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Sepsis-Related Mortality Rates and Trends Based on Site of Infection

OBJECTIVES: Sepsis is defined as life-threatening organ dysfunction triggered by an underlying infection. A recent study noted that the overall sepsis-related mortality rate in the United States is stable. In this study, we evaluated the sepsis-related mortality rates and trends associated with the three most common sites of infection.

DESIGN: Retrospective population-based study.

SETTING: Multiple Cause of Death (MCO) database available through the Centers for Disease Control and Prevention website.

PATIENTS: Decedents with sepsis-related deaths and the source of sepsis were identified using previously validated *International Classification of Diseases* codes.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: From 2004 to 2018, using the MCO, the age-adjusted mortality rate per 1,000,000 population from pulmonary sepsis was 111.8, from abdominal sepsis was 46.7, and from genitourinary sepsis was 52. Mortality rates from all three sites increased. Males had a higher mortality rate from pulmonary sepsis and abdominal sepsis and lower mortality rate from genitourinary sepsis. Black and Native American decedents had the highest mortality rates from all three sepsis sites. Compared with White decedents, Hispanic decedents had a higher mortality rate from pulmonary sepsis but lower rate from genitourinary sepsis. Asian decedents had the lowest mortality rates from abdominal and genitourinary sepsis but similar mortality rates from pulmonary sepsis as White decedents. The mortality rate increased in White and Native American decedents for all three sepsis sites, whereas in Hispanic decedents only abdominal and genitourinary sites increased, and in Black and Asian decedents only abdominal sepsis rates increased.

CONCLUSIONS: Despite the overall stable sepsis-related mortality rates, the rates secondary to pulmonary, abdominal, and genitourinary sepsis are increasing in both sexes and all age groups. This is likely due to improved identification/documentation of a site of infection in patients with sepsis. We noted significant racial variation in mortality rates/trends, which should be considered in future studies.

KEY WORDS: infection, mortality, sepsis, site, source

Sepsis is a life-threatening condition caused by a dysregulated immune response to infection (1). In the United States, sepsis is one of the leading causes of death (2) and was the most expensive medical condition to treat in 2017 (3). There are an estimated 1.7 million adult sepsis cases annually in the United States, and nearly one in three hospitalizations that end in death are associated with sepsis (4). The significant impact of sepsis on the U.S. healthcare system makes examining sepsis epidemiology of paramount importance.

Previous studies have shown an increasing prevalence of sepsis in the United States, partly driven by improved awareness and increased reimbursement

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KEY POINTS

- **Question:** The purpose of this study was to evaluate the sepsis-related mortality rates/trends associated with the three most common sites of infection.
- **Findings:** From 2004 to 2018, the average annual age-adjusted mortality rate per 1,000,000 population from pulmonary sepsis was 111.8, from abdominal sepsis was 46.7 and from genitourinary sepsis was 52. Mortality rates increased 22.4% from pulmonary sepsis, 28.0% from abdominal sepsis, and 53.2% from genitourinary sepsis.
- **Meaning:** The overall stable sepsis-related mortality rates but increasing rates secondary to pulmonary, abdominal, and genitourinary sepsis are likely due to improved identification/documentation of a site of infection in patients with sepsis.

associated with detecting and documenting patients as having sepsis (5). In contrast, the overall sepsis-related mortality rates (on average, 502 deaths per 1,000,000 population) have been stable since 2005 in both males and females (6). However, there were significant differences noted between races in both sepsis-related mortality rates and trends. Previous studies have noted that sepsis-related mortality and outcomes are influenced by the anatomic site of infection that triggers the sepsis (7, 8). To date, sepsis-related mortality rates stratified by the anatomic site of infection have not been evaluated. In addition, site-specific sepsis-related mortality trends have not been evaluated to determine if they are consistent with the overall stable trends noted for sepsis.

The objective of this study is to better describe the epidemiology of sepsis stratified by the three most common sites of infection (pulmonary, abdominal, and genitourinary tract) and demographics using the Multiple Cause of Death (MCO) database available through the Centers for Disease Control and Prevention (CDC).

