In Death, Truth Lies: Why Do Patients with Sepsis Die?

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Yes, they still die. Yes, we still do our best not to let them die. And no, ultimately, we do not know why they die, do we?

It is no news that, even today, sepsis is associated with high mortality. All of us who regularly practice intensive care medicine have seen our patients with sepsis die. Yet, it seems acceptable to claim that we do not know ultimately *why* these patients die. Some die despite full continuing therapeutic efforts, although others die after therapy has been withheld or withdrawn. Most patients who die with or because of sepsis, die with established multiple organ dysfunction or failure.[1–3] Although the clinical cause of death can be classified as "refractory septic shock," "multiple organ failure," or "acute circulatory failure," the actual causes and mechanisms for treatment failure and death remain mostly unidentified.

Sepsis has perplexed clinicians for centuries. One of the few breakthroughs in understanding sepsis came from the Hungarian obstetrician Ignác Semmelweiss working in Austria. He was puzzled by the high mortality rate in one of the two obstetrics clinics in Vienna 150 yr ago. Although merely 3% of mothers died from childbed fever in the second clinic, mortality was some 18% in the first clinic of obstetrics. In the first clinic, it was customary for clinicians and students alike to perform autopsies (bare-handed) before examining the mothers during labor. After his colleague Dr. Kolletschka, a professor of pathology, died from sepsis (open wound in his finger during autopsy!), Semmelweiss realized, on reading through the autopsy report, that Kolletschka's autopsy findings were identical with those of mothers dying from childbed fever.

> ". . . suddenly a thought crossed my mind: childbed fever and the death of professor kolletschka were one and the same . . . his . . . sepsis and childbed fever must originate from the same source. [the cause] was to be found in the fingers and hands of students and doctors, soiled by recent dissections . . . [and they] . . . carry those death-dealing cadavers' poisons into the genital organs of women in childbirth . . . the first principle is the absorption of the decomposed animal organic substance [by women in labor through the cadaveric particles from the hands of doctors and medical students] . . . as a result of this . . . there is . . . a change in composition of the blood."[4]

In this historical case, postmortem findings in autopsy were a key element suggesting that contaminated hands infected mothers in the first clinic. Even though Semmelweiss tested his novel hypothesis immediately and reduced the mortality in the clinic to below 2%, his discovery was only later appreciated.

In this issue of *Anesthesia & Analgesia*, Austrian investigators have addressed postmortem findings in sepsis anew: Torgersen et al.[5] report a reappraisal of the importance of postmortem investigation and findings in different organs in an attempt to elucidate mechanisms of death in patients dying with sepsis or septic shock. The authors painstakingly studied both clinical and postmortem records of all patients who died from sepsis or septic shock in their institution over a period of 10 yr. In almost 80% of the cases an unresolved infectious focus was found postmortem. Moreover, 90% of the patients with prolonged intensive care exceeding 7 days had persistent infectious foci. Only 52 of 97 autopsy-confirmed pneumonias were diagnosed during intensive care unit stay.

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Previous autopsy studies in patients dying in intensive care units, suggest that the rate in discrepancies between pre- and postmortem diagnoses is highly variable,[6–8] ranging from around 5% to 25% of diagnoses considered relevant to death; most of these are infections. Persistent or undiagnosed infections in dying patients are common. Although source control of infections should be emphasized,[9,10] it is unclear to what extent these infectious foci, many of them undiagnosed pneumonias, contributed to the deaths.

Rather than supplying the reader and clinician with new insights into mechanisms of death in sepsis, Torgersen et al. offer confirmation of previous reports on inadequate premortem diagnoses. The reader should notice, however, the large number of autopsies performed in the authors' institution, and thereby be alerted to the high credibility of the present investigation.

The authors quite correctly point out the limitations of this investigation. The uncontrolled, retrospective design of the study limits the conclusions. Furthermore, it is reasonable to assume that autolysis takes place soon after death. Thereby, some of the findings may be related to autolysis only. In addition, the macroscopic level of tissue-specific analyses clearly limits the value of the present report if the goal was to identify new mechanisms of death. The only way to overcome this problem would be to perform a prospective trial with early postmortem biopsies or autopsy comparing tissue-specific findings in septic patients to those of patients dying from other causes, such as rapidly progressing circulatory failure due to myocardial infarction. One such trial was reported just recently,[11] with the limitation of a missing "control" group. Those authors also "only" report the histopathological findings in the liver based on immediate liver biopsy after death.

