

Epidemiology of intensive care unit-acquired sepsis in Italy: results of the SPIN-UTI network

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Key words: Healthcare-associated infections, surveillance, sepsis, mortality

Parole chiave: Infezioni correlate all'assistenza, sorveglianza, sepsi, mortalità

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Abstract

Background. Sepsis is the major cause of mortality from any infectious disease worldwide. Sepsis may be the result of a healthcare associated infection (HAI): the most frequent adverse events during care delivery especially in Intensive Care Units (ICUs). The main aim of the present study was to describe the epidemiology of ICU-acquired sepsis and related outcomes among patients enrolled in the framework of the Italian Nosocomial Infections Surveillance in ICUs - SPIN-UTI project.

Study design. Prospective multicenter study.

Methods. The SPIN-UTI network adopted the European protocols for patient-based HAI surveillance.

Results. During the five editions of the SPIN-UTI project, from 2008 to 2017, 47.0% of HAIs has led to sepsis in 832 patients. Overall, 57.0% episodes were classified as sepsis, 20.5% as severe sepsis and 22.5% as septic shock. The most common isolated microorganisms from sepsis episodes were *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The case fatality rate increased with the severity of sepsis and the mean length of ICU-stay was significantly higher in patients with ICU-acquired sepsis than in patients without.

Conclusions. Our study provides evidence that ICU-acquired sepsis occurs frequently in Italian ICU patients and is associated with a high case fatality rate and increased length of stay. However, in order to explain these findings further analyses are needed in this population of ICU patients.

Introduction

Sepsis, a life-threatening organ dysfunction due to a dysregulated host response to an infection (1), is the major cause of mortality from any infectious disease worldwide (2). The global epidemiological burden of sepsis is difficult to ascertain, however, estimates report that it affects every year more than 30 million people worldwide, leading to 6 million deaths (<http://www.who.int/sepsis/en/>). Unfortunately, partly due to the ageing population, the increased use of immunosuppressive drugs and antibiotic resistance, the incidence of sepsis continues to rise (3). Around 70% of sepsis cases are community-acquired (4), but sepsis may also be the result of a healthcare associated infection (HAI): the most frequent adverse events during care delivery. In Europe, about 80,000 hospitalized patients are estimated to have at least one HAI on any given day (5) and in high-income countries about 30% of patients in Intensive Care Units (ICUs) have at least one such infection (6). Particularly, in Europe, among patients staying in an ICU for more than two days, 8.0% presented

with at least one HAI (7). Approximately two to ten percent of hospitalized patients and twenty to fifty percent of critically ill patients will develop at least one episode of sepsis during their admission (8-10). Notably, it has been reported that median costs of hospitalization, median length of hospitalization and of ICU stay and hospital mortality were higher for hospital-acquired sepsis than for community acquired sepsis (11). Thus, the World Health Organization (WHO) response to sepsis includes efforts to prevent HAIs (6), especially in ICUs.

The main aim of the present study was to describe the epidemiology of ICU-acquired sepsis and related outcomes among patients enrolled in the framework of the Italian Nosocomial Infections Surveillance in ICUs - SPIN-UTI project.

Methods

Study design

The present study was conducted in the framework of the SPIN-UTI project, established in Italy in 2005 by the Italian Study Group of Hospital Hygiene (GISIO)

of the Italian Society of Hygiene, Preventive Medicine and Public Health (SIItI) (12-15). The SPIN-UTI project has adopted a protocol based on that from the Hospitals in Europe Link for Infection Control through Surveillance (HELICS) network (16), subsequently updated in accordance with the European Centre for Disease Control and Prevention (ECDC) HAIICU protocol (17). A validation study on the SPIN-UTI surveillance data was also performed to determine the sensitivity, specificity, and positive and negative predictive values of HAI data (18). Hospital participation was voluntary and results were handled confidentially. Patients were prospectively included, and all data were collected for each patient staying longer than two days in the ICU. Using a web-based data collection procedure by four electronic data forms, data regarding characteristics of Hospitals and ICUs, patients, infections and associated microorganisms were collected (12, 13). Since 2006 at present, six editions of the project have been conducted. Types of infection under surveillance were: pneumonia, bloodstream infections (BSIs), central venous catheter-related bloodstream infections (CRIs) and urinary tract infections (UTIs). The indicators obtained from surveillance included cumulative incidence and incidence density. Starting from 2008, surveillance of ICU-acquired sepsis has been added in the SPIN-UTI protocol, as severity of HAIs, using the definition of sepsis of the Consensus Conference American College of Chest Physicians/Society of Critical Care Medicine (19). Thus, in the present study, results of the last five editions of the SPIN-UTI project, from 2008 to 2017, have been included. Case fatality rate was computed as the proportion of patients who die of sepsis among all individuals diagnosed with sepsis during the study period. Mortality rate was calculated by dividing the number of deaths by the population at risk during the study period.

