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Prevalence, risk factors and outcomes of patients coming from the community with sepsis due to multidrug resistant bacteria

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Abstract

Background: Although previous studies showed an increasing prevalence of infections due to multi-drug resistant (MDR) bacteria in the community, specific data on sepsis are lacking. We aimed to assess prevalence, risk factors and outcomes of patients with sepsis due to MDR bacteria.

Methods: An observational, retrospective study was conducted on consecutive adult patients coming from the community and admitted to the Policlinico Hospital, Milan, Italy, with a diagnosis of sepsis between January 2011 and December 2015. Primary study outcome was in-hospital mortality.

Results: Among 518 patients, at least one MDR bacteria was isolated in 88 (17%). ESBL+ *Enterobacteriaceae* were the most prevalent MDR bacteria (9.7%) followed by MRSA (3.9%). Independent risk factors for sepsis due to MDR bacteria were septic shock (OR: 2.2; $p = 0.002$) and hospitalization in the previous 90 days (OR: 2.3; $p = 0.003$). Independent risk factors for sepsis due to ESBL+ bacteria were hospitalization in the previous 90 days (OR: 2.1; $p = 0.02$) and stroke (OR: 2.1; $p = 0.04$). A significantly higher mortality was detected among patients with vs. without MDR bacteria (40.2% vs. 23.1% respectively, $p = 0.001$). Independent risk factors for mortality among patients with sepsis were coagulation dysfunction (OR: 3.2; $p = 0.03$), septic shock (OR: 3.2; $p = 0.003$), and isolation of a MDR bacteria (OR: 4.6; $p < 0.001$).

Conclusion: In light of the prevalence and impact of MDR bacteria causing sepsis in patients coming from the community, physicians should consider ESBL coverage when starting an empiric antibiotic therapy in patients with specific risk factors, especially in the presence of septic shock.

Keywords: Septic shock, Pneumonia, MRSA, Pseudomonas, ESBL producer *Enterobacteriaceae*

Summary

Specific risk factors for MDR bacteria and EBSL+ Enterobacteriaceae are found in a population of 518 patients with sepsis coming from the community. Isolation of a MDR bacteria is associated with higher mortality rates and is an independent risk factor for mortality.

Introduction

Sepsis is a major health-care problem which affects millions of people each year worldwide with an increasing incidence over the last decades [1]. More than one third of patients with sepsis die during their hospital stay and the economic impact of sepsis is relevant, with a mean and median hospital and intensive care unit (ICU) cost of $32,421 and $27,461 per single patient, respectively [2, 3]. Recently, a new definition of sepsis and an update of the Surviving Sepsis Campaign guidelines have been published to improve sepsis diagnosis, to standardize communication between clinicians and researchers, and to spread an evidence based approach for the management of septic patients [1, 4].

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These guidelines confirm the appropriateness of initial antibiotic therapy as a crucial variable in septic patients [1, 5–9]. Among the major contributors of the increasing rates of inappropriate empiric antimicrobial treatment, the spread of antimicrobial resistance seems to be one of the most relevant [5, 6]. An update on sepsis epidemiology due to multi-drug resistant organisms (MDRO) and on its associated risk factors would be very helpful for clinicians to early detect patients requiring a broader antibiotic coverage.

Several experiences reported on risk factors for MDRO infections, enrolling heterogeneous patient populations. Some of them considered infections due to specific MDRO, mainly methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* [10–15], while others included patients with infection limited to one organ, such as pneumonia and urinary tract infections [16–20]. Finally, few other studies have been published on the impact of bacterial resistances in bloodstream infections, regardless the presence of sepsis [21–23]. No previous studies specifically evaluated prevalence, characteristics, and risk factors for MDRO in a specific sample of patients with sepsis.

The aim of this study was to assess prevalence, characteristics, risk factors, and outcomes of patients suffering of sepsis due to MDRO.

Materials and methods

Study design and study patients

This was an observational, retrospective study enrolling consecutive adult patients coming from the community and admitted to the Emergency Department (ED) of the IRCCS Fondazione Ca′ Granda, Ospedale Maggiore Policlinico of Milan, Italy, with sepsis between January 2011 and December 2015. Patients ≥18 years of age fitting sepsis criteria were included [4]. Patients admitted to the ED of the Policlinico Hospital coming from other hospitals were excluded. The study was approved by the ethical committee (262_2017bis) of the IRCCS Fondazione Ca′ Granda, Ospedale Maggiore Policlinico of Milan, Italy, whereas informed consent was waived due to the retrospective and observational nature of the study according to the Italian law on observational studies.

Data collection

Demographics, comorbidities, risk factors for MDRO, Charlson Comorbidity Index, clinical, laboratory and microbiological findings on admission, site of infection, disease severity (organ dysfunction, septic shock, SOFA score) empiric antibiotic therapy, vasopressor use and invasive mechanical ventilation data were recorded [24, 25].