In which part of the report by Torgersen et al. is the truth? Where does it lie? Is unresolved infection and inadequate source control revealed? This is obviously sad but true. We cannot follow the 2000-yr-old rule by Galenos: "Ubi Pus, Ibi Evacua." Does knowledge of the organ-specific macroscopic pathologies lead to new discoveries of mechanisms? Probably not. We can even argue that the postmortem findings lie at the organ level when time-related autolysis proceeds; we do not know if these findings are specific for sepsis. Furthermore, the functional changes of a specific organ are often greater than the macro- and microscopic findings observed in autopsy.[12] In the present retrospective trial, most of the organs were indeed examined in an attempt to uncover new mechanisms; still, many unanswered questions remain. It may well be that more information on new mechanisms could be obtained if immediate postmortem tissue samples were available for analyses.

To be provocative, one could claim that most of the postmortem autopsy studies that focus on different organs have not provided researchers or clinicians with novel information on mechanisms of death, even though attempts have been made to carefully describe all the organs in death. However, in contrast to what Semmelweis proposed almost 150 yr ago, blood and its composition have rarely if ever been considered in this context. Is it possible that the composition and flow characteristics of blood change within the elastic pipelines, to the extent that function of multiple organs is compromised? As is the case in all postmortem (sepsis) studies, blood was not examined by Torgersen et al. Although much research in sepsis has focused on circulation and mediators in the blood, the physical characteristics of the blood have been largely overlooked. This is understandable. Blood changes the minute the sample is drawn, or the minute the patient dies; hence, research on fluid mechanic/fluid dynamic behavior of blood is challenging. Ironically, Semmelweiss talks about disintegration of blood, blood poisoning by definition. The fundamental question is whether blood poisons the tissue and organs, or alternatively, is itself literally poisoned, not only by bacteria, but by other bacterial or "animal" (= human?) material/particles.

Does looking at the composition of blood seem too far-fetched? There are several arguments in favor of taking a closer look at the composition of blood in sepsis. Blood, as a non-Newtonian fluid, does not have a constant viscosity.[13,14] Blood flow can be turbulent,[15] and non-Newtonian fluids with turbulent flow properties experience drag reduction (Toms' effect[16]) (reviewed in Ref. 17). Minute (parts per million) concentrations of a high-molecular-weight (from 600 kD up) polymer in a fluid dramatically reduce friction resistance without changing the viscosity; examples of such polymers are DNA[18] and hyaluronan, a structural component of vascular wall glycocalyx.[19] Furthermore, bacteria produce drag-reducing polymers.[20] High DNA concentrations in sepsis are associated with high mortality.[21,22] Based on this, it can be hypothesized that DNA, hyaluronan and bacterial products induce drag reduction in blood during sepsis. Fluid mechanics of blood change: Toms' effect changes the flow behavior (not viscosity) of blood, contributing to the characteristic hyperdynamic systemic circulation and low arterial blood pressure in sepsis. If this is the case, removing or cleaving high-molecular-weight polymers should restore normal rheological characteristics of blood.

To summarize: The article by Torgersen et al. re-emphasizes the importance of infectious source control in sepsis. This message from their article is clear, and provides once again an important reminder for the clinician. Actual new mechanisms leading to death, however, are NOT proposed in their study. To reveal new insights into the pathophysiology and treatment of sepsis, instead of focusing only on the inflammatory networks, mitochondrial alterations, or apoptotic events, maybe we should ask whether the blood indeed is "poisoned" in sepsis, as suggested in

1861 by Semmelweiss. Hypothetically, as a consequence, the composition and fluid dynamic nature of blood may be altered.

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Macroscopic Postmortem Findings in 235 Surgical Intensive Care Patients with Sepsis

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BACKGROUND: Although detailed analyses of the postmortem findings of various critically ill patient groups have been published, no such study has been performed in patients with sepsis. In this retrospective cohort study, we reviewed macroscopic postmortem examinations of surgical intensive care unit (ICU) patients who died from sepsis or septic shock.
METHODS: Between 1997 and 2006, the ICU database and autopsy register were reviewed for patients who were admitted to the ICU because of sepsis/septic shock, or who developed sepsis/septic shock at a later stage during their ICU stay and subsequently died from of sepsis/septic shock. Clinical data and postmortem findings were documented in all patients.
RESULTS: Postmortem results of 235 patients (84.8%) were available for statistical analysis. The main causes of death as reported in the patient history were refractory multiple organ dysfunction syndrome (51.5%) and uncontrollable cardiovascular failure (35.3%). Pathologies were detected in the lungs (89.8%), kidneys/urinary tract (60%), gastrointestinal tract (54%), cardiovascular system (53.6%), liver (47.7%), spleen (33.2%), central nervous system (18.7%), and pancreas (8.5%). In 180 patients (76.6%), the autopsy revealed a continuous septic focus. The most common continuous foci were pneumonia (41.3%), tracheobronchitis (28.9%), peritonitis (23.4%), uterine/ovarial necrosis (9.8% of female patients), intraabdominal abscesses (9.1%), and pyelonephritis (6%). A continuous septic focus was observed in 63 of the 71 patients (88.7%) who were admitted to the ICU because of sepsis/septic shock and treated for longer than 7 days.
CONCLUSIONS: Relevant postmortem findings explaining death in surgical ICU patients who died because of sepsis/septic shock were a continuous septic focus in approximately 80% and cardiac pathologies in 50%. The most frequently affected organs were the lungs, abdomen, and urogenital tract. More diagnostic, therapeutic and scientific efforts should be launched to identify and control the infectious focus in patients with sepsis and septic shock.
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The annual incidence of sepsis is 750,000 cases in the United States, and this number increases by 9% each year.[1,2] Although the mortality rate has declined to 18%,[3] the absolute number of sepsis-related deaths is increasing. Accordingly, sepsis places a major burden on the United States health care system, with annual costs of $16.7 billion.[4] Based on the Surviving Sepsis Campaign recommendations, the treatment of sepsis patients must concentrate on rapid control of the infectious focus, early administration of broad-spectrum antibiotics, as well as supportive and adjunctive therapies.[5]