MATERIALS AND METHODS

Study Design and Source of Data

In this population-based study, all data were obtained from the MCO) database available on the CDC

Wide-ranging Online Data for Epidemiologic Research (CDC Wonder) website (9). The death certificate data obtained from the state registries are compiled and published on the CDC Wonder website as aggregate data and mortality rates. The MCO) database contains up to 20 causes of death, a single underlying cause of death (UCD), and demographic data for each U.S. decedent. The UCD is defined by the World Health Organization as “the disease or injury which initiated the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury.” The diseases are coded using the *International Classification of Diseases*, 10th Revision (ICD-10). In 1999, the MCO) database converted from *International Classification of Diseases*, 9th Revision to exclusively ICD-10 coding. Detailed information about the database is available in our previous publication (10). All data are publicly available and do not contain any patient identifiers. This study which is part of our larger epidemiological project titled “Current Trends in Sepsis-Related Mortality in the United States” was reviewed and the need for informed consent was waived by the Loma Linda University Health Institutional Review Board (No. 5210024) on January 14, 2021. All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975.

Study Definitions and Variables

Similar to prior studies (6), ICD-10 codes were used to identify patients with sepsis and infections listed among any of the 20 causes of death irrespective of the UCD (**e-Table 1**, <http://links.lww.com/CCX/B70>). ICD-10 coding does not contain a separate code for septicemia or sepsis. Instead, the appropriate code for the underlying systemic infection is used (**e-Table 1**, <http://links.lww.com/CCX/B70>), or code A41.9 (sepsis, unspecified organism) is assigned if the type of infection or causal organism is not further specified (6, 11). To identify the anatomic site of sepsis, we used ICD codes for “sepsis” combined with “pneumonia” (pulmonary sepsis), “intra-abdominal infections” (abdominal sepsis), and “genitourinary infections” (genitourinary sepsis) (**e-Table 1**, <http://links.lww.com/CCX/B70>). Similar to prior studies, the specific terms for sites of infection were chosen a priori and were comprehensive as shown in **e-Table 1** (<http://links.lww.com/CCX/B70>). Of note, the subcategorizations for the

site of sepsis are not mutually exclusive. All decedents in the United States from 2004 to 2018 identified using the above search criteria were included in our analysis. Age-adjusted mortality rates were stratified by year of death, sex, age group, race-ethnicity (race), geography, and place of death. The race was categorized according to U.S. census standards as non-Hispanic White (White), Hispanic, Asian-Pacific Islander (Asian), non-Hispanic Black (Black), and American Indian-Alaska Native (Native American). The place of death was categorized as inpatient, outpatient/emergency department (outpatient), home, hospice, and nursing home/long-term care (nursing home). UCD was examined using ICD-10 codes for the respective source of infection (i.e., pneumonia for pulmonary sepsis), sepsis, malignant neoplasms (C00–C97), diabetes mellitus (E10–E14), dementia (G20–G21, G30), and cirrhosis (K70, K73–K74). These were chosen as they were the most common UCDs for all three infection sites. We

performed a single exploratory analysis to examine the overall mortality rates and trends for decedents coded with pneumonia, intra-abdominal, and genitourinary infections, both with and without sepsis.

Statistical Analysis

To identify differences in mortality between sites of infection, age-adjusted mortality rates were calculated to compare the groups over time. Age-adjusted mortality rates were used instead of crude mortality rates to ensure that the differences in death rates were not due to the differences in the age distribution of the populations being compared. The mortality rates were calculated using the July 1st population projections from the U.S. Census Bureau for the corresponding year. Similar to other recent studies (12), age-standardized mortality rates were calculated by standardizing to the 2000 U.S. standard population, which provides the

