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Sepsis-related mortality in the Czech Republic: multiple causes of death analysis

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ABSTRACT

Aim: Sepsis represents an increasingly frequent complication in the survival of the hospitalized persons. The nation-wide burden of the sepsis-related mortality in the Czech Republic has not yet been analysed. The present study aims to assess the trends and the disparities in the sepsis-related mortality in the Czech Republic for the period 1998–2011 using multiple causes of death reported on the death certificates.
Materials and methods: Individual death records provided by the Institute for Health Information and Statistics were used to identify sepsis-related deaths based on the codes of the 10th revision of the International classification of the diseases (ICD-10). Frequencies, age-standardized rates and comorbidity patterns were studied.
Results: A total of 41,425 cases (3%) out of 1,456,539 deaths within the period 1998–2011 were associated with sepsis. In 2011, sepsis was reported in 8% of all in-hospital deaths. Sepsis is the most likely to be reported as immediate cause of death (66%), which results in its considerable underestimation in the underlying cause of death statistics. The sepsis-related mortality almost tripled between 1998 and 2011, and the most of the increase is attributable to persons aged 65 and over. In 44% of cases, circulatory disease or cancer was reported as the underlying cause of death. Significant associations with sepsis were however found for infectious diseases, diseases of skin, and metabolic or musculoskeletal disorders.
Conclusion: Multiple cause of death analysis of sepsis-related mortality revealed that sepsis represents a growing burden related to the population ageing and increased prevalence of complications of chronic diseases. The observed upward trends, as well as the expected continuation of the ageing process, may result in further increase of sepsis-related mortality. Preventive measures in the clinical management of sepsis are recommended.

KEYWORDS

sepsis – septicaemia – mortality – comorbidity – ageing

SOUHRN

Pechholdová M.: Vliv sepse na úmrtnost v České republice: analýza vícečetných příčin úmrtí
Cíle: Sepse je stále častější komplikací u hospitalizovaných pacientů. Tato problematika však v rámci České republiky zatím nebyla podrobně analyzována. Předložená studie podchycuje trendy a specifika úmrtnosti související se sepsí v České republice v období 1998–2011 na základě individuálních dat z úmrtních listů včetně tzv. vícečetných příčin úmrtí.
Materiál a metody: Pro identifikaci úmrtí souvisejících se sepsí byla využita data z úmrtních listů obsahujících některý z kódů sepse podle 10. revize Mezinárodní klasifikace nemocí (MKN). Data byla poskytnuta Ústavem zdravotnických informací a statistiky (ÚZIS). Byla provedena analýza frekvencí, standardizovaných měr úmrtnosti a komorbidity.
Výsledky: Sepse byla identifikována u 41 425 případů úmrtí (3 %) z celkových 1 456 539 v období 1998–2011. V rámci úmrtí hospitalizovaných pacientů byla v roce 2011 sepse přítomna u 8 % případů. Sepse je nejčastěji (z 66 %) certifikována jako bezprostřední příčina úmrtí, což vede k jejímu významnému podhodnocení při zahrnutí pouze tzv. základní příčiny úmrtí, která je běžně publikována ve statistikách zemřelých. Úmrtnost související se sepsí se mezi roky 1998–2011 ztrojnásobila, především důsledkem nárůstu výskytu u starších osob (65 let a více). Ve 44 % případů bylo základní příčinou úmrtí některé z kardiovaskulárních onemocnění. Analýza relativní komorbidity však prokázala, že nejvyšší riziko rozvoje fatální sepse mají pacienti s infekčním, kožním, metabolickým nebo muskuloskeletálním onemocněním.
Závěr: Analýza vícečetných příčin úmrtí poukázala na rostoucí riziko rozvoje sepse jakožto fatální komplikace základního onemocnění. Příčiny je možné spatřovat v demografickém stárnutí populace a s ním související epidemiologickou zátěží: chronickými nemocemi. Pozorovaný dosavadní nárůst a očekávané pokračování populačního stárnutí tak může vést k dalšímu zvyšování míry ohrožení pacientů sepsí. V souladu s mezinárodními studiemi proto doporučujeme zvážit přijetí klinických doporučení pro prevenci a léčbu sepse.