Although the autopsy is one of the most important tools of quality assurance in critical care medicine,[6] postmortem examination rates have continued to decrease during recent years.[7] All medical specialities are involved in this decline, especially internal medicine, surgery and intensive care, all with current autopsy rates of <7%.[8] While detailed analyses of the postmortem findings of critically ill cancer,[9] trauma,[10] cardiologic,[11] and pediatric[12] patients have been published, no such study has been performed in sepsis patients. Detailed knowledge of postmortem findings in these patients could not only improve our understanding and treatment of sepsis, but also provide direction for future research strategies.

This retrospective cohort study reviews the macroscopic postmortem examinations of 235 surgical intensive care unit (ICU) patients who died from sepsis or septic shock. Since this is an uncontrolled study, we

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did not intend to define macroscopic pathologies specific for patients dying from sepsis.

METHODS

The medical database of a 12-bed general and surgical ICU in a tertiary university hospital was reviewed for patients who were admitted to the ICU between January 1, 1997, and September 30, 2006, because of sepsis/septic shock, or who developed sepsis/septic shock during their ICU stay and subsequently died from sepsis/septic shock. The study ICU receives patients after elective or emergency surgery, but occasionally treats surgical and nonsurgical patients with internal medical diseases.

According to the American College of Chest Physicians and the Society of Critical Care Medicine criteria,[13] sepsis was defined as the presence of two or more signs of systemic inflammation in association with an infectious focus. Septic shock was defined as persistent hypotension (mean arterial blood pressure <70 mm Hg) which did not respond to fluid resuscitation and subsequently required either inotropic or vasopressor drugs in patients with sepsis. The clinical records of all patients were checked to verify that sepsis/septic shock persisted until death, and the results of the microbiological specimens of each patient were retrieved to confirm infection.

After identification of the patients from the institutional database, the autopsy registers of the Institute of Pathology and the Institute of Forensic Medicine, both at the Innsbruck Medical University, were searched for the final reports of the postmortem examinations. According to Austrian law,[14] an autopsy should be conducted in all patients dying in the ICU. The retrospective study protocol was approved by the Ethics Committee of the Innsbruck Medical University.

Sepsis Therapy

As part of the clinical routine, patients with sepsis and septic shock were treated as follows: diagnosis of the septic focus was based on the patient's history, clinical examination, microbiological cultures, and imaging studies. If a septic focus was amenable to mechanical evacuation, either surgical and/or percutaneous/endoscopic interventional techniques were applied. Broad-spectrum antibiotics (mostly ureidopenicillins, chinolones or carbapenems) were empirically administered and de-escalated after reception of microbiological culture results. Hemodynamic stabilization was attempted as early as possible using combined crystalloid/colloid-based fluid resuscitation as well as norepinephrine and milrinone as the first-line vasopressor and inotropic drugs. In cases of advanced shock states, epinephrine, hydrocortisone (up to 300 mg/d; since 1999) and/or arginine vasopressin (since 1998) were additionally administered. Mechanical ventilation was based on pressure-control and pressure-support modes, with the goal of maintaining peak inspiratory pressures <30 mbar. Continuous veno-venous hemofiltration was started early in the course of sepsis-associated renal failure. Since 2001, whenever technically possible, filtration rates of >35 mL/min were used. A balanced enteral/parenteral nutrition plan targeting early enteral feeding as well as stress ulcer and deep vein thrombosis prophylaxis was applied in all patients. Beginning in 2001, parenteral vitamin C, selenium and glutamine were routinely administered. Tight glucose control aiming at serum levels between 80 and 150 mg/dL was implemented in 2003. Patients were analgosedated using a continuous midazolam and/or sufentanil infusion as clinically indicated.

