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**Epidemiology of sepsis in Internal Medicine Units of Apulia: results of SEMINA (SEpsis Management in INternal medicine Apulia) study**

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**Parole chiave:** *Unità di Medicina Interna, Sepsi, Criteri Sepsi-3, pazienti anziani, SOFA score*

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# Abstract

***Background.*** *The prevalence and mortality of sepsis in Internal Medicine Units (IMUs) is poorly understood as most of the data derive from studies conducted in Intensive Care Units. Aim of SEpsis Management in INternal medicine Apulia (SEMINA) study was to determine the prevalence of sepsis and the characteristics and outcomes of patients with Sepsis-3 criteria admitted in Apulia’s Internal Medicine Units for over six months.*

***Methods.*** *The SEpsis Management in INternal medicine of Apulia study was a prospective, multicentre, observational study. Adult admissions to the 13 Apulia Region’s Internal Medicine Units between November 15, 2018 and May 15, 2019 were screened for sepsis according to the Sepsis-3 criteria. Medical data were collected in electronic case report form.*

***Results.*** *Out of 7,885 adult patients of the Internal Medicine Units, 359 (4.55%) fulfilled the inclusion criteria, and 65 of them (18.1%) met the septic shock criteria. The patients enrolled were elderly, suffering from chronic poly-pathologies and from cognitive and functional impairment. The respiratory system was the most common site of infection and the most common pathogens isolated from blood cultures were Staphylococcus spp., E. coli, Klebsiella spp., Enterococcus spp. and Acinetobacter spp. The in-hospital fatality rate was 31.2% and was significantly higher for septic shock. Sequential Organ Failure Assessment score, dementia and infections from Acinetobacter spp. were independent risk factors for mortality.*

***Conclusions.*** *A high prevalence of sepsis and a high fatality rate were detected in Apulia Region’s Internal Medicine Units. The high fatality rate observed in our study could be related to the underlying diseases and to the vulnerability of elderly patients admitted to our Internal Medicine Units.*

# Introduction

Sepsis is a life-threatening condition triggered by a dysregulated host response to infection (1). Despite improved healthcare, sepsis mortality rate remains high, about 25% for sepsis and 40-50% for septic shock (2, 3). In the last decades the incidence of sepsis in developed countries has increased, probably due to the ageing population and, consequently, more chronic illnesses, as well as to antibiotic resistance (4, 5). The World Health Organization (WHO) 2020 Global Report on the epidemiology and burden of sepsis reported an estimated 49 milion cases of sepsis and 11 milion sepsis-related deaths observed worldwide in 2017 (6). Currently, the patients admitted to hospital with sepsis criteria are more often the elderly and suffer from chronic diseases and from cognitive and functional impairments. The association between acute and chronic diseases is the characteristic of older patients admitted to Internal Medicine Units (IMUs), who have a high complexity due to advanced age, chronic poly-pathologies and functional loss, and therefore require a global approach and sub-intensive care (7, 8). Traditionally, patients with sepsis were more often admitted to Intensive Care Units (ICUs). Currently, however, the hospitalization of these patients in Internal Medicine Units (IMUs) is increasingly frequent ( 9-11).

Few data are available on the characteristics and outcomes of patients with sepsis admitted to IMUs, whereas the greatest amount of information on this pathology comes from studies carried out in ICUs.

Furthermore, the literature data are not homogeneous, as the criteria for sepsis diagnosis have changed over time and crossed over different studies. In 2016, the third version of sepsis criteria (Sepsis-3) was introduced. It is based on the organ dysfunction in order to improve risk stratification among patients with suspect infection (1). The clinical data used for the new definition were derived from patients hospitalized in ICUs. To date, few studies have used this criterion in identifying patients with sepsis admitted to IMUs.

Therefore-, aim of SEMINA (SEpsis Management in INternal medicine Apulia) study was to describe the epidemiology of sepsis and the characteristics and outcomes of patients with sepsis (according to Sepsis-3 criteria) admitted to Apulia IMUs for over six months.

# Materials and methods

## Study design

The SEMINA study was a prospective, observational, multicentre, cohort study designed by the Apulian section of FADOI (Italian Scientific Society of Hospital Internal Medicine) to evaluate the prevalence, the characteristics and the outcomes of sepsis patients admitted to IMUs in Apulia region (Italy).

The recruitment of the centres was on a voluntary basis, with no financial incentive.

The study did not involve any deviations from routine medical practice, but the authorization of the Ethics Committee of each participating centre was required.

Between November 15, 2018 and May 15, 2019, consecutive adult patients (> 18 years) newly admitted to the IMUs of participating centres with Sepsis-3 criteria were included after issuing their informed consent. In addition to incoming patients, all hospitalized patients were screened over time to identify the onset of hospital-acquired sepsis. The only exclusion criterion was the patient’s denial of informed consent.

Patients were followed up until hospital discharge, transfer to ICUs or death.

## Definitions

The Sepsis-3 criteria were used to select patients to be enrolled. Therefore the inclusion criteria were: patients with a suspicion of infection on admission or during the hospital stay and an acute sequential organ failure assessment (SOFA) score increase of >2 points, considering baseline score to be zero (1).

The SOFA score had to be recorded on the day of admission or 2 days later, as organ dysfunction can occur even after the diagnosis of infection (12). For patients with hospital-acquired sepsis, the SOFA score had to be calculated when infection was suspected.

Suspected infection was defined by blood culture sampling and by concomitant administration of intravenous antibiotics as indicated by the Sepsis-3 document. Hospital acquired sepsis was defined as sepsis manifested > 48 hours after hospital admission. Septic shock was defined as the use of vasopressors needed to maintain mean arterial pressure > 65 mmHg) and lactate levels > 2 mmol/L.

