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THE KEY ROLE OF THE PATHOLOGIST IN SEPSIS-RELATED RISK AND CLAIMS MANAGEMENT OF TERTIARY HOSPITALS

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ABSTRACT

Sepsis is one of the leading causes of death even in the tertiary hospitals of Western Countries and sepsis-related in-hospital mortality contributes to define hospital performance and quality of care. A better understanding of its epidemiological and pathological characteristics seems the key to tailor public health interventions aimed at reducing its incidence, morbidity and mortality. A retrospective analysis of 109 autoptic cases of inpatients that acquired sepsis in a tertiary hospital was performed. In particular, we identified and analysed the recurrent anamnestic/clinical factors and histopathological features. The most common continuous foci were due to respiratory infections. Subendocardial myocardial ischaemia was the clinical cause of death in 56.8% of the study population. An inflammatory infiltrate was identified in specimens of the lung (28.4%), liver (28%), heart (23.5%) and kidneys (15%). Common findings were arteriosclerosis and atherosclerosis (57%), steatosis (24.5%), diffluent spleen (18%) and colliquation of adrenal glands (16.6%). The comorbidities and the autoptic features founded are consistent with the previous evidences in sepsis field. Clinical autopsy is certainly a useful tool to collect data on sepsis, but we did not find any feature that can be considered specific or sensitive for the diagnosis of sepsis. More efforts should be made in the direction of a multidisciplinary approach to in-hospital sepsis autopsies to grant pathologists a key role in the management of claims and clinical risk.

1. Introduction

Sepsis is a complex process with a broad spectrum of clinical severity that represents a major public health problem in terms of morbidity, mortality and economical cost.

This syndrome can cause a vast range of adverse clinical outcomes, due to negative fall-outs of the body's systemic response to an infection. In other words, sepsis is characterized by single or multiple organ dysfunction or failure, eventually leading to death (1).

In 2016 it was described as a life-threatening organ dysfunction caused by a dysregulated host response to infection (2).

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However, since in scientific literature the definitions are highly heterogeneous, it is difficult to compare the incidence rates reported by different authors. The latest estimates in the United States and in Europe range between 0.4/1000 and 1/1000 (3,4).

From an epidemiological point of view, many studies showed a substantial increase in the incidence of sepsis in recent decades, while, in the same period of time, its mortality dropped (5).

However, despite advances in the clinical management of septic patients, sepsis is still the second cause of death among inpatients of non-coronary ICUs (6). A recent meta-analysis (considering data collected from 1979 to 2015), identified an in-hospital mortality of 17% for sepsis and 26% for severe sepsis. Through an extrapolation of data from high-income countries, it has been suggested that 31.5 million cases of sepsis occur globally each year. Of these cases, 19.4 million corresponded to severe sepsis, with potentially 5.3 million deaths per year (7). Missed/mis-diagnoses and delay in treatment are major determinants of in-hospital mortality. These factors are influenced by many variables, like: the type and the virulence of the pathogens, the general health status and the efficiency of the immune system of the patient, and the sepsis clinical presentation.

This kind of considerations is relevant in the field of public health, since in-hospital mortality is considered a strong indicator of quality of care and hospital performance.

As said, sepsis is a leading problem also from an economical perspective: in 2011 the annual cost of hospital care for patients with sepsis accounted for more than $20 billion (5.2% of total US healthcare costs)(8).

Considering the autoptic aspects, the diagnosis of sepsis is often very challenging. There are no precise algorithmsfor post-mortem diagnosis but the collection of clinical data and sterile samples for microbiological tests are generally considered essential (9). In this field, a critical aspect of autopsies is to obtain clinical data and sufficient samples to perform diagnostic testing. Microbiological results are not always reliable: blood cultures can be contaminated during sample collection or due to bacterial translocation, and antibiotic therapy can lead to negative bacteraemia (10). In fact, negative cultures occur in the 28%-49% of septic cases and are associated with greater acute organ dysfunction and higher mortality (10,11).

From a medico-legal point of view, having valid and precise criteria for the post-mortem diagnosis of sepsis is very important also because of the increase of compensation claims for healthcare-associated infections and sepsis (12).