KLÍČOVÁ SLOVA

sepse – septikémie – úmrtnost – komorbidita – stárnutí

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BACKGROUND

Sepsis is a life-threatening condition resulting from the patient's incapacity to cope with generalized spread of an infectious agent in the bloodstream. Fatal cases of sepsis arise from systemic inflammatory response accompanied by blood clotting and subsequent (multiple) organ failure. Sepsis is one of the most lethal conditions in

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health care facilities: case-fatality varies between 20 and 50 percent [1], compared to only 2 percent for non-sepsis patients [2]. The development of sepsis not only decreases the patient's survival chances, but also extends the length of hospitalization and significantly increases the health care costs [1–3]. An increase in sepsis incidence has been recently observed in numerous epidemiological studies conducted in developed countries affected by the demographic ageing [3–4]. In the U.S. study based on private hospital discharge records, the annual incidence rate increase of 7–8% was observed between 2000 and 2008 [2]. In a recent study on Germany, based on the diagnosis related groups (DRG) federal statistics, the incidence of sepsis rose by 5.7% per year between 2007 and 2013 [3]. In spite of declining case-fatality rates, the rise in the sepsis incidence rates results in a continuous increase of sepsis-related mortality [1, 2, 5–8].

So far, epidemiological analyses of sepsis in the Czech Republic are scarce [9]. In foreign studies, two types of statistical resources on sepsis are used: hospital discharge records and death certificates. In the Czech Republic however, hospital discharge records are not systematically collected. Death records routinely collected by the Czech Statistical Office contained (until 2013) only the underlying cause of death (UCOD), defined by the World health organization (WHO) as "the disease or injury which initiated the train of morbid events leading directly or indirectly to death or the circumstances of the accident or violence which produced the fatal injury". By this definition, and due to the comorbid nature of sepsis, underlying cause-based statistics systematically underestimate the population-level burden of sepsis [4, 10–12]. Moreover, sepsis is among the causes the most affected by changes in the WHO rules for selection of the underlying cause of death: in the 10th revision of the International classification of diseases (ICD), sepsis is given preference over pneumonia if both conditions are reported on the death certificate [13]. This change resulted in a partially artificial increase in sepsis-related UCOD mortality observed in many countries after adoption of the 10th ICD revision [14, 15]. The increase was so pronounced that sepsis, even as underlying cause, has recently become leading infectious disease, and is largely responsible for the upward trend of infectious mortality (ICD chapter A00-B99) across all developed countries including the Czech Republic (according to the datasets provided by the international Human cause-of-death database (www.causesofdeath.org). While the UCOD-based trends are biased by coding practice and underestimation, the burden of sepsis can be more accurately estimated using the multiple cause of death data (MCOD). Multiple causes of death data are, in fact, the only source for analysis of sepsis-related mortality available at national level, and unlike hospital discharge records, which are restricted to hospitalized cases, all sepsis deaths are included [12]. Not only the data is statistically robust, it also allows for analysing time trends in long series (in the US for example, multiple causes of death have been collected since 1968), disparities by age, sex, or other available variables, and comparison between countries [16]. This study is assessing sepsis-related mortality and its time trends in the Czech Republic using previously unpublished dataset of multiple causes of death collected for the period 1998–2011 by the Institute of Health Information and Statistics (IHIS).