Risk factors for MDRO

The following risk factors for MDRO were recorded: nursing home or extended care facility residency, hospitalization for ≥2 days in the preceding 90 days, antimicrobial therapy in the preceding 90 days, home infusion therapy (including antibiotics), home wound care, indwelling bladder catheter, indwelling intravascular devices, chronic renal failure, chronic dialysis at least during the prior 30 days, day hospital attendance for infusion therapy or blood transfusions, mild, moderate and severe immunodepression [26].

Study outcomes and definitions

The primary study outcome was in-hospital mortality. Secondary study outcome was length of hospital stay (LOS).

Sepsis and septic shock were defined according to the Third International Consensus Definitions for Sepsis and Septic Shock [4]. Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction was identified as an acute change in total SOFA score ≥ 2 points following the infection. Septic shock was defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are severe enough to increase significantly mortality. This condition was identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥65 mmHg and having a serum lactate level > 2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

Severe immunodepression was defined by the presence of at least one of the following medical conditions: active hematologic malignancy, transplantation, immunosuppressive therapy, chemotherapy and radiotherapy in the 30 days before the ED admission. Mild-to-moderate immunodepression was defined by the presence of at least one of the following medical conditions: chronic systemic steroid therapy (prednisone ≥25 mg daily), active solid malignancy, splenectomy, and autoimmune disease.

In-hospital mortality was defined as all-cause mortality occurring during hospitalization. LOS was calculated as the number of days from the date of hospital admission to the date of discharge.

Microbiological data and empiric antibiotic therapy

Microbiological results performed within 48 h since hospital admission were recorded, including blood, sputum, tracheobronchial aspirate, urine, wound, and mucosal swab cultures, as well as *Legionella pneumophila* and *Streptococcus pneumoniae* urinary antigens. Species identification and antimicrobial susceptibility testing were performed using an automated system (Vitek 2®; BioMérieux); susceptibility break-points were based on Anti-microbial Susceptibility Testing (EUCAST) guidelines. [EUCAST breakpoint table version 1.2 to table version 5.0].

MRSA, *Pseudomonas aeruginosa* resistant to three classes of antibiotics among antipseudomonal penicillins, antipseudomonal cephalosporins, carbapenems, quinolones, and aminoglycosides, vancomycin-resistant *Enterococcus*, *Acinetobacter baumanii*, ESBL producing *Enterobacteriaceae,* carbapenemase-producing *Klebsiella pneumoniae*, and other pathogens with acquired non-susceptibility to at least one agent in three or more antimicrobials categories were considered as MDR bacteria [27].

Empiric antibiotic therapy administered in the ED after diagnosis of sepsis and septic shock was recorded, together with its appropriateness according to the antibiotic susceptibility of the isolated pathogen and the agreement with local guideline (see Additional file 1: Table S1).

Statistical analysis

An *ad hoc* electronic form was used to collect all demographic, epidemiological, clinical, and microbiological variables. Qualitative and quantitative data were summarized with absolute and relative (percentage) frequencies and medians (interquartile ranges, IQR) according to their non-parametric distribution, respectively. Statistical differences of qualitative and quantitative variables were assessed with chi-squared or Fisher exact, when appropriate, and Mann-Whitney tests, respectively. Logistic regression analyses were carried out to assess the relationship between MDRO or ESBL+ infection and the collected covariates. A two-tailed p less than 0.05 was considered statistically significant. The statistical software STATA 14 (StataCorp LP, Lakeway Drive, College Station, USA) was used to perform all statistical computations.

Results

Study population

A total of 663 consecutive patients with sepsis were enrolled during the study period (56.6% males, median [IQR] age: 80 [71–87] years). The final study population consisted of 518 patients (78.1% of the total enrolled) who underwent at least one bacteriological test within the first 24 h after hospitalization.

Demographics, comorbidities, risk factors for MDRO, clinical, and laboratory findings on admission, site of infection, disease severity, therapy prescribed within 24 h after admission are summarized in Table 1: lung (59.9%) and urinary tract (36.4%) were the most common sites of infection. A total of 146 (28.2%) patients had septic shock.

Three hundred ninety-seven patients (76.6%) had at least one risk factor for MDRO: hospitalization in the previous 3 months (28.4%), day hospital attendance (19.3%), severe immunodepression (18.9%), and antibiotic therapy in the last 90 days (15.5%) were the most frequent risk factors for MDRO.

Prevalence and characteristics of patients with sepsis due to MDRO and ESBL+ bacteria

Cultures were performed on blood (n = 446, 86.1%) and sputum (n = 25, 4.8%) samples, tracheobronchial aspirates (n = 27, 5.2%), urine (n = 189, 36%] and other (n = 47, 9.1%) samples. Microbiological findings are summarized in Table 2. At least one pathogen was isolated in 305 patients (58.9%) and, among them, 198 (44.5%) had bacteremia.

At least one MDRO was isolated in 88 patients (17% among the entire population and 29.1% among culture positive patients), with ESBL+ *Enterobacteriaceae* being the most prevalent isolates (50 patients, 9.7%), including 43 (8.3%) patients with ESBL+ *E. coli* and 7 (1.4%) with ESBL+ *K. pneumoniae*. The second most prevalent MDR bacteria were MRSA (20 patients, 3.9%).