Microorganisms were defined as multidrug-resistant (MDR) if resistant to at least one agent in three or more antimicrobial classes, and pandrug-resistant (PDR) if resistant to all agents in all antimicrobial classes (13).

## Data collection

The data were collected in electronic case report forms (eCRF). Detailed information about the study and the eCRF compilation were provided to all participants during a preliminary meeting. Information recorded included: demographic information (age, sex, place of origin <home, long-term facility, others hospitals>); clinical data (temperature, blood pressure, respiratory rate, Glasgow Coma Scale (GCS), hospital length of stay, concomitant diseases, site of infection); antibiotic treatment in the previous month; laboratory data and results of microbial cultures and antimicrobial resistance; SOFA score at enrollment; treatment data.

The total number of hospitalizations during the period of the study was also required for each centre.

### Outcomes

The primary study outcome was inhospital fatality rate; secondary outcome were ICUs transfer and IMUs length of stay.

Case fatality rate was calculated by dividing the number of patients who die of sepsis by all patients diagnosed with sepsis during the study period; the resulting ratio was then multiplied by 100 to get a percentage.

### Statistical analyses

Data are summarized as the mean ± standard deviation for continuous variables or frequency and percentage for categorical variables. The patients’ characteristics were compared by using Student’s t-test (continuous data) and chi-squared or Fisher’s exact test (categorical data) when appropriate. For the in-hospital mortality outcome, a backward stepwise procedure was performed (p>0.05 to remove). The variables included were gender (female vs male), age, admission category, comorbidities, estimated glomerular filtration rate (eGFR), Glasgow Coma Scale, SOFA Score, septic shock, previous use of antibiotics, hospital acquired sepsis, site of infection, blood culture positive, *Acinetobacter* spp, *E. coli*, *Enterococcus* spp, *Staphylococcus* spp and multidrug resistance. The model was used to select, among patients’ characteristics and available risk factors, independent predictors of in-hospital mortality.Odds Ratio with 95% Confidence Interval (95%CI) were reported. P value < 0.05 was considered to be statistically significant. All analyses were performed using STATA version 16 (StataCorp, College Station, Texas).

# Results

|  |
| --- |
| Figure 1 - Flow chart of the study |

A total of 13 IMUs from 11 hospitals, including 4 University Clinics and 1 private hospital, all of them in Apulia, participated in this study. The flowchart of the study is shown in Figure 1. There were 7885 adult IMU admissions between November 15, 2018 and May 15, 2019. Of these, 359 (4.55%) fulfilled the inclusion criteria and constituted the SEMINA cohort. Mean age was 78 +13 years and 55.7% of patients were female. The majority of patients came from home (82.5%). The most common comorbidities were cardiovascular diseases, diabetes, dementia and COPD (chronic obstructive pulmonary disease). Mean length of IMU stay was 14 + 10 days. The mean SOFA score was 6.2 + 2.9. According to the Sepsis-3 definitions, 65 (18.1%) patients were identified as having septic shock. The characteristics of the two patient groups, with sepsis and septic shock, are shown in Table 1. Patients with septic shock were more frequently women (70.8%) and more frequently came from nursing homes (21.5% vs 9.5%, p= 0.006); they had higher SOFA score (8.6+3.1 vs 5.7+2.6, p<0.001), lower Glasgow Coma Scale (9.6+4.2 vs 12.1+3.6, p<0.001) and had more frequently previous use of antibiotics (47.7% vs 29.6%, p=0.005) than patients with sepsis. The most common sites of infection were the respiratory system (30.1%) and urinary system (21.4%); 29.8% of patients had a primary bacteremia. The site of infection was not identified in 28 cases (7.8%). Table 1 details the distribution of infection site in the total number of people infected and in the 2 subgroups, sepsis and septic shock. Except for urinary infections, more frequent in the sepsis group (p=0.047), the distribution of infections was similar among patients with sepsis and septic shock.

## Microbiological results

In the SEMINA cohort 44.3% of patients (n=159) tested positive blood cultures, 25% (n=90) had negative blood cultures and other positive cultures, 30.6% (n=110) had negative cultures. Among patients with negative blood cultures and other positive cultures, 52 patients (14.5%) had positive urine cultures, 17 patients (4.7%) had positive expectorated sputum and 21 patients (5.8%) had positive soft tissue and skin cultures. Gram negative bacteria were the prevalent organisms in positive blood cultures, accounting for 54.7% (n=87), while Gram-positive bacteria accounted for 48.4% (n=77); 10 (6.2%) patients had mixed infections and 5 patients (3.1%) had *Candida* spp. infections. The proportions of isolated microorganisms were not significantly different among patients with sepsis and sepsis shock. The distribution of microorganisms isolated from blood cultures of SEMINA patients, according to their clinical conditions and antibiotic resistance, is shown in Table 2. The most common isolated pathogens by blood culture were *Staphilococcus* spp. (39.6%), *E. coli* (23.9%), *Enterococcus* spp. (8.2%), *Klebsiella* spp. (7.5 %), and *Acinetobacter* spp. (7.5%). 6.3% of *Staphilococcus* *aureus* isolates were identified as MRSA (Methicillin-Resistant *Staphylococcus Aureus*). 41.7% of *Acinetobacter* spp. isolates, 30.8% of *Klebsiella* spp. isolates, 18.4% of *E. coli* and 15.4% of *Pseudomonas* spp. were resistant to carbapenem. Overall we observed a prevalence of 13.2% (21 patients) of sepsis caused by carbapenemresistant pathogens. The diagnosis of MDR was made by blood culture in 38 isolates (23.9%), while only 1 isolate was PDR for *Klebsiella Pneumoniae*. The most common MDR strains were *Staphylococcus* spp (12/38) followed by *E. coli* (8/38). Considering all positive culture, 44 patients (17.7%) infected by MDR bacteria were identified.