A sample of inpatients died of sepsis to identify anamnestic and clinical predictors of prognosis and the recurrent histopathological features were analyzed. Collecting and sharing this kind of data can contribute to implement the clinical and autoptic diagnostic algorithms. Moreover, it can help to tailor risk management programmes to reduce hospital mortality and thus improve the hospital performance.

2. Material and methods

An observational, retrospective study was conducted to analyse the main epidemiological characteristics and post-mortem alterations of hospital-acquired sepsis. The study sample was composed by cases present in the hospital database and in the clinical autopsies register of the Institute of Pathology of an Italian tertiary hospital. Considering only those died from hospital-acquired sepsis or septic shock between 2012 and 2016, 139 cases were found.

Excluding the 30 paediatric cases, we obtained a sample of 109 adults (aged ≥18years). All the final pathology reports were reviewed in detail. Data on age, sex, comorbidities, hospital units where death occurred, sources of infections and autoptic findings were stored and analysed. The study conformed to the principles outlined in Declaration of Helsinki.

3. Results

The largest proportion of patients with nosocomial sepsis came from the critical care units (intensive care, emergency department and coronary intensive care unit) (75.8%), followed by those from surgical and medical units (Figure 1).

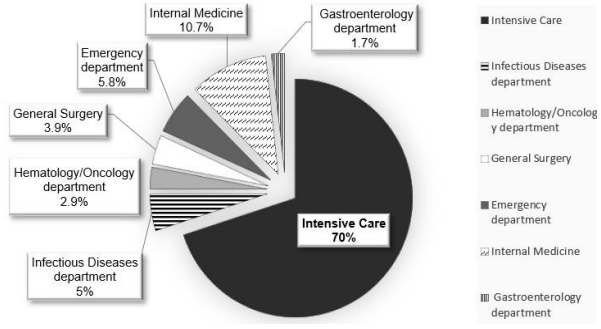
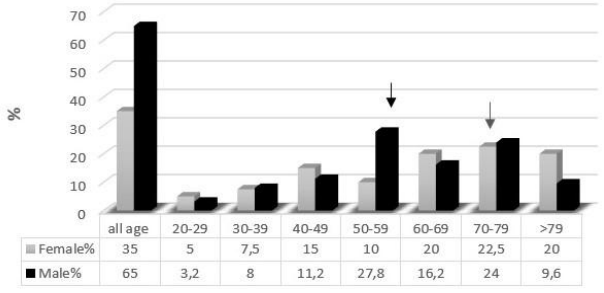


Figure 1. Discharge departments of patients with nosocomial sepsis enrolled in the study

Regarding gender, males were more likely to develop sepsis than females (65% vs 35%). The average age of the inpatients that died from 2012 to 2016 was 61.5 years. Regarding age, female patients were older than males: 68% of male subjects were aged between 50 and 80 years, whereas 62.5% of females were aged between 60 and >79 years (Figure 2).



	all age	20-29	30-39	40-49	50-59	60-69	70-79	>79
Female%	35	5	7,5	15	10	20	22,5	20
Male%	65	3,2	8	11,2	27,8	16,2	24	9,6

Figure 2. Age and gender of patients with nosocomial sepsis enrolled in the study

Information regarding comorbidities and source of infection were obtained from medical reports and pathology reports review. Regarding comorbidities that could affect the negative outcomes of patients, we found neoplastic diseases in the 35% of cases, of which 5% were metastatic. A high prevalence of arteriosclerosis and atherosclerosis (57%) was observed.

Clinical conditions that negatively affected the outcome of the analysed cases were: transplant (of liver or kidney), prosthetic heart valves, dialysis, AIDS, obesity and splenectomy.

Approximately 12% of the sample had disseminated intravascular coagulation (DIC).

During the study period, 35% of sepsis cases were due to respiratory infections (pneumonia/bronchopneumonia), 26.3% to genitourinary infections (cystitis and pyelonephritis), 18.4% to a gastrointestinal source (peritonitis, cholangitis, and hepatic abscess), 14% to a heart infection (pericarditis, myocarditis, and endocarditis), 5.1% to the central nervous system (encephalitis) and 1.5% to other sources (skin/soft tissue infection) (Figure 3).