Autopsy Details

After death, bodies were transferred to a cooling chamber (temperature 3.8–4°C, relative humidity 85%) which is close to the department in the basement of the hospital. Only in rare exceptions did the time delay between death and transfer to this cooling chamber exceed 1 h. On the morning of the next working day, the corpses were transported either to the Institute of Pathology or the Institute of Forensic Medicine, where the autopsy subsequently took place. As part of the institutional routine, the postmortem examination was performed in all study patients as follows: A vertical incision from suprasternal notch to the symphysis was used to expose internal organs. The organs were removed in four blocks: 1) heart and lungs, 2) liver and gastrointestinal tract, 3) urogenital system, 4) brain. Afterwards, all organs were systematically examined for macroscopic pathologies. Internal examination of the extremities, spinal column and facial skull was performed only in the case of clinically suspected pathologies. The definitions of specific postmortem findings are presented in Table 1. Whenever macroscopically unclear lesions were detected, tissue samples were taken for histological analyses to either confirm or refute the macroscopic diagnosis. Therefore, only clear or histologically confirmed diagnoses were entered into the final autopsy record, which served as the basis for data documentation in this analysis.

Data Documentation

The following variables of all study patients were extracted from the institutional database: gender, age, chronic disease status, classification of the American Society of Anesthesiologists,[15] the Simplified Acute Physiology Score II,[16] time of onset of sepsis, the source of infection, the pathogen type cultured, presence of sepsis or septic shock[13]; the number of failing organs, defined according to the Goris multiple organ dysfunction syndrome score (data supplement available at www.anesthesia-analgesia.org)[17]; need for continuous veno-venous hemofiltration; presence of acute respiratory distress syndrome, defined according to

Table 1. Definitions of Postmortem Findings

Postmortem findings of the heart	
Myocardial ischemia	Diffuse or localized red-blue (yellow-tan at later stages) lesions of the myocardium optionally rimmed by a hyperemic zone with or without occlusion of the supplying coronary artery
Acute dilatative heart failure	New dilatation of the right or left ventricular chamber accompanied by an arched apex
Pericarditis	Reddened and granular pericardium optionally accompanied by pericardial effusion
Pericardial effusion	Fluid collection in the pericardial cavity
Myocarditis	Diffuse or patchy myocardial lesions of flabby consistence with either pale or hemorrhagic foci
Endocarditis	Friable, bulky or destructive vegetations on cardiac valves containing fibrin, inflammatory cells, and pathogens on histology
Postmortem findings of the lungs	
Pulmonary edema	Lungs are 2–3 times their normal weight (800 g) and sectioning reveals frothy, blood-tinged fluid
Pneumonia	Consolidated lung areas (increased in volume) with patchy infiltrations rendering pus on sectioning
Pleural effusions	Fluid collection in one or both pleural cavities (blood, hematothorax; pus, pleural empyema)
Tracheobronchitis	Reddened, edematous mucosa of substantial parts of the tracheobronchial tree optionally accompanied by serous or mucous secretion
Pulmonary embolism	Partial or total occlusion of a pulmonary artery by a venous thrombus
Pulmonary hemorrhage	Consolidated lung areas with hemorrhagic infiltrations
Pleuritis	Reddened, edematous pleura optionally accompanied by a fibrinous exudate
Pulmonary infarction	Raised, red-blue (red-brown at later stages), wedge-shaped areas extending to the lung periphery optionally accompanied by fibrinous pleuritis
Atelectasis	Consolidated (dark blue-red) lung areas reduced in volume rendering no pus on sectioning
Postmortem findings of the abdomen	
Liver	
Steatosis	Yellow, greasy and readily fractured liver with increased weight (>2000 g)
Hypoxic liver damage	Diffuse, patchy and pale alterations localized in the central region of the liver lobules
Cholangitis	Optionally purulent inflammation of the extra/intrahepatic bile ducts with or without necrotic infiltration of portal fields
Cholecystitis	Enlarged and tense gallbladder with bright-red to green-black patchy discoloration and optionally fibrin-layered serosa or suppurative exudate
Gastrointestinal tract	
Mesenteric ischemia	Diffuse or localized bowel alterations with dilatation, edema and wall thickening (optionally intraluminal gas) with or without occlusion of the supplying mesenteric artery
Gastritis	Edematous gastric mucosa with vascular congestion but maintained mucosal barrier
Gastrointestinal hemorrhage	Intraluminal blood originating from lesions of the gastrointestinal tract
Gastroduodenal ulcer	Erosions of the gastric or duodenal mucosa equal to or greater than 0.5 cm in diameter
Chronic peritonitis	Continuous localized or diffuse inflammation of the peritoneum with suppurative or fibrinous exudate
Hemorrhagic infarction	Diffuse or localized bowel alterations with congestive edema, wall thickening, dusky to purple-red discoloration and hemorrhagic lesions with or without luminal blood
Ascites	Serous fluid collection in the abdominal cavity
Anastomosis dehiscence	Leakage of a surgical anastomosis
Spleen	
Spleen infarction	Pale and wedge-shaped areas of the spleen optionally accompanied by fibrin coverage of the splenic capsule
Septic spleen alterations	Enlarged (>125 × 75 × 50 mm) and soft spleen with deliquescent splenic parenchyma on incision
Pancreas	
Pancreas ischemia	Diffuse or localized, pale or reddish areas of the pancreatic parenchyma
Necrotizing pancreatitis	Blue-black hemorrhagic areas interspersed with foci of yellow-white, chalky fat necroses near or within the pancreas