Demographics, comorbidities, risk factors, clinical and laboratory findings on admission, site of infection, disease severity, appropriateness of empiric antibiotic therapy, vasopressor use and invasive mechanical ventilation of the study sample are reported in the online supplement according to the presence of MDRO (Additional file 1: Table S2) and ESBL+ bacteria (Additional file 1: Table S3).

Independent risk factors associated to MDRO and ESBL+ infection in patients with sepsis

After adjusting for several confounders, independent risk factors associated with the occurrence of sepsis due to MDRO and ESBL+ bacteria are reported in Tables 3 and 4. Significant independent risk factors for sepsis due to MDRO were septic shock (OR: 2.2; 95% CI: 1.3–3.7, p = 0.002) and hospitalization in the past 90 days (OR: 2.3; 95% CI: 1.3–4.1, p = 0.003). Significant independent risk factors for sepsis due to ESBL+ bacteria were hospitalization in the past 90 days (OR: 2.1; 95% CI: 1.2–3.9, p = 0.02) and stroke (OR: 2.1; 95% CI: 1.0–4.1, p = 0.04).

Study outcomes

In-hospital mortality was 25.7% (n = 133). Among patients with septic shock 69 (47.3%) died. Demographics, comorbidities, risk factors, clinical laboratory, and microbiological findings on admission, site of infection, disease severity, appropriateness of empiric antibiotic therapy, vasopressors use and invasive mechanical ventilation of patients who died versus those who survived are summarized in Table 5.

The median (IQR) LOS was 13 (8–21) days. Among patients with MDRO the median (IQR) LOS was 15 (9–22) days and in-hospital mortality was 40.2% (35 patients), while among those without MDRO infection LOS was 13 (8–21) days (p = 0.36) and mortality was 23.1% (n = 98) (p = 0.001).

Among patients with ESBL+ infection the median (IQR) LOS was 15 (9–21) days and in-hospital mortality was

Table 1 Study population. (518)

Demographics characteristics	
Female, n (%)	220 (42.5)
Median (IQR) age, years	80 (71–87)
Comorbidities, *n (%)*	
Median (IQR) Charlson comorbidity index	6 (5–8)
Hypertension	289 (55.8)
Diabetes mellitus	124 (23.9)
Ischemic heart disease	109 (21.0)
COPD	114 (22.0)
Stroke	83 (16.0)
Dementia	79 (15.3)
Chronic heart failure	50 (9.7)
Chronic liver disease	38 (7.3)
Peripheral vascular disease	28 (5.4)
Hemiplegia	21 (4.1)
Cirrhosis	25 (4.8)
Risk factors for MDR pathogens, *n (%)*	
Patients with at least one risk factor for MDR pathogens	397 (76.6)
Hospitalization in the past 90 days	147 (28.4)
Median (IQR) LOS	13 (8–21)
Day hospital attendance in the past 90 days	100 (19.3)
Antibiotic therapy in the past 90 days	80 (15.5)
Severe immunosuppression	98 (18.9)
Mild /moderate immunosuppression	83 (16.0)
Solid cancer	73 (14.1)
Chronic steroid therapy	68 (13.1)
Haematological malignancy	45 (8.7)
Chemotherapy	28 (5.4)
AIDS	3 (0.6)
Chronic renal failure	96 (18.5)
Dialysis	16 (3.1)
Home wound care/infusion therapy	82 (15.8)
Indwelling bladder catheter	70 (13.5)
Nursing home or LTCF residency	45 (8.7)
Indwelling intravascular catheters	31 (6.0)
Clinical findings	
Median (IQR) body temperature, °C	38.0 (37.1–38.7)
Median (IQR) systolic blood pressure, mmHg	110 (90–135)
Median (IQR) diastolic blood pressure, mmHg	60 (50–70)
Median (IQR) mean blood pressure, mmHg	77 (63–92)
Median (IQR) heart rate, bpm	102 (88–120)
Median (IQR) oxygen saturation, %	95 (91–97)
Median (IQR) respiratory rate, bpm	22 (18–30)
Median (IQR) shock index	0.9 (0.7–1.2)