MATERIALS AND METHODS

Individual death records with multiple cause of death information were obtained from the Institute of Health Information and Statistics for the period 1998–2011. The IHIS dataset contains 4-digit ICD-10 codes entered by the certifying practitioners at the moment of diagnosis. A maximum of six causes were retained, three in part I of the death certificate (conditions directly leading to death) and three in part II (contributory diseases not directly linked to death). The average number of reported diagnoses per death certificate was 3.4 [17]. The underlying cause of death, selected at the Czech Statistical Office and merged to the IHIS dataset ex-post, is listed as the 7th cause-of-death variable (due to the application of coding rules such as linking several diagnoses into one code, or due to inquiries on further precision of the diagnosis, the UCOD may be different from any MCOD listed on the first six positions). The IHIS dataset also contains following identification variables: age, sex, date of death, place of death, marital status, education, autopsy status, and NUTS-3 region. Due to record linkage failures or incomplete data collection, the dataset covers 94% percent of all deaths.

The whole period of 1998–2011 was covered by the 10th revision of the ICD (Czech Republic adopted ICD-10 in 1994). In accordance with previous studies [3, 4, 12], sepsis-related cases were defined as deaths where: A02.1 (salmonella septicaemia), A22.7 (anthrax septicaemia), A26.8 (erysipelothrix septicaemia), A32.7 (listerial septicaemia), A40.0 (septicaemia due to *Streptococcus*, group A), A40.1 (septicaemia due to *Streptococcus*, group B), A40.2 (septicaemia due to Streptococcus, group C), A40.3 (septicaemia due to streptococcal pneumonia), A40.8 (other streptococcal septicaemia), A40.9 (streptococcal septicaemia, unspecified), A41.0 (septicaemia due to *Staphylococcus aureus*), A41.1 (septicaemia due to other specified staphylococcus), A41.2 (septicaemia due to other unspecified staphylococcus), A41.3 (septicaemia due to *Haemophilus influenzae*), A41.4 (septicaemia due to anaerobes), A41.5 (septicaemia due to other Gram-negative organisms), A41.8 (other specified septicaemia), A41.9 (septicaemia, unspecified), A42.7 (actinomycotic septicaemia), B00.7 (herpesviral septicaemia), B37.7 (candidal septicaemia), P36 (bacterial septicaemia of new-born), R65.1 (systemic inflammatory response syndrome of infectious origin without organ failure) or R65.2 (systemic inflammatory response syndrome of infectious origin with organ failure) was mentioned at any position of the certificate. Additionally, the dataset enabled to include post-procedural cases of sepsis: T81.4 (infection following a procedure), T80.2 (infections following infusion, transfusion and therapeutic injection), and T88.0 (infection following immunization). In 2010, the WHO introduced a new code for septic shock (R57.2) in a frame of the classification updating process. This code was not used in the Czech statistics in the covered period.

The frequencies based on age, place of death, position on the death certificate, underlying cause and type of sepsis-related mortality were computed for the pooled

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data (1998–2011). To compute annual age-specific mortality rates, population counts were downloaded from the Human mortality database (www.mortality.org). As a measure of the underestimation of the role of the given disease in routine mortality statistics, we compute the standardised ratio of the multiple to the underlying cause (SRMU), defined as the ratio between the age-standardized multiple-cause mortality rate and the age-standardized underlying-cause death rate [16]. For the SRMU calculation, duplicate ICD codes (where sepsis was reported more than once) were eliminated.

To assess the comorbidity, we compute first the frequencies of common occurrence of sepsis and other causes of death (grouped into 74 categories, see [17] for the full list). Next, to measure the strength of the associations, the cause-of-death association indicator (CDAI) according to the following formula [16] was computed as:

$$CDAI_{u,c} = \frac{\sum_x \frac{{}_u d_{c,x}}{{}_u d_x} . \bar{d}_x}{\sum_x \frac{d_{c,x}}{d_x} . \bar{d}_x} \times 100$$

where ${}_u d_{c,x}$ = number of deaths observed at age x with underlying cause u and contributing cause c;
${}_u d_x$ = the number of deaths observed at age x with cause u as the underlying cause;
$d_{c,x}$ = the total number of deaths observed at age x with cause c as the contributing cause (regardless of the underlying cause);
d_x = the total number of deaths observed at age x (regardless of the underlying cause);
$\bar{d}_x$ = the standard number of deaths at age x (based on the 2009 WHO life table for high-income countries).