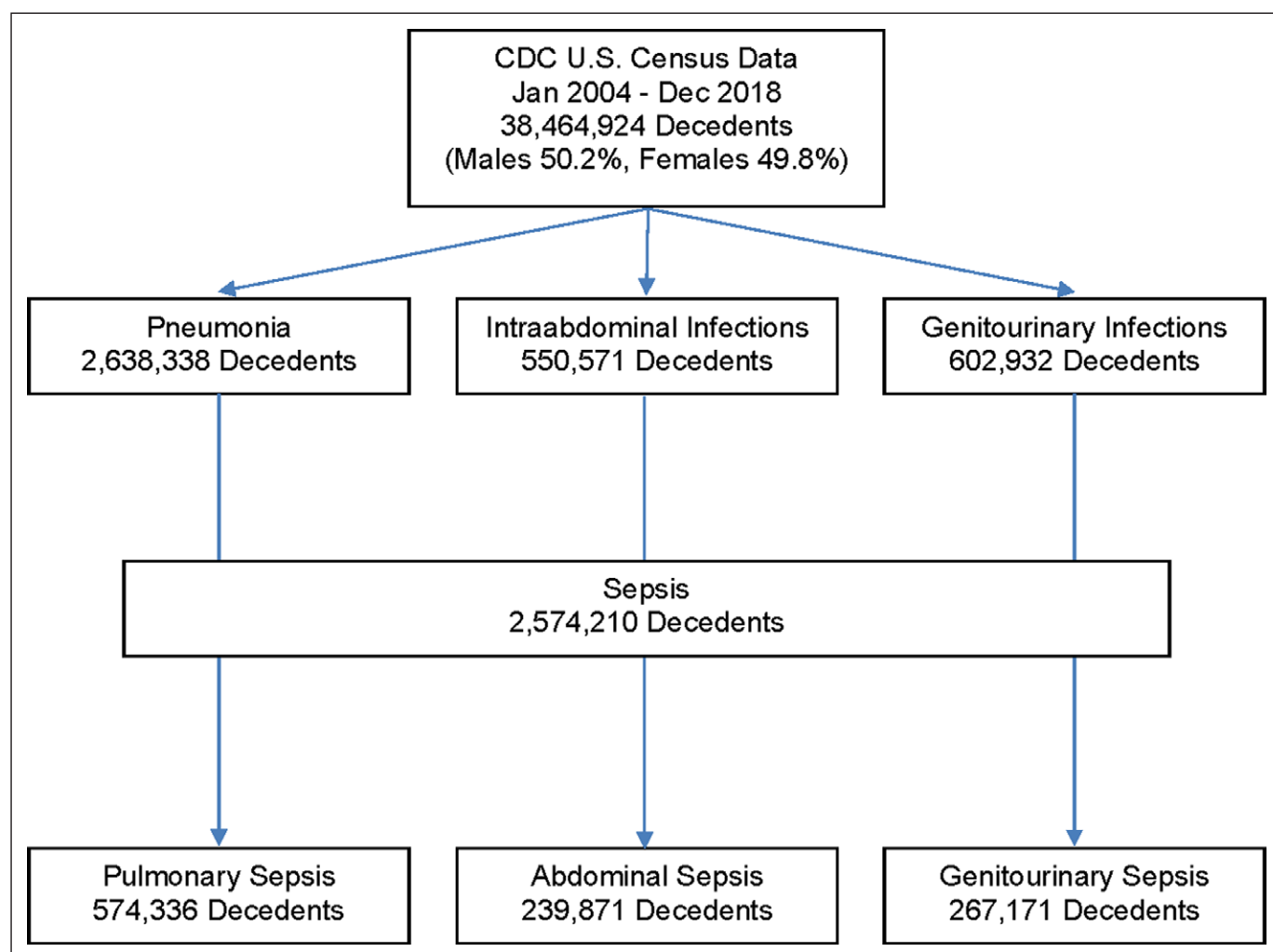


Figure 1. Flowchart showing the study cohort. CDC = Centers for Disease Control and Prevention.

