HHS Public Access

Author manuscript

*Crit Care Med*. Author manuscript; available in PMC 2020 September 01.

Published in final edited form as:

*Crit Care Med*. 2019 September ; 47(9): 1169–1176. doi:10.1097/CCM.0000000000003817.

# Epidemiology of Hospital-Onset versus Community-Onset Sepsis in U.S. Hospitals and Association with Mortality: A Retrospective Analysis Using Electronic Clinical Data

**Chanu Rhee, MD, MPH**[1,2], **Rui Wang, PhD**[1], **Zilu Zhang, BS**[1], **David Fram, BA**[3], **Sameer S. Kadri, MD, MSc**[4], **Michael Klompas, MD, MPH**[1,2] **CDC Prevention Epicenters Program**

[1]Department of Population Medicine, Harvard Medical School/Harvard Pilgrim Health Care Institute, Boston, MA.

[2]Department of Medicine, Brigham and Women's Hospital, Boston, MA.

[3]Commonwealth Informatics, Waltham, MA.

[4]Critical Care Medicine Department, Clinical Center, National Institutes of Health, Bethesda, MD.

## Abstract

**Objectives—**Prior studies have reported that hospital-onset (HO)-sepsis is associated with higher mortality rates than community-onset (CO)-sepsis. Most studies, however, have used inconsistent case-finding methods and applied limited risk-adjustment for potential confounders. We used consistent sepsis criteria and detailed electronic clinical data to elucidate the epidemiology and mortality associated with HO-sepsis.

**Design—**Retrospective cohort study

**Setting—**136 U.S. hospitals in the Cerner HealthFacts dataset

**Patients—**Adults hospitalized in 2009–2015

**Interventions—**None

**Measurements and Main Results—**We identified sepsis using CDC Adult Sepsis Event criteria and estimated the risk of in-hospital death for HO-sepsis versus CO-sepsis using logistic regression models. In patients admitted without CO-sepsis, we estimated risk of death associated with HO-sepsis using Cox regression models with sepsis as a time-varying covariate. Models were adjusted for baseline characteristics and severity-of-illness. Among 2.2 million hospitalizations, there were 95,154 sepsis cases: 83,620 (87.9%) CO-sepsis and 11,534 (12.1%) HO-sepsis (0.5% of hospitalized cohort). Compared to CO-sepsis, HO-sepsis patients were younger (median 66 vs 68 years) but had more comorbidities (median Elixhauser score 14 vs 11), higher Sequential Organ Failure Assessment scores (median 4 vs 3), higher ICU admission rates (61% vs 44%), longer hospital length-of-stay (median 19 vs 8 days), and higher in-hospital mortality (33% vs 17%) ($p<0.001$ for all comparisons). On multivariate analysis, HO-sepsis was associated with higher

**Corresponding Author:** Chanu Rhee, MD, MPH (crhee@bwh.harvard.edu), Address: Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, 401 Park Drive, Suite 401, Boston, MA 02215, Phone: 617-509-9987, Fax: 617-859-8112.

mortality versus CO-sepsis (odds ratio 2.1, 95% CI 2.0–2.2) and patients admitted without sepsis (hazard ratio 3.0, 95% CI 2.9–3.2).

**Conclusions—**HO-sepsis complicated 1 in 200 hospitalizations and accounted for 1 in 8 sepsis cases, with 1 in 3 patients dying in-hospital. HO-sepsis preferentially afflicted ill patients but even after risk-adjustment they were twice as likely to die as CO-sepsis patients; in patients admitted without sepsis, HO-sepsis tripled the risk of death. HO-sepsis is an important target for surveillance, prevention, and quality improvement initiatives.

**Keywords**

sepsis; hospital-onset sepsis; community-onset sepsis; Adult Sepsis Event; epidemiology

## INTRODUCTION

Sepsis is a leading cause of death in hospitalized patients.[1, 2] Local and national initiatives now seek to improve early sepsis recognition and treatment. To date, much of this effort has focused on patients presenting to the hospital with sepsis.[3–7] However, epidemiologic studies suggest that hospital-onset sepsis may account for 10–20% of sepsis cases and is associated with worse outcomes compared to community-onset sepsis.[8–10]

More attention is now being directed towards improving recognition and treatment of hospital-onset sepsis [11], but there remain important gaps in our knowledge. In particular, it is unclear to what degree the poor outcomes associated with hospital-onset sepsis are due to patient's underlying comorbidities and severity-of-illness versus modifiable factors such as quality of care.[2] Prior studies provide limited insight into this question and the true epidemiology of hospital-onset sepsis since most have used administrative data to identify sepsis. Administrative data are unreliable for sepsis surveillance, however, because clinicians and hospitals differ widely in their diagnosis patterns as well as their completeness and specificity of coding for sepsis and organ dysfunction.[12–14] In addition, administrative analyses use present-on-admission codes to differentiate hospital versus community-onset-sepsis but these are often inaccurate and variably used by hospitals.[15–17] Finally, administrative data do not allow for detailed risk-adjustment for patients' severity-of-illness on admission and at the time of sepsis onset.