## Hospital-acquired sepsis

Only 25 (7%) patients had hospitalacquired sepsis. This subgroup exhibited more severe disease than those with community-acquired sepsis, with long hospital stay (20 + 11 vs 13 + 10; p<0.002) and high in-hospital fatality rate (n=10; 40%). The site of infection more common was the respiratory system (36%) and the most common isolated microorganisms from

Table 1 - Characteristics of SEMINA patients and comparison between patients with sepsis and those with septic shock.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | All patients n=359 | Sepsis n=294 | Septic Shock n=65 | **p-value** |
| Patients Characteristics  Age (Mean±SD) | 78 + 13 | 78 +12 | 78+14 | 0.952 |
| Female sex (%) | 55.7 | 52.4 | 70.8 | 0.007 |
| Admitted from home (%) | 82.5 | 85.7 | 70.8 | 0.004 |
| Admitted from nursing home (%) | 11.7 | 9.5 | 21.5 | 0.006 |
| Previous use of antibiotics (%) | 32.9 | 29.6 | 47.7 | 0.005 |
| Hospital acquired sepsis n (%) | 25 (7) | 20 (6.8) | 5 (7.7) | 0.789 |
| Comorbidities (%) Diabetes | 36.8 | 38.1 | 30.8 | 0.268 |
| Coronary Artery Disease | 18.9 | 19.0 | 18.5 | 0.913 |
| Heart Failure | 44.8 | 43.5 | 50.8 | 0.289 |
| COPD | 29.5 | 29.9 | 27.7 | 0.720 |
| Cancer | 15.9 | 17.3 | 9.2 | 0.105 |
| Dementia | 35.4 | 35.7 | 33.8 | 0.776 |
| Glasgow Coma Scale (mean ± SD) | 11.6±3.8 | 12.1±3.6 | 9.6±4.2 | <0.001 |
| SOFA score (mean±SD) | 6.2±2.9 | 5.7+2.6 | 8.6+3.1 | <0.001 |
| Lenght of stay(days±SD) | 14+10 | 14+10 | 13+10 | 0.549 |
| Source of infection n (%) Respiratory | 108 (30.1) | 83 (28.2) | 25 (38.5) | 0.104 |
| Urinary | 77 (21.4) | 69 (23.5) | 8 (12.3) | 0.047 |
| Primary bacteremia | 107 (29.8) | 90 (30.6) | 17 (26.2) | 0.477 |
| Skin and soft tissue | 17 (4.7) | 16 (5.4) | 1 (1.5) | 0.329 |
| Intra-abdominal | 14 (3.9) | 7 (2.4) | 7 (10.8) | 0.006 |
| Catheter-related | 6 (1.7) | 3 (1.0) | 3 (4.6) | 0.075 |
| Unknown | 28 (7.8) | 24 (8.2) | 4 (6.2) | 0.582 |
| Endocarditis | 1 (0.3) | 0 (0.0) | 1 (1.5) | 0.181 |
| Spondylodiscitis | 1 (0.3) | 1 (0.3) | 0 (0.0) | 1.000 |
| **Outcome** n (%) Improved | 228 (63.5) | 200 (68) | 24 (33.8) | <0.001 |
| Dead | 112 (31.2) | 79 (26.9) | 33 (50.8) | <0.001 |
| Transferred to ICUs | 19 (5.3) | 11 (3.7) | 8 (12.3) | 0.011 |

Abbreviations: yrs=years; SD=standard deviation; n=number; COPD=chronic obstructive pulmonary disease; ICUs=intensive care units.

Table 2 - Distribution of microorganisms isolated from blood cultures according to clinical conditions and antibiotic resistance

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | All patients n=359 | Sepsis n=294 | Sepsis Shock n=65 | **p-value** |
| **Positive blood culture n (%)** | 159 (44.3) | 133 (45.2) | 26 (40.0) | 0.442 |
| **Gram positive n (%)** | 77 (48.4) | 66 (49.6) | 11 (42.3) | 0.495 |
| *Staphilococcus* spp*.* | 63 (39.6) | 52 (39.1) | 11 (42.3) | 0.760 |
| *MRSA* | 4 (6.3) | 3 (5.8) | 1 (9.1) |  |
| *MDR* | 12 (19.0) | 7 (13.5) | 5 (45.5) |  |
| *Streptococcus* spp*.* | 2 (1.3) | 2 (1.5) | 0 (0.0) | 1.000 |
| *Enterococcus* spp*.* | 13 (8.2) | 13 (9.8) | 0 (0.0) | 0.129 |
| *Carbapenem-resistant* | 1 (7.7) | 1 (7.7) | 0 (0.0) |  |
| *MDR* | 5 (38.5) | 5 (38.5) | 0 (0.0) |  |
| *Listeria* | 1 (0.6) | 1 (0.8) | 0 (0.0) | 1.000 |
| **Gram negative n (%)** | 87 (54.7) | 70 (52.6) | 17 (65.4) | 0.232 |
| *Acinetobacter spp.* | 12 (7.5) | 9 (6.8) | 3 (11.5) | 0.417 |
| *Carbapenem-resistant* |  | 4 (44.4) | 1 (33.3) |  |
| *MDR* | 3 (25.0) | 3 (33.3) | 0 (0.0) |  |
| *Aeromonas* | 1 (0.6) | 1 (0.8) | 0 (0.0) | 1.000 |
| *Chlamidia* | 1 (0.6) | 1 (0.8) | 0 (0.0) | 1.000 |
| *E. coli* | 38 (23.9) | 33 (24.8) | 5 (19.2) | 0.542 |
| *ESBL* | 7 (18.4) | 5 (15.2) | 2 (40.0) |  |
| *Carbapenem-resistant* | 7 (18.4) | 5 (15.2) | 2 (40.0) |  |
| *MDR* | 8 (21.1) | 7 (21.2) | 1 (20.0) |  |
| *Citrobacter* | 1 (0.6) | 1 (0.8) | 0 (0.0) | 1.000 |
| *Enterobacter* | 1 (0.6) | 1 (0.8) | 0 (0.0) | 1.000 |
| *Klebsiella* spp*.* | 12 (7.5) | 9 (6.8) | 3 (11.5) | 0.461 |
| *Carbapenem-resistant* | 4 (30.8) | 3 (30.0) | 1 (33.3) |  |
| *MDR* | 2 (15.4) | 1 (10.0) | 1 (33.3) |  |
| *PDR* | 1 (7.7) | 0 (0.0) | 1 (33.3) |  |
| *Morganella* | 2 (1.3) | 2 (1.5) | 0 (0.0) | 1.000 |
| *Proteus spp.* | 8 (5.0) | 3 (2.3) | 5 (19.2) | 0.003 |
| *Carbapenem-resistant* | 2 (25.0) | 0 (0.0) | 2 (40.0) |  |
| *MDR* | 4 (50.0) | 1 (33.3) | 3 (60.0) |  |
| *Providencia* | 1 (0.6) | 1 (0.8) | 0 (0.0) | 1.000 |
| *Pseudomonas* spp*.* | 13 (8.2) | 10 (7.5) | 3 (11.5) | 0.448 |
| *Carbapenem-resistant* | 2 (15.4) | 1 (10.0) | 1 (33.3) |  |
| *MDR* | 4 (30.8) | 2 (20.0) | 2 (66.7) |  |
| *Serratia* | 1 (0.6) | 1 (0.8) | 0 (0.0) | 1.000 |
| **Fungi, n (%)** *Candida* spp. | 5 (3.1%) | 4 (3.0%) | 1 (3.8%) | 1.000 |