Institutional Ethics Committee clearance was obtained to analyze anonymously the data.

Statistical analyses

Statistical analyses were performed using the SPSS software (version 22.0, Armonk, NY: IBM Corp). Descriptive statistics were used to characterize the population using frequencies, means \pm standard deviations (SDs), median values and interquartile ranges (IQRs). Categorical variables were compared using the chi square-test, and continuous variables by Student's t-test. $P \leq 0.05$ was considered significant.

Results

During the five editions of the SPIN-UTI project, from 2008 to 2017, a total of 13,512 patients admitted to 76 Italian ICUs of 55 Hospitals were enrolled for a total of 142,190 patient-days. A summary of patients' characteristics is shown in Table 1.

A total of 1,933 patients acquired at least one HAI (14.3 per 100 patients) and 3072 HAIs were acquired during ICU stay, thus, the cumulative incidence of ICU-acquired infection was 22.7 per 100 patients and the incidence density was 21.6 per 1000 patient-days.

Data on severity of ICU-acquired infections were reported for 2795 HAIs of which 47.0% (N = 1314) were followed by sepsis in 832 patients (6.1% of all patients and 43% of infected patients). Data on patients with ICU-acquired sepsis were recorded and a summary of characteristics is shown in Table 1.

The cumulative incidence of ICU-acquired sepsis was 9.7 per 100 patients and the incidence density was 9.2 per 1000 patient-days. Overall, 57.0% of episodes was classified as sepsis, 20.5% as severe sepsis and 22.5% as septic shock. The most common type of infection leading to

Table 1 - Main characteristics of patients

Variables*	All patients	Patients with ICU-acquired sepsis
Patients	13,512	832
Males	8,690 (61.8)	509 (61.9)
Mean age in years \pm SD	66 \pm 16.3	63.7 \pm 16.6
Median age in years (IQR)	69 (58-78)	68 (55-76)
Median SAPS II score at admission (IQR)	39 (27-54)	47 (35-59)
Trauma	490 (3.7)	68 (8.3)
Impaired immunity	740 (5.5)	78 (9.5)
Administration of antibiotics within 48 hours of admission	8,351 (62.6)	654 (79.5)
Type of ICU admission		
- Medical	7,083 (52.9)	450 (54.7)
- Scheduled surgery	3,475 (26.0)	100 (12.2)
- Unscheduled surgery	2,833 (21.1)	273 (33.2)
Origin of patients		
- Other ward of this/other hospital	9,073 (68.2)	589 (71.8)
- Another ICU	304 (2.3)	36 (4.4)
- Community (home)	3,798 (28.4)	186 (22.7)
- Long-term care facility	142 (1.1)	9 (1.1)
Median length of stay in ICU in days (IQR)	6 (4-11)	25 (15-40)
Mortality/Case fatality rate	2,556 (19.2)	370 (46.0)

* Categorical variables are reported as number and %.

Abbreviations: ICU, intensive care unit; IQR, interquartile range; SAPS, Simplified Acute Physiology Score; SD, standard deviation.

sepsis was pneumonia (45.3%), followed by BSIs (31.5%), CRIs (14.8%) and UTIs (8.4%). Overall, the most common isolated microorganisms from sepsis episodes were *Acinetobacter baumannii*, *Klebsiella pneumoniae* (15.9%, each) and *Pseudomonas aeruginosa* (13.1%).

Overall ICU mortality was 19.2%. Particularly, mortality was significantly higher in patients with HAI than in patients without HAI (31.4% versus 16.2%; $p < 0.001$; RR: 3.091; CI95%: 2.781-3.435). Among infected patients, case fatality rate was 46.0% in patients with ICU-acquired sepsis and 31.4% in infected patients without sepsis ($p < 0.01$; RR: 1.466; CI95%: 1.304-1.649). The case fatality rate increased with the severity of sepsis, from 36.4% in patients with sepsis, 45.3% in patients with severe sepsis, to 69.3% in patients with septic

shock ($p < 0.01$). Mean length of ICU-stay was significantly higher in patients with ICU-acquired sepsis than in patients without ICU-acquired sepsis (31.2 versus 24.3 days; $p < 0.01$).

Discussion and conclusions

In 2017, the Seventieth World Health Assembly underlined the lack of integrated approaches for the prevention and clinical management of sepsis and thus highlighted the need to improve strategies for the prevention of infections and sepsis. Infections which may lead to sepsis can often be prevented through appropriate hand hygiene and other infection prevention and control best practices, also in the healthcare setting where forms of septicaemia associated with

HAIs are often severe and hard to control (20).

Many of previous studies have described the epidemiology of sepsis worldwide, but the majority of them have not differentiated community-acquired sepsis (sepsis presenting on hospital admission) from healthcare-associated sepsis (sepsis with prior healthcare exposures) or hospital-acquired sepsis (cases developing at a later point of hospitalization, as ICU-acquired sepsis) (11). Particularly, although some study reported the frequency of sepsis secondary to HAIs, i.e. healthcare-associated sepsis (10, 21-23), data regarding ICU-acquired sepsis are lacking. Our study, conducted using data collected during a ten years period within the Italian SPIN-UTI network, offers epidemiologic evidences to deepen our understanding of the Italian burden of ICU-acquired sepsis.