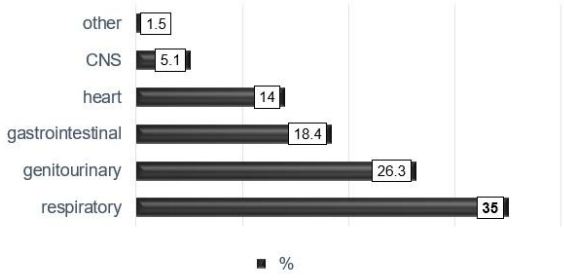


Figure 3. Source of infection of patients with nosocomial sepsis enrolled in the study

Males were more likely to have respiratory infections than women (32% vs. 26.7%), whereas females more commonly developed sepsis originating from genitourinary sources. Bacteria that were isolated at microbiological testing are reported in Table 1. As displayed, the isolated bacteria were mainly gram-negative, with the exception of those found in respiratory tract (that were chiefly gram-positive).

ISOLATED BACTERIA	BLOOD	U.T.	R.T.	S.S.T.	G.I.T.	C.V.C.-U.C.
Gram-negative Bacteria	17.5%	7.9%	37.7%	14.0%	7.0%	15.8%
Gram-positive Bacteria	12.3%	6.8%	57.5%	11.0%	4.0%	8.2%

Table 1. Isolated bacteria (bacteria were isolated in blood, urinary tract (U.T.), respiratory tract (R.T.), skin and soft tissues (S.S.T.), gastro-intestinal tract (G.I.T.), central venous catheter and urinary catheter (C.V.C.-U.C.).

Multiple macroscopic and microscopic alterations were identified in most of the analysed sample, with greater frequency in cardiovascular system, respiratory tract and abdominal organs. Changes were not observed/indicated in 86 (78%) reports in the central nervous system and 30% in the kidneys/urinary tract.

The main pathological findings were (divided on the basis of the anatomical localization) and reported in Table 2-4:

- cardiovascular system: subendocardial myocardial ischaemia (56.8%), atherosclerosis (57%), hydropic degeneration/interstitial oedema (24.7%) and sclerosis/interstitial fibrosis (19%) (Table 2);
- lungs: pulmonary oedema/congestion (69.6%), intra-alveolar haemorrhage (15.6%) and desquamative alveolitis (12%) (Table 2);
- abdomen: hepatic congestion (37.2%), gastroduodenal ulcer (27.4%) and diffluent spleen (18%) (Table 3);
- kidneys and urinary tract: kidney swelling/oedema (30.3%) and sclerosis (12%) (Table 4);
- central nervous system: brain oedema/congestion (34.3%%) and intracerebral haemorrhage (16.6%) (Table 4).

Heart Diseases		%	Lung Diseases	%
Myocardial Ischaemia Subendocardial		56.8	*Emphysema*	8
Sclerosis/Interstitial Fibrosis		19	*Pulmonary Oedema/Congestion*	69.6
Interstitial Oedema		14.7	*Atelectasis*	4
Lymphocytic Infiltrate		23.5	*Pneumonia/ Bronchopneumonia*	42
Heart Infections (19.6%)	*Pericarditis*	8.8	*Inflammatory Infiltrate*	28.4
	Myocarditis	5.8	*Pleuritis*	5
	Endocarditis	4.8	*Pulmonary Infarction*	0.9
Arteriosclerosis/Atherosclerosis		57	*Desquamative Alveolitis*	12
Hydropic Degeneration		10	*Fibrosis*	0.9
Myocytolysis - "Wavy Fibres"		26	*Intra-Alveolar Haemorrhage*	15.6
Others *Amyloidosis* *Blood extravasation* *Arteritis*		n=2 n=4 n=1	*Others* *ARDS* *Thromboembolism*	n=1 n=3
No Alterations		8.5	*No Alterations*	5.8

Table 2 - Heart and Lung diseases observed in patients with nosocomial sepsis enrolled in the study