Abbreviations: MRS=Methicillin-Resistant *Staphylococcus aureus*; MDR=Multidrug-resistant; PDR=Pandrug Resistant.

Table 3 - Univariate analysis comparing characteristics of survivors and non survivors

|  |  |  |  |
| --- | --- | --- | --- |
|  | Survivors n=247 | Non-survivors n=112 | **p-value** |
| Female sex n (%) | 139 (56.3) | 61 (54.5) | 0.749 |
| Age (mean±SD) | 77±13 | 82±10 | <0.001 |
| Admitted from home n (%) | 212 (85.8) | 86 (76.8) | 0.035 |
| Admitted from nursing home n (%) | 23 (9.3) | 19 (17.0) | 0.037 |
| Hospital acquired sepsis n (%) | 15 (6.1) | 10 (8.9) | 0.325 |
| Diabetes n (%) | 91 (36.8) | 41 (36.6) | 0.966 |
| Coronary Artery Disease n (%) | 42 (17.0) | 26 (23.2) | 0.164 |
| Heart Failure n (%) | 105 (42.5) | 56 (50.0) | 0.186 |
| COPD n (%) | 71 (28.7) | 35 (31.3) | 0.630 |
| Cancer n (%) | 41 (16.6) | 16 (14.3) | 0.578 |
| Dementia n (%) | 71 (28.7) | 56 (50.0) | <0.001 |
| Creatinine mg/dL (mean±SD) | 1.6±1.1 | 2.0±1.3 | 0.003 |
| eGFR mL/min/1.73 m2 (mean ±SD) | 50±32 | 40±30 | 0.005 |
| Glasgow Coma scale (mean±SD) | 12.7±3.3 | 9.2±3.9 | <0.001 |
| SOFA score (mean±SD) | 5.3±2.5 | 8.3±2.8 | <0.001 |
| Sepsis Shock n (%) | 32 (13.0) | 33 (29.5) | <0.001 |
| Previous use of antibiotics n (%) | 71 (28.7) | 47 (42.0) | 0.013 |
| Length of stay in days (mean±SD) | 15±9 | 11±11 | <0.001 |
| Length of stay < 5 days n patients (%) | 6 (2.4) | 37 (33.0) | <0.001 |
| Blood culture positive n (%) | 116 (47.0) | 43 (38.4) | 0.130 |
| Blood culture negative n (%) | 131 (53) | 69 (61.6) | 0.130 |
| *Staphylococcus* spp n (%) | 48 (19.4) | 15 (13.4) | 0.163 |
| *E. coli* n (%) | 32 (13.0) | 6 (5.4) | 0.030 |
| *Klebsiella* spp n (%) | 8 (3.2) | 4 (3.6) | 0.999 |
| *Enterococcus* spp n (%) | 11 (4.5) | 2 (1.8) | 0.360 |
| *Acinetobacter* spp n (%) | 3 (1.21) | 9 (8.0) | 0.002 |
| Multidrug resistance\* n (%) | 32 (13) | 12 (10.7) | 0.549 |
| Respiratory infections n (%) | 78 (31.6) | 30 (26.8) | 0.359 |
| Urinary infections n (%) | 56 (22.7) | 21 (18.8) | 0.402 |
| Primary bacteriemia n (%) | 73 (29.6) | 34 (30.4) | 0.878 |
| Skin and soft tissue n (%) | 13 (5.3) | 4 (3.6) | 0.484 |
| Intra-abdominal infections n (%) | 8 (3.2) | 6 (5.4) | 0.381 |

\* all cultures from MDR bacteria were considered

Abbreviations: yrs=years; n=number; SD=standard deviation; COPD=chronic obstructive pulmonary disease.