In our study 832 patients (6.2% of those admitted) developed sepsis during ICU-stay, similar frequency (5.6%) was reported in a previous Italian study (8). In the European Sepsis Occurrence in Acutely Ill Patients (SOAP) study conducted to report the frequency of sepsis in European ICUs and to identify various etiological, diagnostic, therapeutic, and prognostic factors, it has been reported that during ICU-stay sepsis was acquired by 8.8% of patients, although variation in participating countries was observed (22). The present study confirms previous results that the site of infection more common was the respiratory one (8, 10, 22) and that Gram-negative bacilli predominated (10; 24-26). Particularly, *A. baumannii*, *K. pneumoniae* and *P. aeruginosa* accounted for 44.9% of reported isolates from sepsis episodes. Notably, as previously reported (27-30), these microorganisms are often multidrug resistant and associated with hospital outbreaks, in a way that the effective control and treatment of HAIs caused by these pathogens represent a significant challenge for clinicians and infection control professionals.

Sepsis is a disease with a high risk of mortality (31). In our study a high case fatality rate was reported with 46% of patients with ICU-acquired sepsis dying in the ICU, rising to 69.3% in patients with septic shock. This finding confirms previous evidences that death rates increase stepwise according to sepsis severity (22, 32). Furthermore, in patients with ICU-acquired sepsis case fatality rate was higher than in infected patients without sepsis and in patients without HAIs (46.0%, 31.4% and 16.2%, respectively), confirming previous results (8, 10, 22). Similarly, the length of ICU-stay was significantly higher in patients with ICU-acquired sepsis than in patients without sepsis (8).

Our study provides evidence that ICU-acquired sepsis occurs frequently in Italian ICU patients and is associated with a high case fatality rate and increased length of ICU-stay. However, in order to explain these findings further analyses are needed to investigate determinants of higher case fatality rate and of increased length of ICU-stay in this population of ICU patients in order to develop preventive interventions, optimal treatment strategies and to reduce mortality. Particularly, in the framework of sepsis as a public health problem, strategies should be designed for the prevention of infection and/or of sepsis events, identifying the characteristics of individuals at high risk. Furthermore, the early recognition and treatment of sepsis together with interventions targeting the long-term consequences of sepsis are essential (33). Finally, more specific innovative approaches to prediction and treatment of sepsis should be explored (2), also considering the personalized medicine approach and the use of biomarkers to help stratify patients based on risk profiles to predict adverse clinical outcomes (34).

Acknowledgements

The Authors wish to thank all colleagues from the GI-SIO-SItI for their close co-operation during surveillance

studies, and all physicians and nurses in the participating hospitals for providing surveillance data. The Authors have no conflicts of interest to declare.

Riassunto

Epidemiologia delle sepsi acquisite in terapia intensiva in Italia: risultati del network SPIN-UTI

Introduzione. La sepsi rappresenta la principale causa di morte a seguito di una malattia infettiva in tutto il mondo. La sepsi può essere il risultato di un'Infezione Correlata all'Assistenza (ICA) specialmente nelle Unità di Terapia Intensiva (UTI). L'obiettivo principale del presente studio era di descrivere l'epidemiologia della sepsi e i relativi esiti nei pazienti inclusi nel Progetto Sorveglianza Prospettica delle Infezioni Nosocomiali nelle UTI - SPIN-UTI del GISIO-SiI.

Disegno dello studio. Studio prospettico multicentrico.

Metodi. La rete SPIN-UTI ha adottato i protocolli europei per la sorveglianza delle ICA basata sul paziente.

Risultati. I risultati delle cinque edizioni del progetto SPIN-UTI, dal 2008 al 2017, dimostrano che il 47,0% delle ICA hanno dato origine a sepsi in 832 pazienti. Complessivamente, il 57,0% degli episodi è stato classificato come sepsi, il 20,5% come sepsi grave e il 22,5% come shock settico. I microrganismi più frequentemente associati agli episodi di sepsi erano *Acinetobacter baumannii*, *Klebsiella pneumoniae* e *Pseudomonas aeruginosa*. La letalità aumentava con la gravità della sepsi e la durata media della degenza in terapia intensiva era significativamente più alta nei pazienti con sepsi rispetto ai pazienti senza sepsi.

Conclusioni. Lo studio fornisce evidenze che la sepsi acquisita nelle UTI si verifica frequentemente nelle UTI italiane ed è associata a letalità e all'allungamento della durata della degenza. Tuttavia, al fine di spiegare questi risultati, sono necessarie ulteriori analisi per individuare i determinanti degli esiti avversi nei pazienti ricoverati in terapia intensiva.

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