The CDAI measures the deviation from the independence between the two causes of death. Values significantly higher (at the 95% confidence level) than 100 point at a non-random positive association between the two causes.

RESULTS

Out of a total of 1,456,539 deaths in the sample, sepsis was identified as a part of the lethal process in 41,425 cases (2.8%). If only deaths taking place in hospitals are considered (805,281), the presence of sepsis on the death record increased to 4.5% of cases on average. In 2011, sepsis was reported in 7.9% of all hospital deaths. The frequency characteristics of sepsis-related deaths as observed in 1998–2011 in the Czech Republic are provided in Table 1. Sepsis occurred almost equally among males and females (49 *versus* 51%). In 73% of the observed cases, patients were older than 65 years. Sepsis deaths took place almost exclusively in hospitals or other health care institutions (in 97% of the cases). In 66% of the cases, sepsis was certified as immediate cause of death (on the first line of the death certificate), while in only 7% of deaths it was proposed as the underlying cause (on the third line of the death certificate). Sepsis is thus confirmed as an important end-stage condition and its successful management has a significant life-saving potential. Regarding the type of the sepsis, the certification is largely unspecific: 76% of cases are diagnosed as unspecified. Among specified types, other Gram-negative (4.6%) and *Staphylococcus aureus* (3.1%) septicamias are predominant, pointing indirectly at the importance of the nosocomial infections (both *S. aureus* and Gram-negative *Pseudomonas* have been identified as major strains in hospital acquired infections) [18].

Table 1. Frequency characteristics of a total of 41,425 sepsis-related deaths in the Czech Republic, 1998-2011

	% of sepsis-related deaths
Male sex	49.0
Age	
0–64	27.2
65–74	24.9
75–84	33.6
85+	14.5
Died in hospital*	97.0
Position on the death certificate	
Immediate	65.9
Antecedent	20.1
Underlying	6.5
Contributory (part II)	7.4
Type	
Streptococcus (A40)	1.1
Staphylococcus aureus (A41.0)	3.1
Other Gram-negative (A41.5)	4.6
Other specified (A41.8)	10.9
Other unspecified (A41.9)	75.5
Post-procedural (T80.2, T81.4, T88.0)	1.0
Other	4.0
Underlying cause of death	
Sepsis	11.4
Other infectious disease (A00-B99)**	0.9
Neoplasms (C00-D48)	17.5
Circulatory diseases (I00-I99)	26.7
Respiratory diseases (J00-J99)	6.7
Digestive diseases (K00-K99)	13.7
Accidents and poisoning (V00-Y89)	3.0
Other diseases	20.2

* or other health care facility
**excluding sepsis

In only 11.4% of the cases, sepsis reported on the death certificate was finally selected as the underlying cause of death. The most frequent underlying cause of death with sepsis as a complication were circulatory diseases