Table 4 - Backward stepwise logistic regression for in-hospital fatality (p>0.05 to remove including variables in Table 3).

|  |  |  |
| --- | --- | --- |
|  | Odds Ratio (95%CI) | **p-value** |
| Female | 0.50 (0.28-0.90) | 0.020 |
| Dementia | 2.01 (1.11-3.62) | 0.021 |
| Glasgow Coma Scale (per 1 point) | 0.89 (0.81-0.98) | 0.013 |
| SOFA score (per 1 point) | 1.42 (1.25-1.61) | <0.001 |
| *Staphylococcus* spp | 0.43 (0.20-0.91) | 0.028 |
| *E. coli* | 0.22 (0.07-0.65) | 0.007 |
| *Acinetobacters* spp | 7.80 (1.67-36.26) | 0.009 |

Abbreviations: 95%CI ,95% Confidence Interval; SOFA, sequential organ failure assessment.

blood culture were *Acinetobacter baumannii* (n=6; 24%) and *Staphilococcus* spp (n=7; 28%).

## Outcomes

112 patients (31.2%) died during hospitalization and 19 (5.3%) were transferred to the ICU (Table 1). The fatality rate of septic shock patients was significantly higher than sepsis patients (50.8% vs 26.9 %, p<0.001). A higher percentage of patients with septic shock was transferred to ICUs (12.3% vs 3.7%).

By univariate analysis, age, coming from nursing homes, SOFA score, septic shock, chronic renal failure, GCS, dementia and previous use of antibiotics were associated with mortality. *Acinetobacter* spp was significantly associated with a higher mortality (p=0.002); most *Acinetobacter* spp were resistant to carbapenem and MDR. Non survivors had a shorter hospital stay with respect to survivors (p < 0.001); 33% of non survivors had a hospital stay of less than 5 days. No increase in fatality rate was found among patients with positive blood culture compared to patients with negative blood culture, respectively 43/159 (27.0%) vs 69/200 (34.5%), p= 0.130. Table 3 shows the characteristics of the patients who survived or died during hospitalization because of sepsis.

A multivariable backward stepwise logistic regression analysis was used to examine variables of in-hospital mortality (Table 4); SOFA score, dementia and infections from *Acinetobacter* spp. were independent risk factors for mortality. Infections with *E. coli* and *Staphylococcus* spp., as well as female sex, were associated with lower mortality. There was a direct relationship between SOFA score and the IMU mortality. Figure 2 shows the SOFA score and the corresponding IMU fatality rates; patients with SOFA score 2-3 on admission had IMU fatality rate of 6.3% whereas those with SOFA score > 12 had a fatality rate of 81.0%.

# Discussion

Our study provides evidence that sepsis is a common problem in IMUs and it is associated with a high fatality rate. This large study, including 7,885 patients from 13 IMUs in Apulia, showed that approximately 4.55% of all IMU patients had sepsis diagnosed with Sepsis-3 criteria, confirming that a high prevalence of patients with sepsis are currently hospitalized outside the ICUs (14, 15).

|  |
| --- |
| Figure 2 - Sequential Organ Failure Assessment (SOFA) Score and corresponding IMUs (Internal Medicine Units) |

fatality rate.

The sepsis prevalence found in our study was higher than that identified by a recent Italian multicentre study on the sepsis epidemiology in IMUs which was 1.78% (11). This result is in line with several epidemiological studies (4, 16) and with the WHO 2020 global report (6) reporting an increase in the incidence of sepsis over years. However, there is a lack of literature data on patients hospitalized with sepsis in

IMUs.

Studies conducted at the ICUs, considered the usual healthcare setting for this problem, have shown at any rate a higher prevalence of sepsis; the earlier Sepsis Occurrence in Acutely III Patients (SOAP) study, a large European study, reported a prevalence of 29.5% (17). More recently, global date from the Intensive Care Over Nation (ICON) audit showed the same prevalence of sepsis among patients admitted to ICUs with a wide range between countries from 13.6 to 39.3% (18).

The patients enrolled in our study were elderly (mean age 78 years), affected by chronic poly-pathologies, frequently showing cognitive and functional impairment. The advanced age and reduced functional state justified their hospitalization in Internal Medicine wards, as observed in the Italian study of A. Mazzone (11).

The severity of the patients’ illness can be assessed by the mean number of organ system failures, indeed the mean SOFA score was 6.2. This value is comparable with that found in studies on patients with sepsis conducted at the ICUs (19, 20).

Only 25 patients ( 7%) developed sepsis during their IMUs stay. Healthcareassociated infections are the most frequent adverse events during hospitalization, especially in ICUs (21). The recent Italian SPIN-UTI study reported a prevalence of 6.2% of ICU-acquired sepsis among patients admitted to the ICUs (22 ). The problem is also common in IMUs and represents a challenge for clinicians.The characteristics of patients admitted to this care setting (elderly, frequently bedridden, using bladder catheters, with altered functional status), are all factors associated with an increased risk of hospital infections (23). In our study, the subgrouop of patients with hospital-acquired infections had more severe disease with longer hospital stay and higher mortality, as evidenced by the SPIN-UTI study. According to the Sepsis-3 definitions, 65 (18.1%) patients were found to have septic shock. As expected it was associated with a higher SOFA score and a higher impairment of cognitive status. Only 19 (5.3%) patients were transferred to the ICUs with a higher frequency among patients with septic shock (12.3% vs 3.7%; p<0.01). These data confirm that only a small percentage of patients with sepsis requires a continuous invasive monitoring which can be ensured in the intensive care environment. The correct care setting for sepsis patients is not well defined, indeed three large multicentre studies have shown that resuscitation protocols guided by the measurement of the central venous pressure (CVP) and of the central venous oxygen saturation (ScvO2) do not improve the outcome of patients with sepsis or septic shock ( 24-26). These data highlight the heterogeneity of sepsis patients and the need to personalize the treatment pathway reserving access to ICUs only for the most seriously ill patients.

The respiratory system was the most common site of infection, as observed in ICU studies (18).