Table 1 Study population. (518) *(Continued)*

Laboratory findings	
Median (IQR) arterial pH	7.5 (7.4–7.5)
Median (IQR) $PaCO_2$, mmHg	30 (25–35)
Median (IQR) PaO_2, mmHg	65 (55–77)
Median (IQR) HCO_3^- mEq/L	21.8 (18.0–24.6)
Median (IQR) PaO_2/FiO_2 ratio	276 (229–333)
Median (IQR) lactate, mEq/L	2.9 (2.1–4.3)
Median (IQR) white blood cells, cell/L^{-1}	12.1 (7.3–17.9)
Median (IQR) platelets, cell/L^{-1}	190.0 (131.0–258.5)
Mean (SD) haemoglobin, g/dL	12.3 (2.3)
Median (IQR) glucose, mg/dL	141 (110–192)
Median (IQR) urea, mg/dL	65 (46–97)
Median (IQR) creatinine, mg/dL	1.6 (1.2–2.4)
Median (IQR) C-reactive protein, g/dL	11.4 (4.5–22.7)
Median (IQR) aspartate aminotransferase U/l	28 (20–50)
Median (IQR) alanine aminotransferase U/l	21 (13–39)
Median (IQR) lactate dehydrogenase	327 (222–457)
Median (IQR) total bilirubin, mg/dL	0.8 (0.5–1.6)
Median (IQR) INR	1.3 (1.2–1.5)
Site of primary infection, *n (%)*	
Lung	273 (59.9)
Urinary tract	166 (36.4)
Abdomen	59 (12.9)
Skin and soft tissue	31 (6.8)
Central nervous system	9 (2.0)
Bone and joints	4 (0.9)
More than one site	82 (15.8)
Unknown origin	62 (12.0)
MOF, *n (%)*	
Metabolic dysfunction	359 (75.6)
Renal failure	223 (43.6)
Hemodynamic failure	200 (39.0)
Cognitive impairment	158 (32.9)
Shock	146 (28.2)
Respiratory failure	94 (18.4)
Liver failure	67 (13.9)
Coagulation dysfunction	56 (12.1)
Haematological dysfunction	51 (9.9)
Antibiotics, *n (%)*	
Azithromycin	40 (5.5)
Piperacillin/Tazobactam	188 (25.9)
Ceftriaxone	164 (22.6)
Levofloxacin	111 (15.3)
Imipenem	66 (9.1)
Vancomycin	51 (7.0)

Table 1 Study population. (518) *(Continued)*

Ciprofloxacin	28 (3.9)
Amoxicillin/Clavulanate	22 (3.0)
Metronidazole	16 (2.2)
Meropenem	5 (0.7)
Ampicillin	7 (1.0)
Amikacin	7 (1.0)
Ceftazidime	5 (0.7)
Others	16 (2.2)
Appropriate empiric antibiotic therapy according to local guidelines	273 (58.3)
Appropriate empiric antibiotic therapy according to antibiotic susceptibility of the isolated pathogen	155 (66.8)
Use of vasopressors	84 (16.2)
Mechanical ventilation	8 (2.5)

n number, *IQR* interquartile range, *COPD* chronic obstructive pulmonary disease, *AIDS* Acquired immune deficiency syndrome; *LTCF* long term care facility, *INR* International normalized ratio; MOF: multi organ failure (other than primary site of infection)

32% ($n = 16$), whereas among those without ESBL+ infection median (IQR) LOS was 13 (8–22) days ($p = 0.73$) and in-hospital mortality was 25.3% ($n = 117$) ($p = 0.27$).

Risk factors for mortality in patients with sepsis

After adjusting for several confounders, including antibiotic therapy, vasopressor exposure and ventilatory treatment, independent risk factors associated with in-hospital mortality in patients with sepsis were: coagulation dysfunction (OR: 3.2; 95% CI: 1.1–8.8, $p = 0.03$), septic shock (OR: 3.2; 95% CI: 1.5–7.0, $p = 0.003$), and isolation of a MDR pathogen (OR: 4.6; 95% CI: 2.0–10.6, $p < 0.001$) (Table 6).

Discussion

The present study shows that more than three quarters of patients admitted to the hospital from the community for sepsis have at least one risk factor for MDRO, while in 17% of patients a MDRO is isolated. Among those, ESBL+ *Enterobacteriaceae* are the most prevalent ones (9.7%). Hospitalization in the previous 90 days and the presence of septic shock are the two independent risk factors associated with MDRO in patients with sepsis, whereas hospitalization in the previous 90 days and stroke are independently associated with infection caused by ESBL producer *Enterobacteraceae*.

Our study is in line with previously published data in terms of frequency of different sites of infection (lung being the first followed by urinary tract), most frequent organs involved in multi-organ failure, percentage of patients with septic shock and mortality rate [28, 29]. The prevalence of MDRO in our study is slightly higher than those previously reported in literature, mainly because of the characteristics of our study sample characterized by elderly patients with several comorbidities and a long history of medicalization [5, 30, 31]. We found a discrepancy between the frequency of risk factors for MDRO and the prevalence of cultures positive for MDRO. We could speculate that not all risk factors for MDRO should be equally weighted and share the same impact on guiding empiric antibiotic therapy in sepsis.