(*Continued*)

Table 1. Continued

Genital tract	
Uterine/ovarian necrosis	Single or multiple areas of hemorrhagic necrosis of the endometrium, uterine wall or ovaria
Postmortem findings of the kidneys/urinary tract	
Cystitis	Reddened, edematous mucosa of the urinary bladder optionally accompanied by a suppurative exudate
Kidney swelling	Diffuse enlargement of the kidney (>120 × 65 × 50 mm) without specific parenchymal pathologies
Kidney ischemia	Sharply demarcated, pale (yellow-white at later stages) areas containing hemorrhagic foci with or without occlusion of the supplying renal artery
Pyelonephritis	Grayish-white discoloration of the pyelum and ureter optionally accompanied by patchy inflammation or necrosis of the renal parenchyma
Postmortem findings of the central nervous system	
Brain edema	Swollen brain with flattened gyri, narrowed sulci and compressed ventricular cavities optionally accompanied by tentorial or foraminal brain herniation
Nonocclusive ischemia	Diffuse or localized, pale and swollen (gelatinous or liquified at later stages) areas of the brain without occlusion of the supplying cerebral artery
Intracerebral hemorrhage	Hemorrhage within the cerebral parenchyma with brownish discoloration at later stages
Encephalitis	Diffuse or localized brain swelling with inflammatory/necrotic alterations of typical cerebral areas (e.g. temporal)

the American-European consensus conference on acute respiratory distress syndrome[18]; length of ICU stay, and the clinical cause of death as documented by a senior intensivist.

Autopsy reports of all study patients were searched for pathologies of the following organ systems: cardiovascular system, lungs, liver, kidneys and urinary tract, gastrointestinal tract, spleen, pancreas, and central nervous system. Pathologies of other organ systems were recorded separately. Postmortem findings of each organ system were entered into the database in a binary fashion. Additionally, the cause of death as documented by the pathologist was recorded for all study patients.

Statistical Analysis

The SPSS software program (SPSS 12.0.1.; SPSS, Chicago, IL) was used for statistical analysis. Descriptive statistical methods were applied to evaluate the frequency of pathologies of single organ systems. In order to compare the frequency of organ pathologies between groups, a χ^2 or Fisher's exact test was used, as appropriate. P values <0.05 were considered as indicating statistical significance. Data are given as mean values ± SD, if not otherwise indicated.

RESULTS

During the study period, 5226 patients were admitted to the ICU. Four-hundred-fifteen patients suffered from sepsis and 442 from septic shock. The ICU morality was 32.3% (n = 277) for all sepsis/septic shock patients (sepsis, 11.8%, n = 49; septic shock, 51.6%, n = 228). An autopsy was performed in 256 of the 277 patients (92.4%). Clinical records, autopsy results, or results of microbiological specimens could be retrieved in 235 of the 277 patients (84.8%) (Tables 2 and 3). The mean storage time of corpses in the cooling chamber before the postmortem examination was 24 ± 20 h.

Pathologies of the cardiovascular system were detected in 126 patients (53.6%) (Table 4). Two of the five patients with endocarditis found on autopsy were admitted to the ICU because of this condition. In 211 patients (89.8%), pathologies of the lungs were observed (Table 5). Fifty-two of the 97 patients in whom pneumonia was found at autopsy were diagnosed as having pneumonia during their ICU stay. One-hundred-twenty-seven (54%), 112 (47.7%), 78 (33.2%), and 20 (8.5%) showed pathologies of the gastrointestinal tract, liver, spleen and pancreas, respectively (Table 6). Patients with biochemical evidence of hepatic dysfunction (increased bilirubin and/or transaminase plasma levels) showed a higher incidence of liver pathologies (27/79 [34.2%] vs 85/156 [54.5%], P = 0.004). Seven of the 20 patients with necrotizing pancreatitis at autopsy were admitted to the ICU because of this condition. In 141 patients (60%), pathologies of the kidneys and the urinary tract were described (Table 7). There was no difference in the incidence of renal pathologies between patients with and without continuous veno-venous hemofiltration (103/170 [60.6%] vs 38/65 [58.8%], P = 0.77). Pathologies of the central nervous system were detected in 44 patients (18.7%) (Table 8). Of the patients who were admitted to the ICU after cardiopulmonary resuscitation or with a primary cerebral pathology (n = 26), 2 were found to have brain edema in the autopsy.