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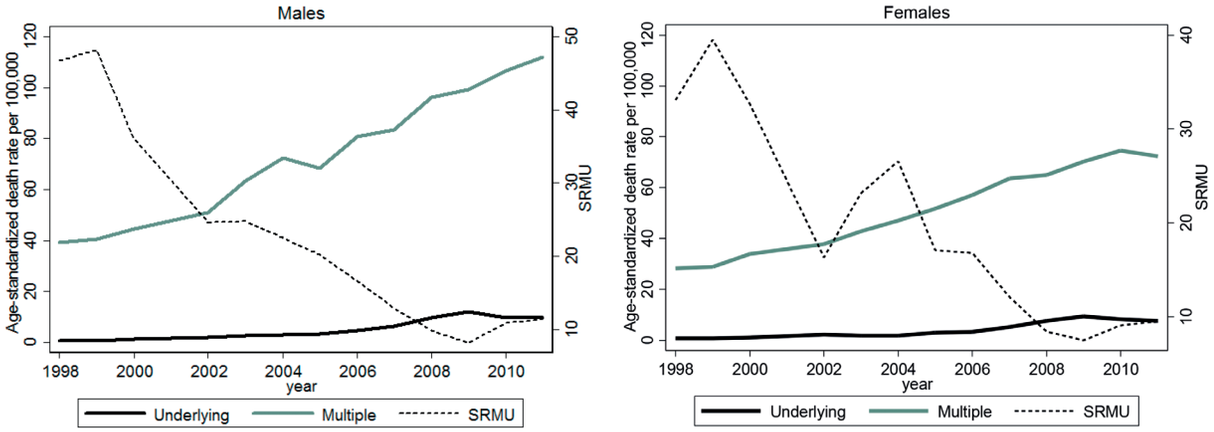

Figure 1. Age-standardized death rates per 100,000 of underlying and multiple sepsis-related mortality and their ratio (SRMU) Czech Republic, 1998–2011

(27%). Neoplasms accounted for 18% of sepsis cases, and digestive diseases were selected as underlying cause of death in 14 % of the cases.

Figure 1 depicts age-standardized mortality rate in sepsis-related mortality between 1998 and 2011 for males and females. Both total and underlying mentions of sepsis-related mortality are plotted on the primary (left) axis, while the ratio between them (SRMU) is plotted against the secondary (right) axis. In both settings, sepsis-related mortality has increased markedly throughout the observed period. The rise of UCOD mortality accelerated after 2006, when the Czech statistical office started to harmonize the rules for selection of the underlying codes with the WHO recommendations [19]. For total mentions of sepsis on the death certificate, a steady increase of was observed for both sexes: the average annual growth rate was 8.7% for males and 7.6% for females. Due to the changes in the coding practices, the SRMU declined from 47 to 11 in males and from 33 to 10 in females, suggesting that sepsis is increasingly recognized as underlying cause of death, but continues to be 10-fold underestimated if multiple causes of death are not considered.

Table 2 displays the differences between the years 1998 and 2011 by sex and age group. The sepsis-related mortality (measured by multiple causes) is systematically higher for males (depending on age group, males had 1.5 to 1.9 times higher mortality than females in 2011), and the sex differentials increased between 1998 and 2011 for all age groups. In both years and sexes, sepsis-related mortality was much higher in the elderly than in the age group 0-64. Finally, the mortality in the age group 65 and over increased 3.1 times in males and 2.7 times in females, while the corresponding relative increase in the age group 0–64 was 2.1 and 2.0. The recent rise of the sepsis-related mortality can thus be mainly attributed to the elderly population.

Table 3 shows the results of the comorbidity analysis for sepsis recorded on the death certificate as a multiple cause. The underlying causes of death listed in Table 2 were found to have a significant positive association with sepsis: the higher the CDAI, the stronger is the chance that if the patient suffers from the given underlying disease, he will develop sepsis in the clinical course. The strongest associations were found for diseases of skin and subcutaneous tissues, diseases of the urinary tract, and other infectious and parasitic diseases (including intestinal infections). Sepsis is thus the most likely to accompany an already developed infectious process (additionally, significant associations were found also for pneumonia and other acute lower respiratory diseases). The second type of association was observed for endocrine diseases (diabetes, obesity) and for malnutrition-related conditions (malnutrition *per* se and non-alcoholic digestive diseases), pointing at high risk of sepsis in patients weakened by metabolic disorders. Finally, chronically disabling conditions like rheumatoid arthritis and other musculoskeletal diseases are strong risk factors for developing sepsis. The associations were consistent across age and sex (the analysis was also performed separately for sex and age group 0–64 and 65+).