Table 2 Microbiological findings

Microbiological, *n (%)*	
Patients with isolated microorganism	305 (58.9)
Patients with at least one MDR organism	88 (17.0)
Patients with at least one ESBL organism	50 (9.7)
E. coli ESBL +	43 (8.3)
Methicillin-resistant S. aureus	20 (3.9)
Proteus spp MDR +	5 (1)
K. pneumoniae ESBL +	7 (1.4)
K. pneumomiae carbapenemase producer	6 (1.2)
P. aeruginosa MDR+	4 (0.8)
Enterococcus spp MDR+	2 (0.4)
Enterobacter spp MDR +	2 (0.4)
Stenotrophomonas maltophilia MDR+	1 (0.2)
E. coli ESBL -	77 (14.9)
Methicillin-sensible S. aureus	24 (4.6)
S. pneumoniae	24 (4.6)
K. pneumoniae ESBL-	17 (3.3)
P. aeruginosa MDR-	25 (4.8)
Candida spp	12 (2.3)
Enterococcus spp MDR-	10 (1.9)
Proteus spp MDR-)	9 (1.7)
Enterobacter spp MDR-	5 (1)
N. meningitides	3 (0.6)
Bacteroides spp	1 (0.2)
Providencia spp	2 (0.4)
Stenotrophomonas maltophilia MDR-	3 (0.6)
C. difficile	4 (0.8)
Aspergillus spp	2 (0.4)
Acinetobacter baumanii	1 (0.2)
Salmonella group B	2 (0.4)
H. influenzae	1 (0.2)
Acinetobacter iwoffii	1 (0.2)
Propiniobacterium	1 (0.2)
Serratia spp	2 (0.4)
Polymicrobial infection	29 (5.6)

n number, *ESBL* extended spectrum beta lactamase, *MDR* multi-drug resistant, *spp* species

Table 3 Logistic regression analysis to assess the relationship between MDR infection and demographic, epidemiological, clinical, and laboratory variables. (518)

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Female	1.2 (0.8–1.9)	0.39	1.2 (0.7–2.0)	0.42
Age	1.0 (1.0–1.0)	0.62	1.0 (1.0–2.0)	0.93
Septic shock	2.1 (1.3–3.4)	0.002	2.2 (1.3–3.7)	0.002
Antibiotic therapy in the past 90 days	1.7 (1.1–3.3)	0.03	1.0 (0.5–2.0)	1.0
Hospitalization in the past 90 days	3.2 (2.0–5.1)	< 0.0001	2.3 (1.3–4.1)	0.003
Indwelling bladder catheter	2.2 (1.3–4.0)	0.006	1.9 (0.9–3.9)	0.11
Home wound care/infusion therapy	2.1 (1.2–3.6)	0.01	1.4 (0.7–2.8)	0.39
Chronic heart failure	2.1 (1.1–4.0)	0.03	1.7 (0.8–3.6)	0.14
Peripheral vascular disease	0.8 (0.3–2.4)	0.70		
Stroke	2.0 (1.2–3.5)	0.01	1.8 (0.9–3.3)	0.08
Dementia	1.9 (1.1–3.3)	0.03	1.6 (0.8–3.0)	0.17
Haematological malignancy	2.2 (1.1–4.3)	0.03	1.6 (0.7–3.6)	0.28
Chronic steroid therapy	2.1 (1.2–3.9)	0.01	1.6 (0.8–3.2)	0.19

Among healthcare-related risk factors, hospitalization in the previous 90 days is the strongest independent variable associated with MDRO-related sepsis. The increasing prevalence of MDRO within the hospital wards, due to an extensive antibiotic use and transmission between healthcare workers and patients, might explain this finding, as previously suggested in published manuscripts [15, 19, 21, 26, 32]. Also, septic shock is a risk factor for sepsis caused by MDRO, although some could argue that septic shock is a marker of disease severity and should not be considered a risk factor itself. As previously reported, markers of disease severity were included as risk factors for MDRO mainly because of the impact that this finding might have in the clinical management. Our finding on septic shock as independent risk factor for MDRO clearly identifies a subgroup of more fragile patients who might deserve a broad-spectrum empiric antibiotic course based on their disease severity and risk of organ failure. In light of the high prevalence of MDRO we found and the high mortality rate of patients with septic shock, an antibiotic prescription for MDRO should be considered in shocked patients, especially if additional risk factors (e.g., previous hospitalization) are concomitant.

Among all MDRO, ESBL producer *Enterobacteriaceae* seems to be the most prevalent (9.7%), with ESBL producing *E. coli* and *K. pneumoniae* being 35% of all *E. coli* and *K. pneumoniae* isolated. These data are similar to those reported in the scientific literature: frequency of sepsis due to gram negative bacteria (GNB) is increasing worldwide and *E. coli* is the most frequent GNB found in septic patients admitted from the community [33–36]. The rate of ESBL production among *Enterobacteriaceae* varies from country to country but it is increasing through all Europe, with Italy having one of the highest prevalence [31]. We specifically identified that hospitalization in the previous 90 days is a specific risk factor for ESBL *Enterobacteriaceae*, showing the

Table 4 Logistic regression analysis to assess the relationship between ESBL infection and demographic, epidemiological, clinical, and laboratory variables. (518)

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Female	1.0 (0.5–1.8)	0.94	1.0 (0.5–1.8)	0.87
Age	1.0 (1.0–1.1)	0.10	1.0 (1.0–1.0)	0.50
Hospitalization in the past 90 days	2.4 (1.3–4.3)	0.004	2.1 (1.2–3.9)	0.02
Indwelling bladder catheter	2.5 (1.3–5.1)	0.008	2.0 (0.9–4.1)	0.08
Chronic heart failure	2.3 (1.0–5.0)	0.04	1.8 (0.8–4.1)	0.18
Stroke	2.5 (1.3–4.9)	0.006	2.1 (1.0–4.1)	0.04
Dementia	2.4 (1.2–4.7)	0.01	2.0 (1.0–4.0)	0.06