In our study we showed positive blood cultures in 44.3% of SEMINA patients in line with literature data showing that only 38-69% of patients with sepsis have bacterial blood stream infections (27). The results of the various studies are difficult to compare, as they depend on the timing of the blood draw, the previous treatment with antibiotics and the presence of viable organisms. In the SEMINA study, blood for culture was drawn before starting empiric antibiotic therapy for the suspected infection, thereby eliminating a confounding factor. The fatality rates were similar among culturepositive versus culture-negative patients (27% vs 34.5%, p=0.130). The literature data relating to outcomes between culturepositive and culture-negative septic patients are controversial. A recent meta-analysis including 7 studies showed that there was no significant difference in mortality between two groups (28).

Gram negative bacteria were more frequently isolated (54.7% versus 48.4%), as observed in recent studies outside the ICUs (14, 29); among patients with septic shock, Gram-negative bacteria were the agents responsible for the infection in two-thirds of cases and 10 patients transferred to ICUs had sepsis from gram negative bacteria. Our findings are in agreement with those of other studies that have shown an increased risk of poor outcomes in patients with Gram negative bacteremia (30, 31).

A high percentage of antibiotic resistance was detected among both Gram-negative and Gram-positive bacteria, in particular we observed that 23.9% of sepsis with positive blood culture were due to MDR bacteria, and 13.2% were due to bacteria resistant to carbapenem. Several studies reported an increased risk of lethality in patients with MDR infections in ICUs (32, 33). However, the literature date are conflicting, indeed some authors have shown that antibioticresistance is not associated with an increase in lethality (34), and that only sepsis due to extensively drug-resistant (XDR) bacteria are a strong predictor of death (35). In agreement with these latest studies, our data did not show increased lethality among patients with MDR isolates, highlighting that other factors might play a predominant role for the risk of death.

In-hospital fatality rates in SEMINA patients was 31.2% and, as expected, there was an increase in fatality rate according to the severity of sepsis, indeed we observed a fatality rate of 26.9% in patients with sepsis and of 50.8% in patients with septic shock. The fatality rate in our study was higher than that observed in the SOAP and ICON studies conducted in European ICUs in 2002 and 2012 respectively (17, 19) and also than that observed in the Italian study of Mazzone conducted in IMUs (11).

The patients observed in our study were older than SOAP and ICON patients and more likely to have cognitive and functional impairments and multiple comorbidities, conditions that identify a vulnerable population at high risk of mortality. Different factors have been related to the risk of inhospital death in our patients including SOFA score, dementia and infections with *Acinetobacter* spp. The association between *Acinetobacter* spp. infection and mortality has been observed in several studies (32, 33). In critically ill patients, *Acinetobacter* spp. colonization is considered a marker of immune dysfunction that occurs in the most advanced stages of sepsis and correlates closely with mortality. Given the high frequency of resistance to many antibiotics, this pathogen has become a challenge in infections in IMUs. In our population 33% of non survivors had a very short hospital stay of less than 5 days; this underlines that a subpopulations of enrolled patients were suffering from serious preexisting diseases and therefore the sepsis could be considered a contributing factor to the death. Few studies have investigated the causes of death in patients with sepsis, whether death after sepsis is related to the sepsis or to the underlying disease. A retrospective study that enrolled 497 patients with positive blood culture sepsis, showed that the underlying disease played a considerable role in the death of sepsis patients (36). Similarly, the high fatality rate observed in our study could be related to the underlying diseases and to the vulnerability of elderly patients admitted to our IMUs. Finally, the adoption of the Sepsis-3 criteria identified a population at greater risk of mortality due to the greater burden of organ dysfunction. Our study confirmed that SOFA score, as indicated by the Sepsis-3 Consensus for intensive care patients (1), is a useful predictor of mortality even for patients with sepsis admitted to IMUs.

## Strengths and limitations of the study

Our study should be interpreted in view of some limitations. The role of empirical antibiotic therapy on patient outcomes was not evaluated and a common resuscitation protocol was not envisaged for all centres. The study did not include information relating to the therapeutic approach to sepsis, indeed the protocol did not involve any deviation from the usual care for sepsis. However, some difference in mortality rate between participating centres was found. This could be related to several factors such as hospital admission rate, hospital size, number of IMU beds and nurse to patients ratio. Further insights are needed to evaluate the role of these parameters on the outcome of sepsis patients. Despite these limitations, this was a prospective, large epidemiology study that provided valuable information about the epidemiology of sepsis in Apulia’s IMUs. The strength of our study was the adoption of a validated criterion for sepsis diagnosis, which required the calculation of the SOFA score for all patients.

# Conclusions

Our study highlighted that sepsis is a pathology with a high prevalence in Internal Medicine Units in Apulia and with high fatality rate. The patients admitted to our wards were elderly, suffering from poly-pathologies and with cognitive and functional impairment. Most of patients had sepsis from gram-negative bacteria, but in a high percentage the blood culture remained negative. Fatality rate was not affected by positive blood culture or by multidrugresistant bacteria, but it was related to vulnerability and functional impairment of the patients. However, further appropriate studies are needed to better clarify the role of patients vulnerability and the underlying diseases on fatality rate in elderly patients with sepsis. Finally, the role of appropriate strategies for the prevention of hospital infections and of adverse effects of sepsis in IMUs, should be evaluated.

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## Riassunto

***Epidemiologia delle sepsi nei reparti di Medicina Interna della Puglia: i dati dello studio SEMINA (SEpsis Management in INternal medicine Apulia)***

**Introduzione.** La prevalenza e la mortalità dei pazienti con sepsi, ricoverati presso le Unità di Medicina Interna, sono poco note poiché la maggior parte dei dati derivano da studi condotti presso le Unità di Terapia Intensiva. Scopo dello studio SEMINA (SEpsis Management in INternal medicine Apulia) è stato determinare la prevalenza della sepsi insieme alle caratteristiche e alla prognosi dei pazienti ricoverati nei reparti di Medicina Interna in Puglia, per un periodo di osservazione di sei mesi, utilizzando i criteri Sepsis-3.