In Table 1, circulatory conditions and neoplasms were reported as frequent underlying causes of death for sep-

Table 2. Age-standardized death rates (per 100,000) for underlying and multiple coding of sepsis, Czech Republic, years 1998 and 2011

		All ages		0-64		65+	
		Underlying	Multiple	Underlying	Multiple	Underlying	Multiple
Males	1998	0.8	39.2	0.3	12.2	3.0	150.7
	2011	9.8	112.1	2.0	25.5	42.3	469.4
Females	1998	0.9	28.3	0.1	6.8	4.0	117.0
	2011	7.6	72.3	0.8	13.4	35.6	315.5

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Table 3. Comorbidity indicator (CDAI) for sepsis reported as multiple cause, Czech Republic 2011, both sexes and all ages combined

Underlying cause of death (with sepsis reported on the certificate)	CDAI	95% CI	ICD-10 codes
Intestinal infectious diseases	571	(432-754)	A00-A09
Other infectious and parasitic diseases	735	(519-1040)	A10-B99 (excluding sepsis)
Malignant neoplasm of lymphatic/haematopoietic tissue	223	(177-281)	C81-C96
Benign neoplasms, in situ neoplasms and neoplasms of uncertain/ unknown behaviourBenign neoplasms, in situ neoplasms and neoplasms of uncertain/unknown behaviour	259	(178-377)	D00-D48
Diseases of the blood(-forming organs) & immunological disorders	271	(151-487)	D50-D89
Diabetes mellitus	264	(225-309)	E10-E14
Malnutrition and other nutritional deficiencies	251	(138-458)	E40-E64
Obesity	294	(151-569)	E65-E68
Other endocrine, nutritional and metabolic diseases	267	(167-426)	E15-E35, E70-E90
Other diseases of the nervous system	172	(116-254)	G00-G13, G22-G26, G32-G37, G42-G99
Other diseases of the circulatory system	125	(111-141)	I26-I28, I34-I38, I70-I98 (excluding I49.0, I95.9)
Pneumonia	252	(219-290)	J12-J18
Other acute lower respiratory diseases	207	(110-392)	J00-J09, J19-J22
Other diseases of the respiratory system	219	(139-345)	J30-J39, J47, J80-J99 (excluding J96.0, J96.9)
Ulcer of stomach, duodenum and jejunum	256	(172-381)	K25-K28
Other diseases of the digestive system	519	(466-578)	K00-K24, K29-K67, K70-K71, K75-K93
Diseases of the skin and subcutaneous tissue	1487	(1185-1865)	L00-L99
Rheumatoid arthritis and osteoarthrosis	224	(112-449)	M05-M06, M15-M19
Other diseases of the musculoskeletal system/connective tissue	645	(414-1006)	M00-M04, M07-M14, M20-M99
Renal failure	277	(223-344)	N17-N19
Other diseases of kidney and ureter	935	(697-1255)	N00-N16
Hyperplasia of prostate	669	(303-1474)	N40
Other diseases of the genitourinary system	941	(754-1173)	N20-N39, N41-N99

sis, but the associations were not confirmed by the CDAIs (see Table 3). Cardiac and oncological patients (with exception of lymphatic, haematopoietic, benign and *in situ* neoplasms) are thus not at significantly increased risk for developing sepsis, even though in absolute terms, they represent (one or the other) 44% of sepsis-related deaths.

DISCUSSION

The analysis of sepsis mortality conducted in this study on multiple causes of death within a 14-year period (1998–2011) provided the first large-scale estimate of the prevalence, the structure, the time trends, the sex differentials, and the comorbidity of sepsis in the Czech Republic. Several similarities with the body of evidence already published in the field of the epidemiological research on sepsis were found. Sepsis-related mortality in the Czech Republic has increased annually by 8–9%, complying with the trends observed in other developed countries (in a study for a Veneto region in Italy [4], sepsis-related mortality increased by 45% between 2008 and 2013, in the U.S., sepsis mortality increased rapidly between 1993 and 2003 [20], although the increase has recently slowed down [12]). Apart from population ageing and increased reporting due to better medical awareness, following explanations were proposed to explain the recent rise of sepsis in the pathological course: increased use of invasive procedures and immunosuppressive therapies, and microbial resistance [3].