Table 5 Study population according to in-hospital mortality. (518)

Variable	Survivors	Death	*p*
Hospital mortality, n (%)	378 (74.0)	133 (25.7)	–
Demographics characteristics			
Female, n (%)	158 (41.8)	59 (44.4)	0.61
Median (IQR) age	78 (69–85)	81 (75–87)	0.01
Comorbidities, *n (%)*			
COPD	85 (22.5)	28 (21.1)	0.73
Diabetes mellitus	99 (26.2)	23 (17.3)	0.04
Hypertension	211 (55.8)	75 (56.4)	0.91
Ischemic heart disease	73 (19.3)	36 (27.1)	0.06
Chronic heart failure	35 (9.3)	15 (11.3)	0.50
Peripheral vascular disease	14 (3.7)	14 (10.5)	0.003
Stroke	54 (14.3)	27 (20.3)	0.10
Hemiplegia	14 (3.7)	7 (5.3)	0.44
Dementia	54 (14.3)	24 (18.1)	0.30
Chronic liver disease	27 (7.1)	11 (8.3)	0.67
Cirrhosis	16 (4.2)	8 (6.0)	0.40
Chronic renal failure	64 (16.9)	31 (23.3)	0.10
Active dialysis	12 (3.2)	4 (3.0)	1.0
Solid cancer	53 (14.0)	20 (15.0)	0.77
Haematological malignancy	28 (7.4)	16 (12.0)	0.10
AIDS	2 (0.5)	1 (0.8)	1.0
Chemotherapy	19 (5.0)	9 (6.8)	0.45
Severe immunosuppression	62 (16.4)	34 (25.6)	0.02
Mild/moderate immunosuppression	61 (16.1)	22 (16.5)	0.91
Chronic steroid therapy	46 (12.2)	22 (16.5)	0.20
Median (IQR) Charlson comorbidity index	6 (4–8)	7 (5–9)	0.001
Risk factors, *n (%)*			
LTCF	27 (7.1)	18 (13.5)	0.03
Antibiotic therapy in the past 90 days	50 (13.3)	30 (22.9)	0.009
Hospitalization in the past 90 days	91 (24.1)	55 (41.4)	< 0.0001
Home wound care/infusion therapy	56 (14.8)	25 (18.8)	0.28
Day hospital attendance	73 (19.3)	25 (18.8)	0.90
Indwelling bladder catheter	49 (12.9)	20 (15.0)	0.55
Indwelling intravascular catheters	24 (6.4)	7 (5.3)	0.65
Clinical findings			
Median (IQR) body temperature, °C	38.0 (37.2–38.8)	37.6 (36.6–38.5)	0.03
Median (IQR) systolic blood pressure, mmHg	113 (90–140)	99 (80–120)	0.0001
Median (IQR) diastolic blood pressure, mmHg	60 (50–73)	55 (46–68)	0.0006
Median (IQR) mean blood pressure, mmHg	78 (63–93)	70 (60–83)	0.0001
Median (IQR) heart rate, bpm	102 (87–120)	103 (88–120)	0.99
Median (IQR) oxygen saturation, %	95 (92–98)	94 (90–97)	0.06
Median (IQR) respiratory rate, bpm	22 (18–28)	28 (18–35)	0.008
Median (IQR) shock index	0.9 (0.7–1.2)	1.0 (0.8–1.3)	0.002
Laboratory findings			