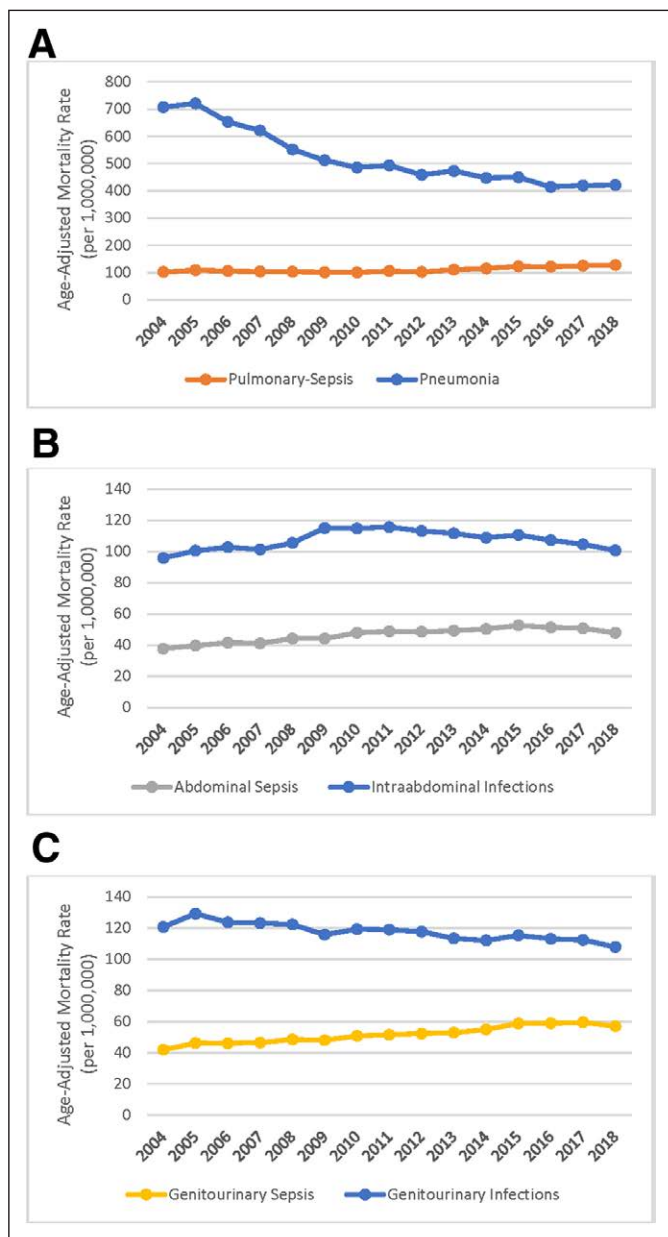


Figure 2. Age-adjusted mortality rates from (A) pneumonia and pulmonary sepsis, (B) intra-abdominal infections and abdominal sepsis, (C) genitourinary infections and genitourinary sepsis, in the United States, 2004–2018.

most current estimates available for age adjustment. Mortality rates are expressed per 1,000,000 persons. % Rate change from 2004 to 2018 was calculated by multiplying the annual percent rate change by 14. Rates are marked as “unreliable” when the death count is less than 20. Poisson regression modeling and negative binomial regression (for overdispersed data, deviance/degrees of freedom > 1) were used to calculate mortality rate ratios (RRs) and to analyze temporal trends in sepsis-related mortality from 2004 to 2018. All

analysis was performed using SPSS Version 27 (IBM Corp, Armonk, NY).

RESULTS

Study Cohort

Using the MCODE data, from 2004 to 2018, there were 2,574,210 deaths from sepsis (Fig. 1). There were 574,336 decedents with pulmonary sepsis (22.3%), 239,871 decedents with abdominal sepsis (9.3%), and 267,171 decedents with genitourinary sepsis (10.4%). There were 71,723 decedents who had more than one of these sources of sepsis.

Overall Trends

The annual average age-adjusted mortality rate per 1,000,000 persons was 111.8 for pulmonary sepsis, 46.7 for abdominal sepsis, and 52 for genitourinary sepsis. The age-adjusted mortality rates from pneumonia and genitourinary infections decreased significantly from 2004 to 2018 (56.0% [−11.2% to −36.4%] and 12.6% [−8.4% to −18.2%], respectively), and intra-abdominal infections decreased since 2011 by 5.6% (0% to −11.2%) (Fig. 2). However, the percentage of decedents with the above infections and concomitant sepsis increased from 2004 to 2018. The overall age-adjusted mortality rate per 1,000,000 persons from pulmonary sepsis increased from 102.8 in 2004 to 128.2 in 2018 (22.4%; $p < 0.001$), abdominal sepsis increased from 37.7 in 2004 to 48.0 in 2018 (28.0%; $p < 0.001$), and genitourinary sepsis increased from 41.8 in 2004 to 57.0 in 2018 (53.2%; $p < 0.001$).

Demographics

e-Table 2 (<http://links.lww.com/CCX/B70>) shows the differences in sepsis-related mortality stratified by demographics and e-Table 3 (<http://links.lww.com/CCX/B70>) shows the percent rate change in mortality rates between 2004 and 2018 stratified by demographics. Compared with females, males had a higher age-adjusted mortality rate from pulmonary sepsis (RR = 1.48) and abdominal sepsis (RR = 1.07) and a lower mortality rate from genitourinary sepsis (RR = 0.88). In pulmonary sepsis, the lowest age-adjusted mortality rate was seen in Asian and White decedents, followed by Hispanic decedents, and the highest was seen in Native American and Black