In 180 patients (76.6%), the autopsy revealed a continuous septic focus. Eighty patients (34%) had 1

Table 2. Characteristics of the Study Population

n		235
Male sex	*n* (%)	153 (65.1)
Age	Yr	68 ± 13
Chronic diseases	*n* (%)	
COPD		123 (52.3)
CRI		107 (45.5)
cAHT		118 (50.2)
CHD		114 (48.5)
CHF		74 (31.5)
Malignant tumor disease		72 (30.6)
Liver cirrhosis		24 (10.2)
ASA classification	*n* (%)	
III		26 (11.1)
IV		117 (49.8)
V		92 (39.1)
SAPS II	Points	52 ± 16
Sepsis at ICU admission	*n* (%)	160 (68.1)
Source of infection	*n* (%)	
Abdomen		110 (46.8)
Lungs		71 (30.2)
Urinary tract		11 (4.7)
Wound/soft tissue		9 (3.8)
Mediastinum		9 (3.8)
Endocardium		6 (2.6)
Others		19 (8.1)
Pathogen type in cultures		6 (2.6)
Gram-positive alone		103 (43.8)
Gram-negative alone		81 (34.5)
Fungal alone		53 (22.6)
Viral alone		1 (0.4)
Parasitic alone		1 (0.4)
Mixed organisms		79 (33.6)
Septic shock	*n* (%)	195 (83)
Failing organs	*n*	5 ± 1.1
Need for CVVHF	*n* (%)	170 (72.3)
ARDS	*n* (%)	57 (24.3)
Length of ICU stay	d	14 ± 15

COPD = chronic obstructive pulmonary disease; CRI = chronic renal insufficiency; cAHT = chronic arterial hypertension; CHD = coronary heart disease; CHF = congestive heart failure; ASA = American Society of Anesthesiologists; SAPS = simplified acute physiology score; ARF = acute renal failure; ICU = intensive care unit; CVVHF = continuous veno-venous hemofiltration; ARDS = acute respiratory distress syndrome.

Table 3. Clinical and Postmortem Causes of Death

		Clinical	Postmortem
Irreversible MODS	*n* (%)	134 (57)	121 (51.5)
Cardiovascular failure	*n* (%)	51 (21.7)	83 (35.3)
Intestinal ischemia	*n* (%)	14 (6)	5 (2.1)
Chronic peritonitis	*n* (%)	9 (3.8)	7 (3)
Pulmonary failure	*n* (%)	9 (3.8)	9 (3.8)
CNS failure	*n* (%)	8 (3.4)	3 (1.3)
Liver failure	*n* (%)	6 (2.6)	4 (1.7)
Uncontrolled hemorrhage	*n* (%)	4 (1.7)	3 (1.3)

MODS = multiple organ dysfunction syndrome; CNS = central nervous system.

focus, 72 patients (30.6%) 2, 21 patients (8.9%) 3, and 7 patients (3%) ≥4 foci. The most frequent foci were pneumonia (41.3%), tracheobronchitis (28.9%), peritonitis (23.4%), uterine/ovarial necrosis (9.8% of female patients), intraabdominal abscesses (9.1%) and pyelonephritis (6%). Of the 71 patients admitted to the ICU because of sepsis/septic shock and treated ≥7 days, a continuous septic focus was observed in 63 (88.7%).

Table 4. Postmortem Findings of the Heart

Myocardial ischemia	*n* (%)	83 (35.3)
Occlusive		10 (4.3)
Nonocclusive		74 (31.5)
Acute dilatative heart failure	*n* (%)	27 (11.5)
Dilatation of left ventricle		13 (5.5)
Dilatation of right ventricle		24 (10.2)
Pericarditis	*n* (%)	21 (8.9)
Pericardial effusion	*n* (%)	8 (3.4)
Myocarditis	*n* (%)	5 (2.1)
Endocarditis	*n* (%)	5 (2.1)

Table 5. Postmortem Findings of the Lungs

Pulmonary edema	*n* (%)	137 (58.3)
Pneumonia	*n* (%)	97 (41.3)
Fungal pneumonia		8 (3.4)
Pleural effusions	*n* (%)	47 (20)
Hematothorax		8 (3.4)
Pleural empyema		2 (0.9)
Tracheobronchitis	*n* (%)	68 (28.9)
Pulmonary embolism	*n* (%)	30 (12.8)
Pulmonary hemorrhage	*n* (%)	16 (6.8)
Shock lungs[a]	*n* (%)	15 (6.4)
Pleuritis	*n* (%)	11 (4.7)
Pulmonary infarction	*n* (%)	10 (4.3)
Atelectasis	*n* (%)	10 (4.3)

[a] Histological diagnosis.

