evaluate the clinical and microbiological risk factors for mortality and the relationship between compliance to sepsis treatments and patients' outcome.

Materials and Methods

Populations and Study Design

The retrospective study was conducted in a polyvalent ICU of a 680-bed tertiary University Hospital over a 6-year period, from the January 1, 2008, to December 31, 2013. We included all consecutive patients aged 18 years or older admitted to our ICU with septic shock sustained by a documented MDR bacteria. Septic shock was defined using the International Sepsis Definitions Conference criteria.[11] The MDR organisms were defined in accordance with the Centers for Disease Control and Prevention[12] and Magiorakos et al.[13] In detail, we defined *Staphylococcus aureus*, *Enterococcus* subspecies, Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter* subspecies as MDR bacteria if the isolate was nonsusceptible to at least 1 agent in $\geq$3 antimicrobial categories listed in the standard definitions for acquired resistance. Patients aged <18 years, with end-stage liver disease, do-not-resuscitate orders, or end-of-life decisions during the ICU stay were excluded from the study. This study was reviewed and approved by the ethics committee of Modena Province (n° 251/12) and because the study was retrospective and did not require any active intervention apart from standard medical care, the ethics committee deemed informed consent unnecessary.

Treatment Protocol

During the analyzed period, the management of patients with septic shock did not change, apart from the use of the recombinant human activated protein C (rhAPC) that was withheld in November 2011, and included 5 resuscitation interventions (resuscitation bundle) and 5 management interventions (management bundle). The components of the resuscitation bundle would have to be completed within 6 hours after shock diagnosis and included collecting blood cultures before administering antibiotics, adequate empirically based antibiotic therapy (within 3 hours of shock diagnosis), controlling the source of the infection, adequate fluid resuscitation before administering vasopressors, and attaining a central venous oxygen saturation >70%. The management bundle included attaining a median glucose concentration of <150 mg/dL in the first 24 hours; reaching a plateau inspiratory pressure (PIP) <30 cmH_2O in patients with acute lung injury/adult respiratory distress syndrome; and administering low-dose hydrocortisone, recombinant rhAPC (until November 2011), and intravenous immunoglobulin M (IgM)-enriched immunoglobulin preparation (IgM preparation). In 2008, after the publication of 3 different meta-analysis on the use of immunoglobulins in patient with sepsis,[14-16] we added to our ICU protocol for the management of patients with septic shock the use of IgM preparation as a possible adjunctive therapy.[17]

Empiric antibiotic therapy was considered appropriate if the microorganisms identified were susceptible in vitro to antibiotic molecules used, and the doses were in agreement with the recommendations by the international evidence-based guidelines on antibiotic therapy for each specific clinical setting. The term adequate fluid resuscitation indicated a central venous pressure >6 mm Hg or >8 mm Hg if the patient was mechanically ventilated or a global end-diastolic volume by transpulmonary thermodilution (PiCCO system, Pulsion, Germany) >700 mL/m^2. Crystalloid and 20% albumin (when serum albumin level <2.0 g/dL) solutions were used for fluid resuscitation. All of the patients received noradrenaline as vasopressor therapy and dobutamine or levosimendan as inotropic drug when indicated. Due to the uncertain evidence on the beneficial effects, the decision to use hydrocortisone, rhAPC, and IgM preparation was at the discretion of the attending physician. When used, hydrocortisone was administered at the dose of 300 mg/day until vasopressors withdrawal, rhAPC at the dose 24 μg/kg/h for 96 hours and IgM preparation at the dose of 250 mg/kg per day for 3 consecutive days. In our management protocol for patients with septic shock, continuous renal replacement therapy (CRRT) was applied after the occurrence of clear signs of kidney failure or pulmonary edema or azotemia higher than 200 mg/dL, intractable metabolic acidosis, and severe electrolyte derangements.

Data Collection

Two of the authors (S.G. and M.E.), not involved in the management of the patients, collected data by an accurate analysis of clinical charts. Any uncertain data were reviewed with the attending physician. The type of admission, relevant preexisting disease, the site of infection, the type of microorganism isolated from the cultures, and if it was an hospital-acquired

infection, Simplified Acute Physiology Score II (SAPS II)[18] and Sequential Organ Failure Assessment (SOFA)[19] scores, and need for mechanical ventilation were recorded. The following were analyzed in patient provided treatment: blood cultures, infection source control, $SvcO_2$ optimization, adequate fluid resuscitation before vasopressors administration, glycemia control, low-dose hydrocortisone administration in association with vasopressor support, rhAPC, PIP <30 cmH_2O in patients with acute lung injury, IgM preparation, CRRT, duration of vasopressors therapy, and duration of mechanical ventilation days. All microbiological data collected and antibiotic drugs used in the 4 days before shock appearance were recorded.