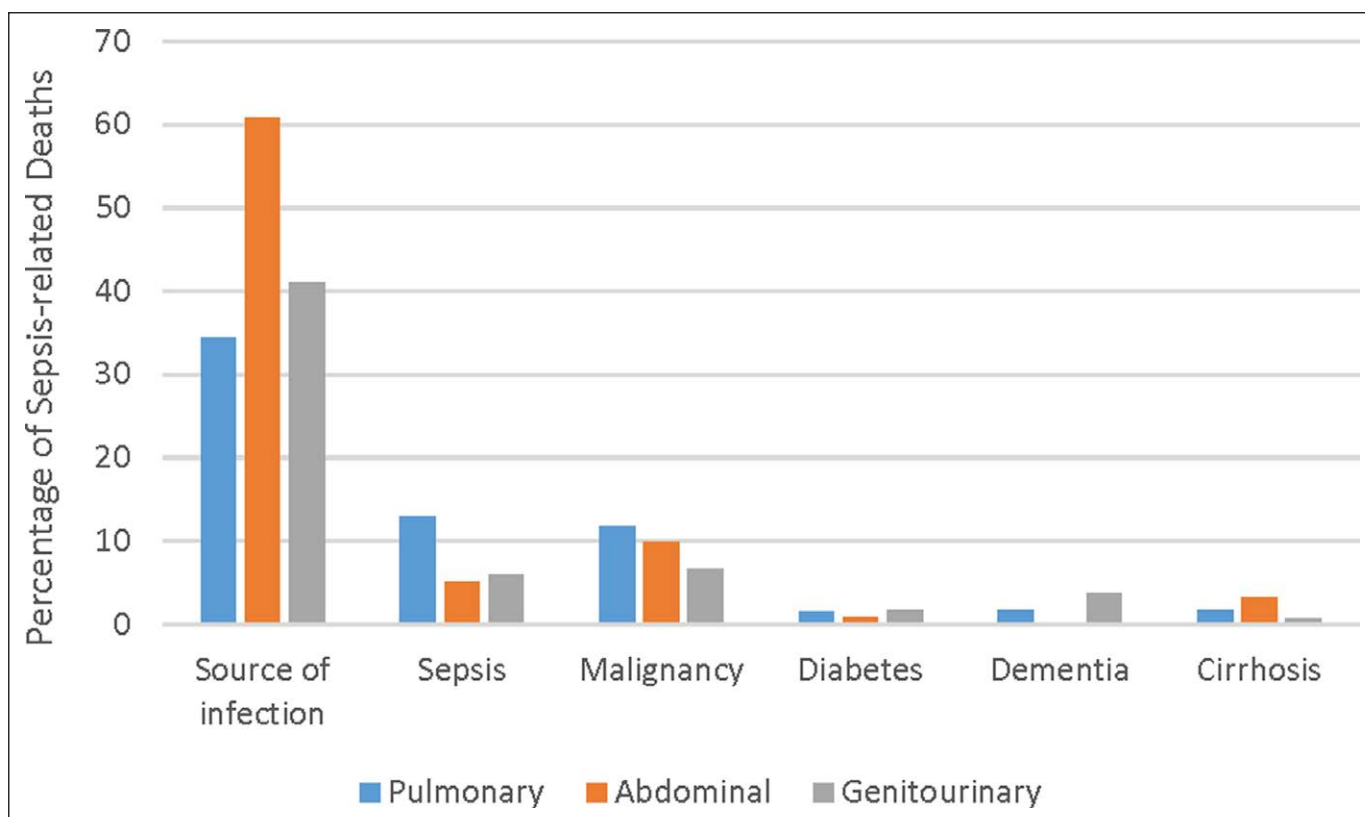


Figure 3. Underlying cause of death in decedents with sepsis in the United States by the anatomic site of infection. Source of infection refers to pneumonia for pulmonary sepsis, intra-abdominal infections for abdominal sepsis, and genitourinary infections for genitourinary sepsis.

decedents. In abdominal sepsis and genitourinary sepsis, the lowest age-adjusted mortality rate was seen in Asian decedents, followed by White and Hispanic decedents, and the highest was seen in Native American and Black decedents. There was a significant increase in sepsis-related mortality rates in association with all three infection sites in both males and females during this period.

The crude mortality rate from sepsis and all three infection sites was lowest in the 0–14 years age group, which increased in every subsequent older age group and was highest in the greater than or equal to 85 age group. There was a significant increase in sepsis-related mortality rates in association with all three infection sites in all age groups during this period.

In pulmonary sepsis, the age-adjusted mortality rate per 1,000,000 increased in Native American ($p < 0.001$) and White ($p < 0.001$) decedents; and was unchanged in Asian ($p = 0.30$), Black ($p = 0.41$), and Hispanic ($p = 0.55$) decedents. The abdominal sepsis mortality rate per 1,000,000 increased in all races ($p < 0.001$ for all races). While for genitourinary sepsis, the mortality rate per 1,000,000 increased in Native American ($p < 0.001$), White ($p < 0.001$), and Hispanic ($p < 0.001$)

decedents; and was unchanged in Asian (mean 30.9; $p = 0.34$) and Black (mean 74.3; $p = 0.99$) decedents.