Table 5 Study population according to in-hospital mortality. (518) *(Continued)*

Variable	Survivors	Death	*p*
Median (IQR) arterial pH	7.5 (7.4–7.5)	7.4 (7.4–7.5)	0.0004
Median (IQR) $PaCO_2$, mmHg	30.0 (26.0–35.0)	31.0 (24.0–36.5-)	0.80
Median (IQR) PaO_2, mmHg	65 (55–76)	67 (55–82)	0.27
Median (IQR) HCO_3- mEq/L	22.0 (18.3–25.0)	20.7 (15.4–24.0)	0.009
Median (IQR) PaO_2/FiO_2 ratio	281.0 (233.0–333.0)	271.5 (222.0–335.5)	0.88
Median (IQR) lactate, mEq/L	2.8 (2.1–4.0)	3.1 (2.1–5.7)	0.02
Median (IQR) white blood cells, cell/L^{-1}	12.2 (7.4–17.8)	12.5 (7.3–19.3)	0.50
Median (IQR) platelet, cell/L^{-1}	198.0 (140.0–254.0)	181.0 (105.5–276.0)	0.45
Mean (SD) haemoglobin, g/dL	12.6 (2.2)	11.4 (2.3)	< 0.0001
Median (IQR) glucose, mg/dL	144.5 (113.0–198.0)	126.5 (100.5–185.0)	0.004
Median (IQR) urea, mg/dL	58 (43–87)	87 (63–145)	< 0.0001
Median (IQR) creatinine, mg/dL	1.5 (1.1–2.1)	2.0 (1.5–4.1)	< 0.0001
Median (IQR) C-reactive protein, g/dL	10.0 (3.8–21.6)	15.7 (7.1–25.9)	0.0006
Median (IQR) Aspartate aminotransferase	28 (20–46)	33 (20–65)	0.05
Median (IQR) Alanine aminotransferase	21 (13–40)	24 (12–39)	0.85
Median (IQR) total bilirubin, mg/dL	0.8 (0.5–1.7)	1.0 (0.6–1.6)	0.52
Median (IQR) INR	1.3 (1.1–1.5)	1.3 (1.2–1.7)	0.40
Site of infection, *n (%)*			
Lung	192 (57.3)	77 (67.0)	0.07
Urinary tract	134 (40.0)	31 (27.0)	0.01
Central nervous system	6 (1.8)	2 (1.7)	1.0
Abdomen	43 (12.8)	16 (13.9)	0.77
Skin and soft tissue)	18 (5.4)	13 (11.3)	0.03
Bone and joints	3 (0.9)	1 (0.9)	1.0
Multiple origin	58 (15.3)	24 (18.1)	0.47
Unknown origin	43 (11.4)	18 (13.5)	0.51
Severity of disease, *n (%)*			
Hemodynamic failure	136 (36.3)	64 (48.9)	0.01
Respiratory failure	71 (19.0)	23 (17.6)	0.71
Renal failure)	153 (41.1)	68 (51.5)	0.04
Liver failure	44 (12.6)	23 (18.1)	0.12
Cognitive impairment	106 (29.9)	49 (40.8)	0.03
Haematological dysfunction	34 (9.0)	15 (11.5)	0.42
Coagulation dysfunction	33 (9.9)	22 (18.0)	0.02
Metabolic dysfunction	261 (74.8)	94 (78.3)	0.43
Shock	75 (19.8)	69 (51.9)	< 0.0001
Microbiological findings, *n (%)*			
Blood cultures performed in the first 48 h	326 (86.2)	114 (85.7)	0.88
Bacteremia	148 (45.4)	48 (42.1)	0.54
Cultures	()	()	
Culture positive	224 (59.3)	77 (57.9)	0.78
Polymicrobial infection	16 (7.1)	13 (16.7)	0.01
MDR pathogen isolated	52 (13.8)	35 (26.3)	0.001
ESBL producer pathogen isolated	33 (8.7)	16 (12.0)	0.27

Table 5 Study population according to in-hospital mortality. (518) *(Continued)*

Variable	Survivors	Death	*p*
MRSA isolated	6 (1.6)	14 (10.5)	< 0.0001
Appropriate empiric antibiotic therapy according to local guidelines	190 (56.6)	77 (61.6)	0.33
Appropriate empiric antibiotic therapy according to antibiotic susceptibility of the isolated pathogen	118 (71,1%)	56 (37,1%)	0,058
Use of vasopressors	49 (13.0)	35 (26.3)	< 0.0001
Mechanical ventilation	4 (1.6)	4 (5.3)	0.09

n number, *IQR* interquartile range, *COPD* chronic obstructive pulmonary disease, *AIDS* Acquired immune deficiency syndrome, *LTCF* long term care facility, *INR* International normalized ratio, *MOF* multi organ failure (other than primary site of infection)

important role played by the contact with health care setting, and suggesting the necessity of administering carbapenems empirically in septic patients with this risk factor. The other risk factor associated with ESBL+ bacteria is a positive history of stroke which could be explained in light of the prolonged hospitalization, nursing home residency or use of indwelling invasive devices (e.g., nasogastric tube, gastrostomy tube, bladder catheter). Considering the prevalence of ESBL *Enterobacteriaceae* and in case a MDRO infection is suspected (e.g., previous hospitalization), an empiric antibiotic therapy including carbapenems for ESBL+ pathogens could be considered, while waiting for culture results.

Sepsis due to MDRO is associated with higher mortality rates and the isolation of a MDRO is an independent risk factor for mortality. We know that patients presenting with MDRO infection have often a high number of comorbidities and a longer medical history, but also that MDRO infection and an inappropriate empirical antibiotic therapy are greatly correlated one to the other [5, 6]. In some studies MDRO infection is an independent risk factor for mortality, whereas in others it is a risk factor for inappropriate antibiotic therapy being the last an independent risk factor for mortality [5, 15].