Data Analysis

Basal characteristics and interventions performed were subdivided and compared in survivors (S) and nonsurvivors (NS) at 30 days after septic shock onset. Differences between the groups were assessed using the Mann-Whitney *U* or Fisher exact test, as applicable. To estimate the independent effect on 30-day mortality of patients' characteristics or single interventions, a multivariate logistic model was applied. In the multivariate analysis were included all variables resulted to be significant or with an alpha level $\leq .10$ at univariate analysis. To rule out possible confounding factors, patients who received and who did not receive IgM were matched 1:1 using a propensity score including as covariates age, type of admission, preexisting diseases, SOFA and SAPS II score, origin of infection, infecting microorganism, and 6- or 24-hour bundle compliance. We compared the 30-day mortality rate between patients who received IgM and patients who did not receive IgM using a logistic regression model stratified to matched pairs. A $P < .05$ was considered as significant. The goodness of fit was assessed by the Hosmer-Lemeshow test. Data analyses were performed by means of SPSS version 20.0 (SPSS, Chicago, Illinois).

Results

In the study period, 381 adult patients with septic shock have been admitted to ICU: 123 (32%) were excluded because of end-stage liver disease, do-not-resuscitate orders, and end-of-life decisions during the ICU stay; in 115 of the remaining (115/258, 45%), the shock was due to infection by no-MDR bacteria, in 94 (36%) by MDR bacteria, and in 49 (19%), we were not able to document the responsible microorganism.

In the 94 patients with MDR infections, the comparison between S and NS showed no differences in age, gender, type of admission, site of infection, hospital-acquired infection, SOFA, and SAPSII scores (Table 1). The S group had less history of cancer ($P < .05$) and higher rate of gram-negative infections, especially *Escherichia coli* and *Klebsiella pneumoniae* but with a lower rate of carbapenem resistance ($P = .051$). The S group had also a shorter duration of mechanical ventilation ($P < .05$; Table 1).

The compliance to sepsis interventions did not show statistical significance between S and NS groups of patients, except for the rhAPC and IgM administrations which were provided more frequently in S ($P < .05$; Table 2).

At the multivariate adjusted analysis, preexisting cancer and MDR infections sustained by *Acinetobacter baumannii* were independently correlated with an increased risk of 30-day mortality after the onset of septic shock, whereas IgM treatment was protective (Table 3).

The comparison between patients treated and those untreated with IgM showed that the 2 groups were similar for incidence of history of cancer and infection sustained by *A baumannii* (Table 4). However, patients treated with IgM preparations had a higher percentage, but not significant, of infections by gram-negative bacteria ($P = .06$), an higher compliance to the treatment of PIP less than 30 cmH_2O in case of acute lung injury ($P < .05$) and twice as many treatments with CRRT than patients without IgM ($P = .01$; Table 4). The 30-day mortality rate was reduced by 23.1% in patients with septic shock by MDR who received IgM compared to the patients who did not receive IgM (Table 4). The propensity score-based analysis, after 1:1 matching with all the variables well balanced, included 74 patients (IgM, n = 37; no IgM, n = 37). The logistic regression analysis indicated that 30-day mortality rate in the treated patients (29.7%) were lower (odds ratio: 0.31, 95% confidence interval: 0.12-0.78, $P = .013$) than in nontreated patients (51.4%).

Discussion

This retrospective study showed that history of cancer and infection sustained by *A baumannii* increase the risk of mortality in patients with septic shock caused by MDR bacteria and that standard sepsis treatments do not seem to provide any protective effect. Adjunctive therapy with IgM preparation, administered within 24 hours after shock appearance, was associated with a decrease in mortality rate.

Several studies have already highlighted the close correlation between increased mortality from septic shock and cancer regardless of the type of microorganism and organ involved.[20] This correlation seems to be the result of concomitant immunosuppressive therapy or a state of higher level of immunodepletion due to the tumor itself. Between different types of cancer, hematological malignancies seem to have a worse prognosis as very recently demonstrated by Torres et al.[21]

We observed a higher occurrence of infection with methicillin-resistant *Staphylococcus aureus*, *A baumannii*, and microorganisms resistant to carbapenems in NS than in S. Namendys-Silva et al have also recently demonstrated a high mortality in critically ill patients infected by *A baumannii*.[22] Acinetobacter baumannii and gram-negative bacteria resistant to carbapenems are almost never eradicated with a single class of antibiotics, but a polypharmacological strategy with the combination of different classes of antibiotics is required. This strategy is infrequently applied during the initial empirical antibiotic treatment, and this could justify the high mortality

Table 1. Main Characteristics of the Studied Patients Subdivided into Survivors and Nonsurvivors 30 Days After Shock Appearance.