Gastrointestinal diseases		%
Liver	Steatosis	24.5
	Hepatic Abscess	1.2
	Inflammatory Infiltrate	28
	Congestion	37.2
	Necrosis	5.8
	Kupffer Cell Hyperplasia	7.6
	Intrahepatic Cholestasis	7
	Cholangitis	**8.8**
	Hepatic Cirrhosis	7.8
	Hepatic Ischaemia	4
	No Alterations	6.8
Gastrointestinal tract	Peritonitis	**12.7**
	Gastrointestinal Haemorrhage	9
	Gastroduodenal Ulcer	27.4
	Ascites	5
	Erosive Oesophagitis	3.9
	Disepithelialization	2.9
	Haemorrhagic Infarction	3
	Other Omental infarction Diverticulitis	 n=2 n=2
Pancreas	Necrotizing Pancreatitis	7.8
	Oedema	3
	Fibrosis	3.9
	Pancreatitis	3
Spleen	Splenomegaly	7
	Splenic Infarction	8.8
	Diffluent Spleen	**18**
	Sclerosis	0.9
	Congestion/Oedema	22
Adrenal glands	Inflammatory Infiltrate	2.6
	Colliquation	16.6
	Hyperplasia	3

Table 3 - Gastrointestinal diseases observed in patients with nosocomial sepsis enrolled in the study

Kidney/Urinary tract Diseases	%	Central Nervous System Diseases	%
Cystitis	16.6	*Brain Oedema/Congestion*	34.3
Kidney Ischaemia	0.8	*Intracerebral Haemorrhage*	16.6
Kidney Swelling/Oedema	30.3	*Encephalitis*	10.7
Pyelonephritis	14.7	*Sclerosis*	3
Endothelial Cell Injury	5.3	*Reduction in Glial Cells*	1.8
Sclerosis	12		
Blood Extravasation	7		
Inflammatory Infiltrate	15		
Necrosis	3	*Others*	
Serous Cyst	11.6	*Amyloidosis*	n=1
Others *Amyloidosis*	n=1	*Cerebral sinus venous thrombosi*	n=3
No Alterations	34.3	*No Alterations*	79

Table 4 - Kidney/urinary tract and Central Nervous system diseases observed in patients with nosocomial sepsis enrolled in the study

4. Discussion

Consistently with previous evidences, data reported that the largest proportion of deaths from nosocomial sepsis occurred in critical care units (75.8%).

A large observational study (*SOAP* study) documented the high frequency of sepsis in ICUs; this analysis involved 198 intensive care units in 24 European countries. Sepsis was present on admission in 777 patients (66%), was developed on the second day of admission in 121 patients (10.3%) and was acquired during the ICU stay in 279 patients (23.7%) (13).

The analysis showed relevant gender disparities, with a clear prevalence of sepsis in males (65% vs. 35%). Data in the literature regarding the correlation between gender and mortality in sepsis are conflicting(14,15).

In the SOAP study, patients with ICU-acquired sepsis were more likely to be male (67.8 vs. 61%) (13).

Sakr et al. investigated the influence of gender on sepsis mortality in a large cohort of ICU patients in Italy; the results showed a higher percentage of males (63.5%), but female gender was independently associated with a higher risk of death (16).

In our sample the median age was between 60 and 70 years and women were older than men (aged >70 years: 42.5% vs. 33%).

Several studies underlined a direct association between age and mortality risk in sepsis. In 2006, Martin et al. conducted a longitudinal observational study to evaluate the correlation between age and outcome of adult sepsis. From the analysis of 10,422,301 sepsis patients, it was shown that case-fatality rates increased linearly with age and that elderly patients (≥65 years old) died earlier during hospitalization (17).Several risk factors determine a strong relationship between sepsis and advanced age. In facts, immunosenescence predisposes the elderly to an increased rate of sepsis. Moreover, T- and B-cell dysfunction and an abnormal cytokine response have been demonstrated in the elderly(18,19). Chronic comorbidities, such as cancer, endocrine disorders (hypoadrenalism, hypothyroidism and hypogonadism diabetes), obesity or malnutrition, the use of invasive devices and factors associated with institutionalization increase the risk of infections and sepsis in elderly patients (20,21).