**Metodi.** Lo studio SEMINA è uno studio prospettico, multicentrico, osservazionale. Tutti i soggetti ricoverati presso 13 Unità di Medicina Interna in Puglia, nel periodo compreso fra il 15 novembre 2018 e il 15 Maggio 2019, sono stati considerati per selezionare i pazienti affetti da sepsi in accordo con in criteri Sepsis-3. I dati di ciascun paziente sono stati raccolti in un apposito database.

**Risultati.** Nel periodo di studio sono stati ammessi 7885 pazienti presso le Unità di Medicina Interna partecipanti; di questi 359 (4.55%) soddisfacevano i criteri di inclusione e un sottogruppo di 65 pazienti (18.1%) aveva i criteri dello shock settico. I pazienti arruolati erano anziani, soffrivano di patologie croniche ed avevano disfunzioni cognitive e funzionali. L’apparato respiratorio è risultato la sede più comune di infezione. I patogeni più frequentemente isolati dalle emocolture sono risultati: *Staphilococcus* spp., *E. coli,* *Klebsiella* spp., *Enterococcus* spp. e *Acinetobacter* spp. La mortalità ospedaliera è risultata del 31.2%, significativamente maggiore per lo shock settico. Fattori di rischio indipendenti per la mortalità sono risultati il SOFA (Sequential Organ Failure Assessment) score, la demenza e le infezioni da *Acinetobacter* spp.

**Conclusioni.** Presso le Unità di Medicina Interna in Puglia sono state riscontrate una elevata prevalenza della sepsi e una elevata mortalità. L’elevato tasso di mortalità osservato nel nostro studio potrebbe essere correlato con le patologie associate e con la vulnerabilità dei pazienti anziani ricoverati presso le Unità di Medicina Interna.

## References

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23; **315**(8): 801-10. doi: 10.1001/ jama.2016.0287.
2. Shankar-Hari M, Harrison DA, Rubenfeld GD, Rowan K. Epidemiology of sepsis and septic shock in critical care units: comparison between sepsis-2 and sepsis-3 populations using a national critical care database. Br J Anaesth. 2017 Oct 1; **119**(4): 626-36. doi: 10.1093/bja/ aex234.
3. Marx G; SepNet Critical Care Trials Group. Incidence of severe sepsis and septic shock in German intensive care units: the prospective, multicentre INSEP study. Intensive Care Med. 2016 Dec; **42**(12): 1980-6. doi: 10.1007/s00134016-4504-3. Epub 2016 Sep 29.
4. De La Rica AS, Gilsanz F, Maseda E. Epidemiologic trends of sepsis in western countries. Ann Transl Med. 2016 Sep; **4**(17): 325. doi: 10.21037/atm.2016.08.59.
5. Fleischmann C, Scherag A, Adhikari NK, et al. International Forum of Acute Care Trialists. Assessment of global incidence and mortality of Hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med. 2016 Feb 1; **193**(3): 259-72. doi: 10.1164/ rccm.201504-0781OC.
6. Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO
7. Verma AA, Guo Y, Kwam JL, et al. Patient characteristics, resource use and outcomes associated with general internal medicine hospital care: the General Medicine Inpatient Initiative (GEMINI) retrospective cohort study. CMAJ Open. 2017 Dec 11; **5**(4): E842-7. doi: 10.9778/ cmajo.20170097. Epub 2017 Dec 13.
8. Buurman BM, Frenkel WJ, Abu-Hanna A, Parlevliet JC, de Rooij SE. Acute and chronic diseases as part of multimorbidity in acutely hospitalized older patients. Eur J Intern Med. 2016 Jan; **27**: 68-75. doi: 10.1016/j.ejim.2015.09.021. Epub 2015 Oct 21.
9. Rohde JM, Odden AJ, Bonham C, et al. The epidemiology of acute organ system dysfunction from severe sepsis outside of the intensive care units. J Hosp Med. 2013; **8**(5): 243-7. doi: 10.1002/jhm.2012. Epub 2013 Feb 8.
10. Whittaker SA, Fuchs BD, Gaieski DF, et al. Epidemiology and outcomes in patients with severe sepsis admitted to the hospital wards. J Crit Care. 2015 Feb; **30**(1): 78-84. doi: 10.1016/j.

jcrc.2014.07.012. Epub 2014 Jul 22.

1. Mazzone A, Dentali F, La Regina M, et al. Clinical features, short-term mortality, and prognostic risk factors of septic patients admitted to internal medicine units: results of an Italian multicenter prospective study. Medicine (Baltimore). 2016 Jan; **95**(4): e2124. doi: 10.1097/ MD.0000000000002124.
2. Verboom DM, Frencken JF, Ong DSY, et al. Robustness of sepsis-3 criteria in critically ill patients. J Intensive Care. 2019 Aug 29; **7**: 46.

doi: 10.1186/s40560-019-0400-6.

1. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012 Mar; **18**(3): 268-81. doi: 10.1111/j.14690691.2011.03570.x. Epub 2011 Jul 27.
2. Esteban A, Frutos-Vivar F, Ferguson ND, et al. Sepsis incidence and outcome: contrasting the intensive care unit with the hospital ward. Crit Care Med. 2007 May; **35**(5): 1284-9. doi: 10.1097/01.CCM.0000260960.94300.DE.
3. Vardi M, Ghanem-Zoubi NO, Bitterman H, et al. Sepsis in nonagenarians admitted to internal medicine departments: a comparative study of outcomes. QJM. 2013 Mar; **106**(3): 261-6. doi: 10.1093/qjmed/hcs221. Epub 2012 Nov 27.
4. Mellhammar L, Wullt S, Lindberg Å, Lanbeck P, Christensson B, Linder A. Sepsis incindence: a population-based study. Open Forum Infect Dis. 2016 Dec 8; **3**(4): ofw207.doi: 10.1093/ ofid/ofw207.
5. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med. 2006 Feb; **34**(2): 344-53.

doi: 10.1097/01.ccm.0000194725.48928.3a.