	All Patients (N = 94)	Survivors (n = 54)	Nonsurvivors (n = 40)	*P* Value
Age, years, mean (SD)	70.9 (12.2)	69.6 (13.4)	72.6 (10.2)	.44
Female, n (%)	36 (38.3)	18 (33.3)	18 (45.0)	.25
Surgical admission, n (%)	42 (44.7)	26 (48.1)	16 (40.0)	.43
Preexisting condition, n (%)				.006
None	29 (30.9)	19 (36.5)	10 (23.8)	
Heart failure	17 (18.1)	9 (17.3)	8 (19.0)	
Chronic obstructive pulmonary disease	8 (8.5)	3 (5.8)	5 (11.9)	
End-stage renal disease	7 (7.4)	4 (7.7)	3 (7.1)	
Cancer	23 (24.5)	7 (13.5)	16 (38.1)	
Diabetes	10 (10.6)	10 (19.2)	0 (0.0)	
Site of infection, n (%)				.31
Pneumonia	51 (54.3)	25 (46.3)	26 (65.0)	
Intra-abdominal	39 (41.5)	23 (36.2)	16 (40.0)	
Blood	24 (25.5)	11 (20.4)	13 (32.5)	
Other	27 (28.7)	19 (35.2)	8 (20.0)	
Hospital-acquired infection, n (%)	60 (63.8)	31 (57.4)	29 (72.5)	.132
Gram negative, n (%)	75 (79.8)	47 (87.0)	28 (70.0)	.042
Gram-negative resistant to carbapenems, n (%)[a]	27 (28.7)	13 (24.1)	14 (35.0)	.051
Microorganisms, n (%)				.028
Pseudomonas aeruginosa	24 (25.5)	14 (25.9)	10 (25,0)	
Escherichia coli	21 (22.3)	15 (27.8)	6 (15.0)	
Acinetobacter baumannii	16 (17.0)	6 (11.1)	10 (25.0)	
MRSA	12 (12.8)	3 (5.6)	9 (22.5)	
Klebsiella pneumonia	10 (10.6)	8 (14.8)	2 (5.0)	
Others	11 (11.7)	8 (14.8)	3 (7.5)	
SOFA, mean (SD)	9.7 (3.5)	9.4 (3.4)	10.1 (3.6)	.243
SAPS II, mean (SD)	58.9 (17.4)	56.1 (15.3)	62.7 (19.6)	.104
Mechanical ventilation, n (%)	85 (90.4)	46 (85.2)	39 (97.5)	.045

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; SAPS II, Simplified Acute Physiology Score II score; SD, standard deviation; SOFA, Simplified Organ Failure assessment score.
[a]Only for patients with infections by gram-negative bacteria.

Table 2. Treatments Provided to the Studied Patients Subdivided in Survivors and Nonsurvivors 30 Days After Shock Appearance.

	All Patients (N = 94)	Survivors (n = 54)	Nonsurvivors (n = 40)	*P* Value
Blood cultures, n (%)	81 (86.2)	46 (85.2)	35 (87.5)	.75
Infection source control, n (%)	90 (95.7)	52 (96.3)	38 (95.0)	.76
Adequate empiric antibiotic therapy, n (%)	66 (70.2)	38 (70.4)	28 (70.0)	.97
Combination therapy for gram negative[a]	14 (81.3)	6 (12.8)	8 (28.6)	.089
Combination therapy for resistant to carbapenem[b]	9 (33.3)	3 (23.1)	6 (42.9)	.29
$ScvO_2$ optimization, n (%)	49 (52.1)	28 (51.9)	21 (52.5)	.95
Adequate fluid resuscitation, n (%)	71 (75.5)	40 (74.1)	31 (77.5)	.70
Glycemia control, n (%)	65 (69.1)	40 (74.1)	25 (62.5)	.23
Steroids, n (%)	70 (74.5)	38 (70.4)	32 (80.0)	.29
rhAPC[c], n (%)	58 (77.3)	37 (86.0)	21 (65.6)	.037
PIP<30 cmH_2O, n (%)	86 (91.5)	51 (94.4)	35 (87.5)	.23
IgM preparation, n (%)	48 (51.1)	33 (61.1)	15 (37.5)	.024
CRRT, n (%)	32 (34.0)	17 (31.5)	15 (37.5)	.543
Duration of vasopressors therapy, days, mean (SD)	7.2 (7.4)	6.5 (5.9)	8.0 (9.1)	.124
Duration of mechanical ventilation days, mean (SD)	10.1 (15.5)	10.1 (13.2)	10.0 (18.3)	.63

Abbreviations: rhAPC, recombinant human activated protein C; PIP, plateau inspiratory pressure; *P* value, comparison between survivors and nonsurivivors; SD, standard deviation; CRRT, continuous renal replacement therapy; IgM, immunoglobulin M; $ScvO_2$, superior cava venous oxygen saturation.
[a]Only in patients with infections by Gram-negative bacteria, n = 75.
[b]Only in patients with infections by Gram-negative bacteria resistant to carbapenems, n = 27.
[c]Patients December 2011, (n = 75).