Comorbidities

In our study, the comorbidities that increased susceptibility to infections were transplant (liver or kidney), prosthetic heart valves, dialysis (chronic kidney disease), AIDS and obesity.

The most prevalent comorbidities were arteriosclerosis and atherosclerosis (57%). The 35% of the sample had cancer (metastatic in the 5% of cases).

In many studies, a relationship between sepsis and these comorbidities has been demonstrated. Cancer is one of the most frequent comorbidities among patients with severe sepsis. The increased susceptibility to infections in oncology patients is due to multiple factors, such as chemotherapy, radiotherapy, invasive procedures and immunodepression (caused by corticosteroids or syndromes like AIDS)(22-24). Regarding AIDS, several authors showed that, after the introduction of anti-retroviral therapy, the majority of HIV-positive patients who are hospitalized or admitted to the intensive care unit die of non-AIDS-related illness, in particular of sepsis (25-27).

Several authors demonstrated that obesity can increase the susceptibility to various types of infections, including postoperative and, more generally, nosocomial infections (28,29). Obese patients suffer from chronic diseases more frequently than no obese patients, especially diabetes mellitus and chronic obstructive pulmonary disease, which are additional risk factors for the onset of sepsis (30,31).

Chronic kidney disease is characterized by uraemia, leukocyte dysfunction, hyper-production of proinflammatory cytokines, and platelet dysfunction (32,33). Many studies have confirmed that chronic kidney disease is an independent risk factor for mortality in patients with sepsis (34,35).

A relevant finding of our study is that 57% of patients suffered from arteriosclerosis and atherosclerosis. In facts, recent studies suggested that a pro-inflammatory state occurs in cardiovascular disease, as well as in acute pancreatitis, sepsis or cancer, which could determine a dysfunctional response to infections (36, 37). Consistently with this, Lemay et al. found that peripheral vascular disease was an independent risk factor for mortality in patients with severe sepsis (38).

Sources of infection

In septic cases the localization of infection source is pivotal, because it influences the selection of the optimal antibiotical therapy.

In our study, during histological postmortem examination, the septic foci were mainly detected in the respiratory tract (38%), genitourinary tract (26.3%) and abdomen (18.4%).

Vincent et al. showed that in ICU-acquired sepsis, the site of infection was more commonly respiratory (79.6%), catheter-related (13.6%) and urinary (17.9%) and less commonly abdominal (10.8%) (13).

These results are consistent with the high frequency of nosocomial infections in the ICU due to the use of mechanical ventilation, CVC and urinary catheters. In mechanically ventilated patients admitted to an intensive-care unit, as many as 7–41% may develop pneumonia (39). In accordance with our results, the frequency of abdominal infections reported in the literature is within the range of 9 to 25% (4,40).

Previous studies found that lungs were the most common site of infection(4). Alberti et al. showed that the lungs represent the source of infection in the 62% of cases, followed by intra-abdominal infections (15%)(41). Quenot et al, in a prospective, multicentre, observational cohort study, analysed 1495 patients with sepsis and confirmed that the primary site of infection at the origin of septic shock was the respiratory tract (53.6%) (42).

Finally, a majority of gram-negative bacteria were isolated in the data reported. This evidence is in concordance with the recent epidemiological data on sepsis: despite gram-positive bacteria are now the most common cause of sepsis, gram-negative bacteria are associated with higher mortality (6).

Autopsy findings

In our study, post-mortem examination showed that more than half of the patients succumbing to sepsis and septic shock had a cardiovascular disease. Subendocardial myocardial ischaemia was the clinical cause of death in 56.8% of the study population.

The causes of myocardial dysfunction in sepsis are not clearly understood. Smeding et al. suggested the possible mechanisms that causealterations of the heart during sepsis. In particular, according to the authors, myocardial infiltration by immune cells and oedema cause changes in blood flow and thus hypoxia-mediated mitochondrial injury. Moreover, the mitochondrial damage can be caused by the increased levels of reactive oxygen species and TNF-α (43).

We also found inflammatory infiltrates in lungs (28.4%), liver (28%), heart (23.5%) and kidney (15%) specimens. Other findings were steatosis in 24.5% of patients, diffluent spleen in 18% of patients and colliquation of adrenal glands in 16.6% of patients.