Underlying Cause of Death

The percent of deaths by UCD is shown in **Figure 3**. In decedents with pulmonary sepsis, pneumonia, sepsis, and malignancies were listed as the UCD in 34.4%, 13%, and 11.8% of patients, respectively. The mortality rate increased from pneumonia ($p < 0.001$), sepsis ($p = 0.07$), and malignancy ($p < 0.001$) (not shown). In decedents with abdominal sepsis, intra-abdominal infections, sepsis, malignancies, and cirrhosis were listed as the UCD in 60.9%, 5.2%, 9.9%, and 3.2% of patients, respectively. The mortality rate increased from intra-abdominal infection ($p < 0.001$), sepsis ($p = 0.04$), malignancy ($p < 0.001$), and cirrhosis ($p < 0.001$) (not shown). In decedents with genitourinary sepsis, genitourinary infection, sepsis, malignancies, and dementia were listed as the UCD in 41.1%, 6.0%, 6.7%, and 3.9% of patients, respectively. The mortality rate increased from sepsis ($p = 0.002$), malignancy ($p < 0.001$), dementia ($p < 0.001$) but was unchanged from genitourinary infection ($p = 0.32$) (not shown).

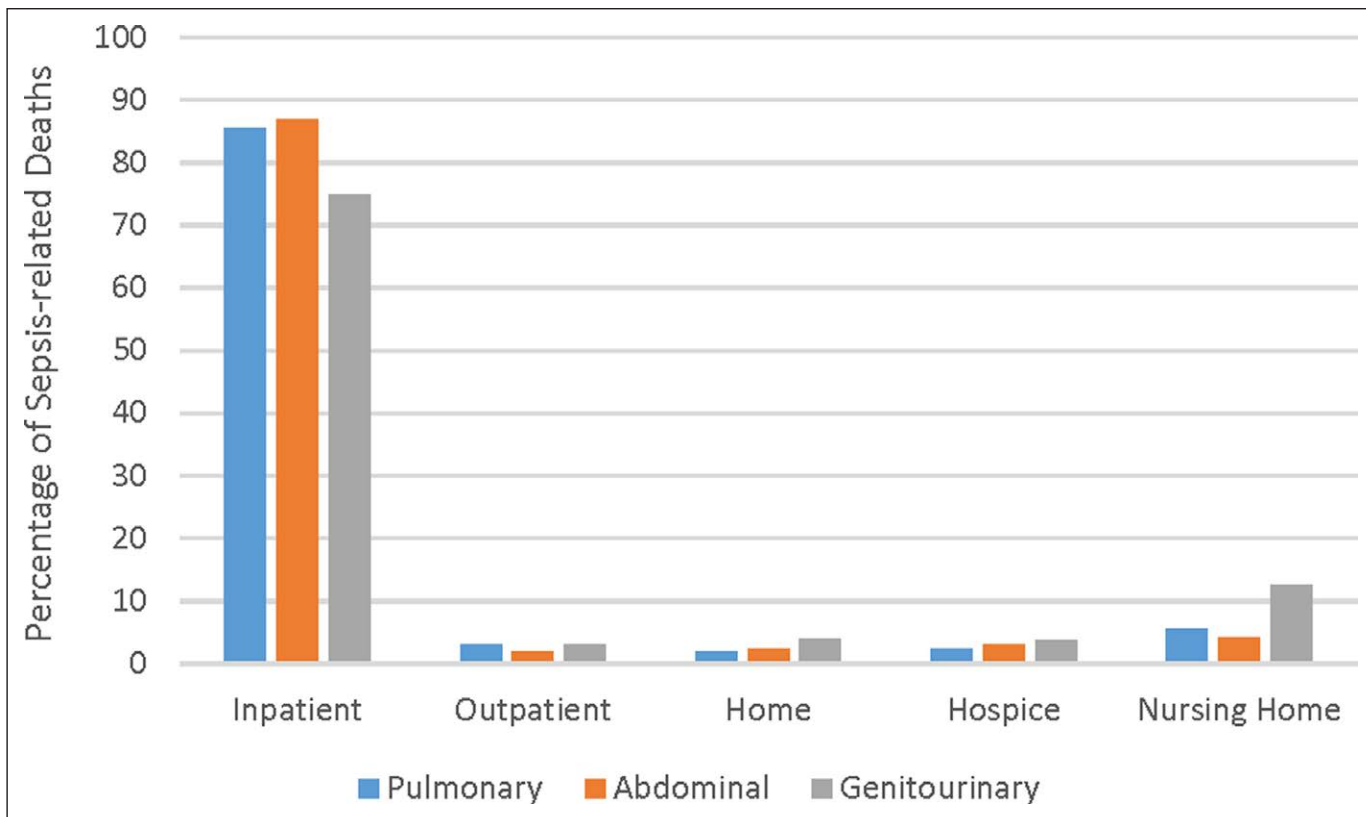


Figure 4. Place of death of decedents with sepsis in the United States by the anatomic site of infection.