Table 3. Multivariate Analysis of Risk Factors for 30 Days Mortality.[a]

	OR	95% CI	*P*
Preexisting condition cancer	2.97	1.14-7.71	.026
Infection by Acinetobacter baumannii	3.2	1.01-10.21	.050
IgM preparation	0.28	0.14-0.59	.001

Abbreviations: CI, confidence interval; IgM, immunoglobulin M; OR, odds ratio; rhAPC, recombinant human activated protein C; SAPS II, Simplified Acute Physiology Score II score.
[a]Multivariate logistic model including all the variables resulted to be significant or with an α level $\leq .10$ at univariate analysis (ie, preexisiting conditions, Gram stain, resistance to carbapenems, type of bacteria, SAPS II, mechanical ventilation, therapy with rhAPC, and IgM preparation). Hosmer-Lemeshow test $P = .55$.

in patients infected with *A baumannii* and carbapemen-resistant bacteria.[23] However, in our cohort, the appropriateness of initial empirical antibiotic therapy was quite similar in the S and NS. Similarly, a recent case–control study showed that in patients with septic shock by MDR bacteria, the use of an appropriate early empiric antibiotic therapy did not reduce the risk of mortality.[24] Preexisting diseases, as for instance cancer, long in-hospital stay, use of invasive devices, multiple surgical procedures, and extensive antibiotic therapies may lead to a severe immune dysfunction that prone patients to colonization and infection by opportunistic, frequently MDR, microorganisms. Therefore, it seems reasonable to consider MDR infections a proxy of patient high complexity whose mortality risk depends on many other factors different by appropriate empirical antibiotic therapy.[25]

Beyond risk factors and initial antibiotic therapy, our study was also aimed to evaluate the possible impact of other sepsis treatments on this specific cohort of patients. Indeed, the application of the sepsis therapies recommended by the evidence-based medicine does not seem to modify the mortality risk. Only rhAPC, no longer available, and IgM preparation were more frequently administered in S. In agreement with data recently published[24] on the effects of therapy with IgM preparation in ICU patients with MDR infections, the use of IgM preparation was independently associated with a survival benefit in our cohort of patients. Immunoglobulins, particularly the IgM class, exert pleiotropic effects on the host inflammatory immune response to infections including antiapoptotic effects on the immune cells and direct anti-inflammatory properties mediated via Fc-γ receptors that may be particularly beneficial in patients with immune dysfunction acting as sort of immune modulatory therapy.[26] As described earlier, patients with MDR infections should be considered at high risk of immune dysfunction, and thus, the use of adjunctive immune modulatory strategies may result beneficial by supporting the activity of antibiotic therapy against microorganisms until the restoring of an appropriate host immune response.

The need for CRRT was double in patients treated compared to those nontreated with IgM. In our management protocol for patients with septic shock, CRRT is recommended only in a late phase, after the occurrence of clear signs of kidney failure or pulmonary edema. Therefore, S have a higher probability to be treated by CRRT than NS. By considering only 30-day survivors, renal dysfunction requiring CRRT was only slightly higher ($P > .05$) in patients treated 12 (36.4%) of 33 than in nontreated 5 (23.8%) of 21 with IgM.

Table 4. Main Characteristics of Patients Treated and Nontreated by IgM.