Table 6. Postmortem Findings of the Abdomen

Liver	*n* (%)	
Steatosis		78 (33.2)
Cholestasis[a]		33 (14)
Hypoxic liver damage		31 (13.2)
Cholangitis		5 (2.1)
Cholecystitis		3 (1.3)
Gastrointestinal tract	*n* (%)	
Chronic peritonitis		55 (23.4)
Mesenteric ischemia		42 (17.8)
Nonocclusive		37 (15.7)
Occlusive		5 (2.1)
Gastritis		24 (10.2)
Ascites		23 (9.8)
Gastrointestinal hemorrhage		13 (5.5)
Anastomosis dehiscence		11 (4.7)
Gastroduodenal ulcer		8 (3.4)
Hemorrhagic infarction		8 (3.4)
Spleen	*n* (%)	
Septic alterations		68 (28.9)
Infarction		15 (6.4)
Pancreas	*n* (%)	
Necrotizing pancreatitis		20 (8.5)
Ischemia		2 (0.9)
Genital system		
Uterine/ovarian necrosis	*n* (%)[b]	8 (9.8)

[a] Histological diagnosis.

[b] *n* (%) of female patients.

Table 7. Postmortem Findings of the Kidneys/Urinary Tract

Cystitis	*n* (%)	83 (35.3)	*n* (%)[a]	58 (34.1)
Kidney swelling	*n* (%)	53 (22.6)	*n* (%)[a]	42 (24.7)
Kidney ischemia	*n* (%)	27 (11.5)	*n* (%)[a]	20 (11.8)
Nonocclusive	*n* (%)	25 (10.6)	*n* (%)[a]	20 (11.8)
Occlusive	*n* (%)	2 (0.9)	*n* (%)[a]	2 (1.2)
Pyelonephritis	*n* (%)	14 (6)	*n* (%)[a]	9 (5.3)

[a] In patients with renal replacement therapy.

Table 8. Postmortem Findings of the Central Nervous System

Brain edema	*n* (%)	32 (13.6)
Nonocclusive ischemia	*n* (%)	8 (3.4)
Intracerebral hemorrhage	*n* (%)	5 (2.1)
Encephalitis	*n* (%)	1 (0.4)

There was no difference in the frequency and pattern of postmortem findings between patients with refractory multiple organ failure and uncontrollable shock as the clinical cause of death. In view of the small sample size in the sepsis group (of 40 patients, 16 died without developing shock), no comparison of the postmortem diagnoses between patients with sepsis and septic shock was performed.

DISCUSSION

The most striking finding of this analysis was that approximately 80% of all study patients still had a septic focus at autopsy. It can be argued that detection of an infectious focus can be expected in patients who die early in the course of sepsis. However, even in patients who were admitted to the ICU because of sepsis and treated for ≥7 days, a sufficient time to control the source of infection, the incidence of a continuous septic focus in the autopsy was approximately 90%. In spite of the fact that immediate removal of the septic focus combined with antibiosis is the cornerstone of sepsis therapy,[5,19] it appeared impossible to control the focus in the vast majority of our study patients, and this seems to have been the main cause of death.

A continuous septic focus continues to stimulate the immune system, finally leading to multiple organ failure and death.[2] Although it sounds simple, and clinicians tend to look for more complex treatment strategies (e.g., adjuvant therapies), our results highlight that source control must be the key component in sepsis management.[5,19] Accordingly, future research should concentrate on improving diagnostic and therapeutic strategies to eliminate the infectious source.

In our patient population, most continuous septic foci detected were located in the lungs, abdomen, female urogenital tract and kidneys. However, it is possible that other potential septic foci, such as intravascular devices or spontaneous bacteremia, cannot be detected on postmortem examination and were thus missed in this analysis. Moreover, some foci, such as the sinuses or the vertebral column, were only examined in the autopsy if there had been clinical evidence of an infection. Thus, the frequency of continuous septic foci may even have been under-estimated by this analysis. Our data also did not show whether the focus was unrecognized or the therapy was insufficient.