Place of Death

The percentage of deaths by location is shown in **Figure 4**. The percentage of deaths in the inpatient setting with pulmonary, abdominal, and urinary sepsis was 85.5%, 86.8%, and 74.9%, respectively. The percentage of deaths in the inpatient setting decreased for abdominal sepsis ($p = 0.03$), was unchanged for pulmonary sepsis ($p = 0.28$) and genitourinary sepsis ($p = 0.17$) over the study period (not shown). The percentage of deaths at home and hospice increased in all three groups ($p < 0.001$ for both locations in all three groups). The percentage of deaths in the nursing home decreased in all three groups ($p < 0.001$ for pulmonary and genitourinary sepsis, and $p = 0.04$ for abdominal sepsis) (not shown).

DISCUSSION

A recent epidemiological study demonstrated stable overall sepsis-related mortality rates in the United States in both males and females (6). To date, studies have not evaluated the sepsis-related mortality rates and trends stratified by the anatomic site of infection. In this study, we examined the overall and demographic-specific sepsis-related mortality rates and

trends for the three most common sites of infection associated with sepsis. Our study demonstrates increasing sepsis-related mortality rates from all three major anatomic sites of infection. In contrast, the overall mortality rates from pneumonia, intra-abdominal, and genitourinary infections have been decreasing. Similar to our findings, Rhee et al (13) noted a steady increase in hospitalizations due to sepsis but stable or decreasing rates of hospitalizations from those same infections. The decline in rates of infection for these three sites are likely due to improvement in the mortality rates of comorbidities that are associated with developing these infections. However, in those who have already developed the infection, the risk of sepsis (and the mortality rate associated with it) has likely not improved. Consistent with this, in a secondary analysis of the UCD in decedents with pneumonia, the mortality rates from malignancy, heart diseases, and chronic lung diseases showed a decline but sepsis as an UCD increased (data not shown). The decrease in pneumonias in those with these chronic diseases could partly be explained by increased pneumococcal vaccination rates. In addition, early use of antimicrobials in those with chronic diseases may have led to decreased

mortality rates from infections but may have unintentionally led to the development of resistant infections and thus higher sepsis rates. The relatively lower decline in intra-abdominal infections may be due to difficulty in diagnosing these infections early since it often requires more intensive diagnostics than infections from pulmonary and genitourinary sources. The doubling of hospitalizations due to *Clostridium difficile* infections from 2001 to 2010 (14) also likely contributed to the increase in intra-abdominal infections that was noted until 2011.

Our finding of increasing sepsis-related mortality rates associated with these three sites of infections contrasts with the overall sepsis-related mortality rates that have been stable, as shown in our recent study (6). This difference is likely due to a proportional decrease in sepsis-related mortality rates from sites other than the three that were examined and/or reduction in cases of sepsis with unspecified/unknown sites. Increased awareness of sepsis and the importance of source control has likely improved efforts to determine the anatomic site of sepsis. Improved documentation on the death certificate, which requires indicating the cause of sepsis when one of the sepsis codes is listed, is another potential reason for the noted increase in sepsis mortality rates associated with these infection sites.

In our study, we noted differences in the site-specific sepsis mortality rates between males and females. Males had a significantly higher mortality rate from pulmonary and abdominal sepsis and a lower mortality rate from genitourinary sepsis. This is consistent with our previous study, which demonstrated that males had an approximately 26% higher age-adjusted sepsis-related mortality rate than females (6). Females likely have a higher incidence of genitourinary infections due to anatomic differences resulting in higher rates of genitourinary sepsis and mortality. The crude mortality rate for all three sources of sepsis was lowest in the less than 15 years age group and increased in every subsequent older age group with the highest rate in the greater than or equal to 85 years age group. There was a higher percentage of genitourinary tract infections in the greater than or equal to 85 years age group compared with the other two sites. In all age groups, there was an increase in sepsis-related mortality associated with the three anatomic sites of infection studied. The greatest increase in mortality rate from 2004 to 2018 was in the 15–64 years age groups for all three

infection sites. This finding is consistent with our prior study and is likely due to increased comorbidities in this age group, especially malignancies (6).