1. Sakr Y, Jaschinski U, Wittebole X, et al. Sepsis in intensive care unit patients: worldwide data from the Intensive Care Over Nations audit. Open Forum Infect Dis. 2018 Nov 19; **5**(12): ofy313. doi: 10.1093/ofid/ofy313.
2. Vincent JL, Lefrant JY, Kotfis K, et al. on behalf of the ICON and SOAP investigators. Comparison of European ICU patients in 2012 (ICON) versus 2002 (SOAP) Intensive Care Med. 2018 Mar; **44**(3): 337-44. doi: 10.1007/s00134-0175043-2. Epub 2018 Feb 15.
3. Klimpel J, Weidhase L, Bernhard M, Gries A, Petros S. The impact of the Sepsis-3 definition on ICU admission of patients with infection. Scand J Trauma Resusc Emerg Med. 2019 Nov 4; **27**(1): 98. doi: 10.1186/s13049-019-0680-9.
4. Haque M, Sartelli M, McKimm J, Bakar MA. Health care-associated infections - an overview. Infect Drug Resist. 2018 Nov 15; **11**: 2321-33. doi: 10.2147/IDR.S177247.
5. Agodi A, Barchitta M, Auxilia F, et al. SPIN-UTI network Epidemiology of intensive care unitacquired sepsis in Italy: results of the SPIN-UTI network. Ann Ig. 2018 Sep-Oct; **30**(Suppl. 2): 15-21. doi: 10.7416/ai.2018.2247.
6. Lanini S, Jarvis WR, Nicastri E, et al; INF-NOS study group. Healthcare-associated infection in Italy: annual point-prevalence surveys, 20022004. Infect Control Hosp Epidemiol. 2009 Jul; **30**(7): 659-65. doi: 10.1086/597596.
7. Yealy DM, Kellum JA, Huang DT, et al; ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. N

Engl J Med. 2014 May; **370**(18): 1683-93. doi: 10.1056/NEJMoa1401602. Epub 2014 Mar 18.

1. Peake SL, Delaney A, Bailey M, et al; ARISE Investigators; ANZICS Clinical Trials Group. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014 Oct 16; **371**(16): 1496-506. doi: 10.1056/NEJMoa1404380. Epub 2014 Oct 1.
2. Mouncey PR, Osborn TM, Power GS, et al; ProMISe Trial Investigators. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015 Apr 2; **372**(14): 1301-11. doi: 10.1056/NEJMoa1500896. Epub 2015 Mar 17.
3. Coburn B, Morris AM, Tomlinson, Detsky AS. Does this adult patient with suspected bacteremia require blood culture? JAMA. 2012 Aug 1; **308**(5): 502-11. doi: 10.1001/jama.2012.8262.
4. Li Y, Guo J, Yang H, Li H, Shen Y, Zhang D. Comparison of culture-negative and culturepositive sepsis or septic shock: a systematic review and meta-analysis. Crit Care. 2021 May 8; **25**(1): 167. doi: 10.1186/s13054-021-03592-8.
5. Rohde JM, Odden AJ, Bonham C, et al. The epidemiology of acute organ system dysfunction from severe sepsis outside of the intensive care unit. J Hosp Med. 2013 May; **8**(5): 243-7. doi: 10.1002/jhm.2012. Epub 2013 Feb 8.
6. Kang CI, Song JH, Chung DR, et al. Risk factors and pathogenic significance of severe sepsis and septic shock in 2286 patients with gram-negative bacteremia. J Infect. 2011 Jan; **62**(1): 26-33. doi: 10.1016/j.jinf.2010.10.010. Epub 2010 Nov 4.
7. Maskarinec SA, Park LP, Ruffin F, et al. Positive Follow-up Blood cultures identify high mortality risk among patients with Gram negative bacteremia. Clin Microbiol Infect. 2020 Jul; **26**(7): 904-10. doi: 10.1016/j.cmi.2020.01.025. Epub 2020 Feb 28.
8. Vardakas KZ, Rafailidis PI, Konstantelias AA, Falagas ME. Predictors of mortality in patients with infections due to multi-drug resistant Gram negative bacteria: the study, the patient, the bug or the drug? J Infect. 2013 May; **66**(5): 401-14.

doi: 10.1016/j.jinf.2012.10.028. Epub 2012 Nov 6.

1. Busani S, Serafini G, Mantovani E, et al. Mortality in patients with septic shock by multidrug resistant bacteria: risk factors and impact of sepsis treatments. J Intensive Care Med. 2019 Jan; **34**(1): 48-54. doi: 10.1177/0885066616688165. Epub 2017 Jan 18.
2. Blot S, Vandewoude K, De Bacquer D, Colardyn F. Nosocomial bacteremia caused by antibioticresistant gram-negative bacteria in critically ill patients: clinical outcome and length of hospitalization. Clin Infect Dis. 2002 Jun 15; **34**(12): 1600-6. doi: 10.1086/340616. Epub 2002 May 23.
3. Santoro A, Franceschini E, Meschiari M, et al. Epidemiology and risk factors associated with mortality in consecutive patients with bacterial bloodstream infection: impact of MDR and XDR bacteria. Open Forum Infect Dis. 2020 Sep 30; **7**(11): ofaa461. doi: 10.1093/ofid/ofaa461.
4. Rannikko J, Syrjänen J, Seiskari T, Aittoniemi J, Huttunen R. Sepsis-related mortality in 497 cases with blood culture-positive sepsis in an emergency department. Int J Infect Dis. 2017 May; **58**: 52-7. doi: 10.1016/j.ijid.2017.03.005.

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