Of all organ pathologies, the most relevant for patient mortality seems to have been pathology of the cardiovascular system, since uncontrollable shock was the clinical cause of death in 25% of the study population and almost all patients had shock. Even though pulmonary pathologies were observed in approximately 90% of patients, pulmonary failure was a rare clinical cause of death. In our study, the most frequent cardiac pathology was myocardial ischemia. One-third of all study patients had a nonocclusive myocardial ischemia. In contrast, occlusive ischemia was observed only in a minority of patients (4.3%). A comparably low incidence of occlusive ischemia has been reported in perioperative myocardial infarction, whose predominant pathophysiologic feature is an imbalance of myocardial oxygen demand and supply.[20] Furthermore, other myocardial pathologies occurring during the last hours before death, such as myocardial stunning or myocardial ischemia, cannot be reliably detected in the postmortem examination. Therefore, the actual frequency of myocardial pathologies may have been higher than suggested by our results.

In contrast to 13 patients with acute left ventricular dilation, 24 patients presented with acute dilation of the right ventricle, suggesting significant right ventricular dysfunction. However, only seven of them sustained pulmonary embolism, suggesting that in these patients either direct right ventricular dysfunction or pulmonary arterial hypertension played the dominant pathophysiologic role. A recent prospective echocardiographic survey of patients with septic shock indicated that ventricular dilation is only a rare (11%) and severe form of septic cardiomyopathy. Isolated or combined systolic and diastolic dysfunction was observed more frequently.[21] Although functional variables by nature cannot be evaluated in the postmortem examination, our findings support current evidence that right ventricular dysfunction is a clinically under-estimated problem in critically ill patients.[22]

Another interesting finding of this study is that brain edema was observed in nearly 15% of patients dying from sepsis. Only two of these patients were admitted to the ICU because of a primary cerebral pathology or after cardiopulmonary resuscitation. Although severe hypotension may cause cerebral hypoperfusion and thus induce brain edema, recent evidence suggests that the pathophysiology of septic delirium may include not only functional but also anatomic components.[23,24] Nonetheless, we cannot exclude the influence of terminal hypoxia and hypotension developing after withdrawal of life-sustaining therapy on the formation of brain edema in our study population.

Due to this study's uncontrolled, retrospective approach, our findings cannot be considered to be specific for patients with sepsis, but may also be seen in critically ill patients dying from other pathologies. Whether these findings are specific for sepsis must be examined in a prospective, controlled trial. However, the aim of this analysis was to offer a cross-sectional overview of macroscopic postmortem findings observed in patients succumbing to sepsis.

There are clearly more limitations deserving consideration when interpreting the results of this analysis. Although the bodies had been cooled rapidly after death, it cannot be excluded that autolysis before autopsy significantly influenced the postmortem findings of our study. Another innate insufficiency of macroscopic postmortem studies is that diagnoses are based on macroscopic and not histological examinations. Even though histological analyses were performed whenever macroscopically unclear lesions were detected, the lack of universal histological examinations is a clear limitation of this analysis. It is possible that histological examinations in all study patients would have revealed more pathologies in certain organ systems, e.g., the kidneys particularly in patients on renal replacement therapy. Similarly, since postmortem diagnoses like pneumonia or tracheobronchitis were based on macroscopic instead of microbiological examinations, the incidence of pulmonary infections may have been over-estimated in our analysis. Furthermore, patients who actually had sepsis but were clinically misdiagnosed as not having sepsis were not included in our study. Omission of these patients could have had a relevant influence on the actual incidence of organ pathologies in patients dying from sepsis or septic shock. Functional problems (e.g., liver, coagulation, etc.) cannot be detected by the pathologist and were equally missed by this analysis. In particular, acute renal injury requiring renal replacement therapy did not have a clear macroscopic correlate. Moreover, since this study included critically ill patients mainly suffering from surgical pathologies, the results cannot be extrapolated to other ICU populations, such as internal or neurological ICU patients.

Finally, during the long study period, new therapeutic interventions were introduced and mortality decreased. However, it is unlikely that these changes influenced the results of our analysis, because no difference in the frequency and pattern of organ pathologies could be observed during the study period (data supplement available at www.anesthesia-analgesia.org).

CONCLUSION

The main clinical and postmortem causes of death in critically ill surgical patients succumbing to sepsis and septic shock were refractory multiple organ dysfunction syndrome and uncontrollable cardiovascular failure. Relevant postmortem findings explaining these results were a continuous septic focus in 80% and cardiac pathologies in 50% of patients. The most frequently affected organs were the lungs, abdomen, and urogenital tract. More diagnostic, therapeutic and scientific efforts should be launched to identify and control the infectious focus in patients with sepsis and septic shock.

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