Our study also revealed significant racial differences in site-specific sepsis-related mortality. The highest mortality rate from pulmonary and genitourinary sepsis was in Black decedents, and from abdominal sepsis was in Native American decedents. Asian decedents had the lowest mortality rates from genitourinary and abdominal sepsis but had similar mortality rates from pulmonary sepsis as in White decedents. Mortality rate in Hispanic decedents was higher than White decedents from pulmonary sepsis but similar for intra-abdominal sepsis and lower for genitourinary sepsis. Racial disparities in sepsis-related mortality are likely multifactorial including differences in environmental factors, access to healthcare, and genetic predisposition (15). Differences in comorbidities such as cancer, diabetes, obesity, and hypertension, which are well known to increase the risk for sepsis, are also possible contributing factors (16, 17). Further research is needed to understand the factors contributing to site-specific racial differences in sepsis.

As expected, the majority of pulmonary, abdominal, and genitourinary sepsis-related deaths occurred in the inpatient setting. There was a significantly higher percentage of deaths from genitourinary sepsis in the nursing home than compared with home or hospice settings. In nursing homes, genitourinary infection is one of the most common causes of sepsis and bacteremia, the majority of which are catheter-related (18). Consistent with prior studies, we noted that the percentage of sepsis-related deaths in the hospice setting increased over our study period for all three sepsis sources (6, 19). This likely reflects policies by the U.S. healthcare system to increase the use of advance directives and improve access to hospice care services toward the end of life.

Implications and Next Steps

The variation in sepsis-related mortality rates and trends based on the site of infection and demographic constitution highlights the importance of considering these differences in the efforts to reduce the burden of sepsis. The site of infection should be an important factor when developing sepsis-related policies and in efforts to target populations with a higher prevalence of sepsis. The anatomic site of infection should be

considered in future research studies as an important variable in evaluating biomarkers, prognostic scoring systems, and outcomes for sepsis. This could result in the development of a more personalized treatment approach based on the site of sepsis.

Strengths/Limitations

This study has several strengths. This is the first study to evaluate sepsis-related mortality rates and trends stratified by the anatomic site of infection. The use of the MCODE database allowed us to capture every death in the United States without sampling, including deaths in nonhospital settings, which accounted for 15–25% of sepsis-associated deaths (which would not be included in studies using hospital discharge databases). Efforts and policies to label patients with sepsis for “benchmarking” or to optimize reimbursement are less likely to influence death certificate documentation of sepsis.

The primary study limitation is that we cannot confirm the accuracy of the data and misclassification of sepsis and infections can result from both inaccuracies in diagnosis and in the documentation on the death certificates. ICD-10 codes for sepsis have been previously used to study sepsis in administrative datasets (20, 21) but to the best of our knowledge, ICD-10 codes for sepsis according to the site of infection have not been validated in U.S. studies. Previous studies have demonstrated lower sensitivity for explicit sepsis codes compared with implicit codes (infection and organ dysfunction). However, the use of explicit codes has a low likelihood of false positives (22), and the sensitivity increases with increased severity of sepsis (23). It is possible that some anatomic sites are more likely to be coded with sepsis than other sites. However, given that this study focused on the three sites that are most commonly known to be associated with sepsis, it is unlikely that this would have been a significant contributing factor for the differences seen. In addition, the focus of this study was to describe the mortality rates and trends for each site associated with sepsis and highlight differences among demographic groups for each site rather than comparing between the different sites.

CONCLUSIONS

From 2004 to 2018, we noted that the sepsis-related mortality rates from the three most common infection

sites (pulmonary, abdominal, and genitourinary) increased in males and females and in all age groups despite overall stable sepsis mortality rates. However, there were gender and racial differences in sepsis-related mortality rates associated with these sites of infections. These differences between the anatomic sites of infection should be considered in future sepsis trials because it could have implications in clinical decision makings and the development of health policies.

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Dr. Nguyen and Ms. Rajah contributed equally to this article.

Dr. Jeganathan conceived the idea and designed the study; he involved in analysis of the data; and he has a master's in clinical research and expertise in statistics. All authors involved in data acquisition. All authors contributed to the data interpretation and edited the article. The article was drafted by all the authors.

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