Compared to the multiple causes of death based studies conducted in Italy [4] and the U.S. [12], the presence of sepsis on the death certificates in the Czech Republic was lower: 6.3% in Italy (2008–2013) and 6% in the US (1999–2005) versus only 3% in the Czech Republic (the average value for 1998–2011). The share however increased from 1% in 1998 to 5% in 2011. Two possible explanations for higher prevalence of sepsis on death certificates in the Italy and the U.S. compared to the Czech Republic can be proposed: in the populations of Italy and the U.S., the share of elderly population is higher due to more advanced process of demographic ageing, which exposes more people at the age-related risk of sepsis. Second explanation focuses at the differences in certification and collection of the multiple causes of death in the Czech Republic: the sepsis may be still under-reported by the physicians on the death certificates, especially for lethal and common conditions like cancer and circulato-

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ry diseases (which have the lowest number of reported comorbidities). Analysis of age-standardized death rates also confirmed that males are at up to 1.9 higher risk of death related to sepsis than women, even though in absolute terms, more patients are women (who have higher chances to survive to old age). Similar sex differentials were observed in Italy [4], Germany [3] and the U.S. [12].
Sepsis is rarely causing the death itself. In most cases it occurs as a complication of an ongoing disease: 86% of sepsis cases were reported as immediate or antecedent cause of death. Inherently, the statistics based on the underlying cause of death strongly underestimate the burden of sepsis. The concept of the underlying cause of death as the unique cause of death for statistical tabulation has been adopted by the WHO Sixth Decennial International Revision Conference in 1948. The main idea behind the underlying cause of death is that if the death should be prevented, the initiating (underlying) cause of death is the primary target for public health measures. However, with increasing length of life, extended survival in chronic diseases, and increasing comorbidity, the treatment of the conditions associated with the main disease becomes increasingly decisive in the survival of the patient. As was shown here on the example of sepsis, multiple causes of death provide important information about the trends and the disparities of the immediate causes of death, and, in the long term, enable to assess the effectiveness of the medical management of these acute-care conditions.
Comorbidity analysis based on evaluating the statistical strength of the associations between diseases revealed that patients with an ongoing infectious disease, disease of skin, and metabolic or musculoskeletal disorder are at a particularly increased risk of dying from sepsis compared to patients with other underlying diseases. In these patients, targeted prevention and treatment of sepsis is the most needed.
So far, sepsis-related mortality has not received much attention in the Czech epidemiological research. The presented study pointed at a serious increase in sepsis-related mortality analogical to recent developments observed in other low-mortality countries. In the future, further progress in life expectancy accompanied by increased survival to advanced ages is expected in the Czech Republic. In both absolute and relative terms, more patients will thus be brought under the risk of developing sepsis. Educational programmes such as was the international "Surviving sepsis campaign" [21–22] and implementation of guidelines for sepsis management in acute care units are highly desirable [3].

CONCLUSION

Multiple causes of death provide an accurate and internationally comparable estimate of sepsis-related mortality. In the Czech Republic, the sepsis-related mortality has virtually tripled between 1998 and 2011. The increase was more pronounced in the elderly population and in males. In 2011, sepsis was reported in 8% of all in-hospital deaths, in 86% of the cases as immediate or antecedent condition. In 44% of the cases, circulatory disease or neoplasm was reported as the underlying cause. The comorbidity analysis revealed that patients previously weakened by infectious or skin diseases, and metabolic or musculoskeletal disorder are at significantly increased risk of developing sepsis. The trends in sepsis-related mortality were similar to other countries. Further increase in sepsis is expected along with the ongoing increase of the length of life. The sepsis burden thus may become more important in the near future.

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proLékaře.cz | 29.11.2026

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