Our study has some limitations, including the retrospective nature and the single-center design. Our primary

Table 6 Logistic regression analysis to assess the relationship between hospital mortality and demographic, epidemiological, clinical, and laboratory variables. (518)

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Female	1.1 (0.7–1.7)	0.61	1.1 (0.5–2.3)	0.79
Age	1.0 (1.0–1.0)	0.01	1.0 (1.0–1.1)	0.053
Septic shock	4.4 (2.9–6.7)	< 0.0001	3.2 (1.5–7.0)	0.003
Nursing home	2.0 (1.1–3.8)	0.03	0.4 (0.1–1.4)	0.14
Antibiotic therapy in the past 90 days	1.9 (1.2–3.2)	0.01	1.1 (0.4–3.0)	0.90
Hospitalization in the past 90 days	2.2 (1.5–3.4)	< 0.0001	1.1 (0.4–2.7)	0.85
Diabetes mellitus	0.6 (0.4–1.0)	0.04	0.8 (0.3–2.1)	0.71
Peripheral vascular disease	3.1 (1.4–6.6)	0.004	1.4 (0.3–5.9)	0.67
Severe immunosoppression	1.8 (1.1–2.8)	0.02	1.9 (0.8–4.9)	0.17
Lung site	1.5 (1.0–2.4)	0.07	1.7 (0.7–4.0)	0.21
Urinary tract site	0.6 (0.4–0.9)	0.01	0.6 (0.3–1.5)	0.27
Skin and soft tissue site	2.2 (1.1–4.7)	0.03	3.2 (0.9–11.4)	0.07
Renal failure	1.5 (1.0–2.3)	0.04	1.5 (0.7–3.1)	0.26
Cognitive impairment	1.6 (1.1–2.5)	0.03	1.5 (0.7–3.0)	0.30
Coagulation dysfunction	2.0 (1.1–3.6)	0.02	3.2 (1.1–8.8)	0.03
SOFA	1.3 (1.2–1.4)	< 0.0001		
Quick SOFA	1.5 (1.1–2.1)	0.008		
MDR pathogen isolated	2.2 (1.4–3.6)	0.001	4.6 (2.0–10.6)	< 0.001
Use of vasopressors	2.4 (1.5–3.9)	< 0.0001		
Polymicrobial infection	2.6 (1.2–5.7)	0.02	2.4 (0.7–7.7)	0.15

outcome was mortality due to all causes during hospitalization, while sepsis-related mortality and long term outcomes would have been additional and interesting primary outcomes. Finally, we found 41.7% of population who received an empiric antibiotic therapy not concordant with local guidelines. Our local guidelines suggest broad antimicrobial spectrum antibiotics in patients with a suspicion of MDRO infection according to a list of risk factors recorded from previously published literature. So far, no specific risk factors for single MDRO in septic patients were identified. For the first time, we showed hospitalization in the previous 90 days and stroke as independently associated with ESBL+ bacterial infection in sepsis. Finally, our results should be interpreted with caution and not be widely generalized, as different causative pathogens of sepsis, different rates of antibiotic resistances, as well as risk factors related to different healthcare organizations might be recognized worldwide.

The strength and novelty of our study lie on a specific analysis of all risk factors for MDRO in a large sample of consecutive patients coming from the community and admitted to the ED, during a 5-year period, with the diagnosis of sepsis according to Sepsis-3 definition [4]. Several studies evaluated risk factors for MDRO in either bacteremic patients or in those affected by single organ disease (e.g., pneumonia). Our study is the first one evaluating all risk factors for MDRO previously published in literature in patients with sepsis regardless the site of infection.

Conclusion

In conclusion, our finding of an isolation of a MDRO in 17% of patients with sepsis coming from the community advocates for a better recognition of possible risk factors for MDRO and especially for ESBL+ *Enterobacteriaceae*. Patients with sepsis who have been hospitalized in the previous 90 days and/or with a history of stroke might be ideal candidate for a broader empiric antibiotic therapy covering ESBL+ *Enterobacteriaceae*, while waiting for microbiological results.

Additional file

Additional file 1: Table S1. Local guidelines for empirical antibiotic therapy in sepsis and septic shock. **Table S2.** Characteristics of the study sample stratified by MDR bacterial infection. (518). **Table S3.** Characteristics of the study sample stratified by ESBL+ bacterial infection. (518). (DOCX 54 kb)

Abbreviations

AIDS: Acquired immune deficiency syndrome; COPD: Chronic obstructive pulmonary disease; ED: Emergency department; ESBL: Extended-spectrum beta-lactamases; GNB: Gram negative bacteria; ICU: Intensive care unit; INR: International normalized ratio; IQR: Interquartile ranges; LOS: Length of hospital stay; LTCF: Long term care facility; MDR: Multi-drug resistant; MDRO: Multi-drug resistant organisms; MOF: Multi organ failure; MRSA: Methicillin-resistant Staphylococcus aureus; SOFA: Sequential Organ Failure Assessment

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

NC, PB, SA and AB conceived of the study, and participated in its design and coordination and helped to draft the manuscript. GS and LS performed the statistical analysis. DS, EC, LL, DP, BV and VM participated to the acquisition and interpretation of data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the ethical committee (262_2017bis) of the IRCCS Fondazione Ca' Granda, Ospedale Maggiore Policlinico of Milan, Italy, whereas informed consent was waived due to the retrospective and observational nature of the study according to the Italian law on observational studies.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interests. SA and GS are Associate Editors of *Multidisciplinary Respiratory Medicine*.

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