Koskinaset al. investigated pathologic changes in the liver of septic patients who died in an intensive care unit. Histology showed portal inflammation in 73.3% of liver biopsies, centrilobular necrosis in 80%, lobular inflammation in 66.7%. The bacterial toxins and sepsis can cause macrovesicular or microvesicular steatosis. However, portal inflammation could not be directly related to sepsis, since it has been associated with prolonged hospitalization, probably because of prolonged exposure to treatment medication (44).

Regarding the splenic alterations, in the past the histological finding of a diffluent spleen – the so-called "septic spleen" - was considered indicative of sepsis (45,46).

Recent studies showed that correlation between acute splenitis and a septic state is no significant. Furthermore, splenic congestion was found to be more likely with non septic causes of death(47). On the other side, in 2006 a Japanese research group showed that splenic volume decreased with increasing severity of sepsis (48).

Typical features in adrenal glands are lipid depletion and hyperplasia, atrophy (if prolonged steroid therapy has been given), and parenchymal haemorrhage (49).

Globally, the results of our autopsies are comparable to those reported by previous authors.

Torgersen et al. studied macroscopic post-mortem findings in 235 surgical intensive care patients with sepsis. In their study, more than half of the patients had refractory multiple organ dysfunction syndrome, and cardiovascular failure was found in 35.3% of cases. Similarly to our results, a septic focus was identified in more than 80% of the autopsies. These data confirm that in patients who died of sepsis, antibiotic treatment failed to control and eliminate the infection. The most frequent source of infection was located in the respiratory tract (pneumonia and tracheobronchitis in 70.2%), abdomen (peritonitis and intra abdominal abscesses in 32.5%), uterine/ovarian necrosis (9.8% of female patients), and pyelonephritis (6%) (50). Moreover, in a recent retrospective analysis of histopathological and microbiological correlations of autopsies, the main causes of death were sepsis with multiple organ dysfunction syndrome (70%) and cardiorespiratory failure (30%).

Instead, the most frequent autopsy findings were pneumonia, cirrhosis, and brain haemorrhage (51).

Limitations

This work has several limitations. The principle is given by the fact that the design of the study and the collection of data in only a tertiary hospital precludes the possibility to generalize the evidences obtained.

5. Conclusions

In conclusion, consistently with previous findings, several anamnestic and clinical factors that are more common among inpatients dead of sepsis were observed. In our opinion, this evidence, obtained in a tertiary hospital setting, is significant because it could support the development of risk management strategies and primary/secondary prevention interventions. As said, the goal of reducing sepsis-related in-hospital mortality is ambitious but has a direct impact on quality of care/hospital performance and thus is economically and legally convenient (52).

Improving clinical autopsy algorithms for diagnosis of sepsis is an issue of utmost importance in order to achieve this result. Our retrospective analysis shows that no macroscopic or microscopic autopsy finding can be considered neither specific nor sensitive to the diagnosis of sepsis. Sepsis results from a generalized activation and systemic expression of host's inflammatory pathway in response to infection. Therefore, the histological changes highlighted by our investigation, such as cardiac hydropic degeneration and interstitial cardiac oedema, pulmonary congestion and intra-alveolar haemorrhage, and hepatic congestion, cannot be considered specific for sepsis. In facts, these changes may be present in various clinical conditions, such as systemic inflammatory response syndrome (SIRS) or prolonged ischaemia (53-56). However, a post-mortem diagnosis of sepsis cannot be based only on microbiological cultures, since a positive result can be due to artefacts, such as contamination (bacteria introduced into the blood or organ sample when it is obtained)(57). Obviously, even solely clinical data are insufficient to obtain a diagnosis. For these reasons, some authors explored the integration of autoptic results with biochemical and immunohistochemical testing aimed at demonstrating the activation of the response to the infectious insult (58-60). In cases of suspected sepsis, a standardized multidisciplinary methodology could help to improve the diagnostic rate (with obvious medico-legal consequences), obtain a precise estimate of its incidence and give the health systems the knowledge and the tools to improve the quality of their services.

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