	No IgM (n = 46)	IgM (n = 48)	*P* Value
Age, years, mean (SD)			
Female, n (%)	19 (41.3)	17 (35.4)	.55
Surgical admission, n (%)	17 (37.0)	25 (52.1)	.14
Preexisting condition, n (%)			.39
None	13 (28.3)	16 (33.3)	
Heart failure	9 (19.6)	8 (16.7)	
Chronic obstructive pulmonary disease	4 (8.7)	4 (8.3)	
End-stage renal disease	4 (8.7)	3 (6.2)	
Cancer	14 (30.4)	9 (18.8)	
Diabetes	2 (4.3)	8 (16.7)	
Site of infection, n (%)			
Pneumonia	27 (58.7)	24 (50.0)	.40
Intra-abdominal	17 (37.0)	22 (45.8)	.38
Blood	9 (19.6)	15 (31.2)	.19
Other	14 (30.5)	13 (27.1)	.58
Hospital-acquired infection, n (%)	27 (58.7)	33 (68.8)	.31
Gram negative, n (%)	33 (71.7)	42 (87.5)	.06
Gram negative resistant to carbapenems, n (%)[a]	13 (28.3)	14 (29.2)	.92
Microorganisms, n (%)			.09
Pseudomonas Aeruginosa	12 (26.1)	12 (25.0)	
Escherichia Coli	6 (13.0)	15 (31.2)	
Acinetobacter baumannii	7 (15.2)	9 (18.8)	
MRSA	10 (21.7)	2 (4.2)	
Klebsiella Pneumonia	5 (10.9)	5 (10.4)	
Others	6 (13.0)	5 (10.4)	
SOFA, mean (SD)	9.3 (3.7)	10.2 (3.2)	.19
SAPS II, mean (SD)	56.8 (18.1)	60.9 (16.8)	.26
Mechanical ventilation, n (%)	42 (91.3)	43 (89.6)	.78
Blood cultures, n (%)	39 (84.8)	42 (87.5)	.70
Infection source control, n (%)	44 (95.7)	48 (95.8)	.96
Adequate empiric antibiotic therapy, n (%)	31 (67.3)	35 (72.9)	.30
$ScvO_2$ optimization, n (%)	25 (54.3)	24 (50.0)	.67
Adequate fluid resuscitation, n (%)	32 (69.6)	39 (81.2)	.19
Glycaemia control, n (%)	33 (71.7)	32 (66.7)	.59
Steroids, n (%)	34 (73.9)	36 (75.0)	.90
rhAPC[a], n (%)	24 (70.6)	34 (80.9)	.20
PIP<30 cmH_2O, n (%)	39 (84.8)	47 (97.9)	.02
CRRT, N (%)	10 (21.7)	22 (45.8)	.01
Duration of vasopressors therapy, days, mean (SD)	7.4 (8.2)	6.9 (6.7)	.72
Duration of mechanical ventilation, days, mean (SD)	11.4 (19.5)	8.8 (10.4)	.42
30 days mortality, n (%)	25 (54.3)	15 (31.2)	.02

Abbreviations: CRRT, continuous renal replacement therapy; IgM, immunoglobulin M; MRSA, methicillin-resistant *Staphylococcus aureus*; PIP, plateau inspiratory pressure; rhAPC, recombinant human activated protein C; SAPS II, Simplified Acute Physiology Score II score; $ScvO_2$, superior cava venous oxygen saturation; SD, standard deviation; SOFA, Simplified Organ Failure assessment score.
[a]Patients December 2011, n = 75.

Nevertheless, a direct harmful effect of IgM therapy on renal function could not be excluded. Previous clinical trials did not report any interference of IgM therapy on kidney, but the possible detrimental effects of the association between IgM therapy and nephrotoxic antibiotics frequently used in patients with MDR infections (eg, colistin, aminoglycosides, and vancomycin) have never been evaluated.

The limitations of our study are mainly due to the design of the study, single center, retrospective, and with a limited number of patients. Specifically, for the beneficial effects of IgM, it must be underlined that, as described in our previous article,[27] a selection bias based on the attending physician for each case cannot be excluded. To evaluate the occurrence of a possible selection bias, we performed a direct comparison of patients who received with those who have not received IgM (Table 4). The groups resulted to be quite similar for the main variables related to a possible selection bias, as for instance age, preexisting diseases, site of infection, and severity scores as well as for treatments provided. Nevertheless, the results should be read with caution and need to be confirmed by more appropriate studies.

Conclusions

Patients with severe sepsis or septic shock by MDR microorganisms are a specific sepsis population with a high mortality risk, despite appropriate treatments, including early antibiotic therapy. As demonstrated also in other experiences,[24] the use of intravenous immunoglobulins in this population seems to be beneficial and may be considered as an adjunctive therapy aimed to support the immune response. However, further appropriate studies are needed to better clarify the immune effects of IgM preparation in this context and the true survival benefit.

Author Contributions

Busani Stefano and Giannella Maddalena designed and carried out the study and drafted the manuscript. Girardis Massimo and Mantovani Elena were involved in acquisition of data. Venturelli Claudia contributed to the analysis of bacterial strains. All other authors contributed to drafting and revising the manuscript. All authors read and approved the final version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Massimo Girardis has consulted for Biotest-Germany, all the other authors declare that they have no competing interests.

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