The U.S. Centers for Disease Control and Prevention (CDC) recently released the Adult Sepsis Event surveillance definition that uses objective clinical data to identify sepsis cases, thereby enhancing the consistency of surveillance across hospitals.[18, 19] Importantly, Adult Sepsis Events flags the day of sepsis onset using clinical criteria, allowing more precise differentiation between hospital-onset versus community-onset sepsis.[19]

In this study, we used CDC Adult Sepsis Event criteria and detailed electronic health record (EHR) data to elucidate the epidemiology of hospital-onset sepsis and its association with mortality in a large set of diverse hospitals.

# METHODS

## Study Design, Data Source, and Population

This was a retrospective cohort study using the Cerner HealthFacts dataset, a de-identified database populated with clinical data from geographically diverse U.S. hospitals.[1, 20–23] The study cohort included adult patients (≥20 years old) admitted as inpatients from January 2009 through September 2015 to 136 hospitals previously used in a national epidemiologic study of sepsis.[1] We included all hospitals that reported all data elements necessary to identify Adult Sepsis Events, including laboratory test results, medications, and blood culture orders. Hospitals did not necessarily report data in each year of the study period. Hospitalizations with missing discharge dispositions or those with *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) rather than ICD-9-CM codes were excluded. This study was approved by the Institutional Review Board at Harvard Pilgrim Health Care Institute with a waiver of informed consent.

## Identifying Hospital-Onset vs Community Onset Sepsis

Sepsis cases were identified using CDC's Adult Sepsis Event criteria, which flag hospitalizations with clinical indicators of *presumed serious infection* and *concurrent organ dysfunction*.[18] This definition is optimized for objective retrospective surveillance using EHR data and has high concordance with Sepsis-3 criteria.[1, 19, 24] Presumed serious infection is defined as a blood culture order and administration of ≥4 consecutive days of new antibiotics starting within +/−2 days. Fewer than 4 antibiotic days are allowed if death, discharge to hospice, or discharge to another acute care hospital occurs before 4 days. Organ dysfunction is defined as the initiation of vasopressors or mechanical ventilation, lactate ≥2.0 mmol/L, doubling in baseline creatinine or decrease in estimated glomerular filtration rate by ≥50%, doubling in total bilirubin to ≥2.0 mg/dL, or ≥50% decrease in platelet count to <100 cells/μL.

As per CDC criteria, sepsis was defined as hospital-onset if the blood culture, first antibiotic day, and organ dysfunction all occurred on hospital day 3 or later (with hospital day 1 being the day of admission).[18] Patients meeting any sepsis criteria before day 3 were defined as community-onset sepsis. Patients with community-onset sepsis who later developed hospital-onset sepsis were counted as community-onset sepsis cases, such that the two groups were mutually exclusive.

## Statistical Analyses

Two sets of modeling analysis results are presented. The first model included patients admitted without community-onset sepsis. To estimate the risk of mortality associated with developing hospital-onset sepsis, we used a Cox regression model with sepsis as a time-varying covariate. We adjusted for baseline characteristics, including demographics (age, sex, race) and comorbidities using the Agency for Healthcare Research and Quality (AHRQ) modified Elixhauser comorbidity index based on ICD-9-CM codes.[25] We also adjusted for some comorbidities not included in the Elixhauser index that might influence sepsis outcomes (leukemia [ICD-9-CM codes 204–208], stem cell transplant [V42.81 and V42.82], and solid organ transplant [V42.0–42.7, V42.83, V42.84, V42.89, V42.9]). We further

adjusted for year of admission, hospital characteristics (region, bed size, and teaching vs non-teaching), admission from a healthcare facility, and severity-of-illness at hospital presentation (using the worst values within +/−1 day of admission) through vital signs (temperature, systolic blood pressure, respiratory rate), Glasgow coma scale, vasopressor use, need for mechanical ventilation, care in the intensive-care-unit (ICU), and laboratory data (serum lactate, creatinine, bilirubin, liver function tests, platelet count, hematocrit, sodium, and anion gap). We also adjusted for positive blood cultures (excluding common skin contaminants) and for suspected infection on admission, defined by sampling of clinical cultures from any anatomic site and any antibiotic administration.

The second model included patients who had sepsis, either of community-onset or hospital-onset. To evaluate the effect of hospital-onset versus community-onset sepsis on risk of mortality, we conducted a multivariate logistic regression analysis. We adjusted for similar covariates as described above except that when controlling for severity of illness, we used the worst physiologic parameters within +/−1 calendar day of sepsis onset (defined as the earliest day the index blood culture was drawn or antibiotic first administered within the window meeting Adult Sepsis Event criteria) for hospital-onset sepsis. In addition, we controlled for source of infection (pneumonia, urinary, intra-abdominal, skin/soft tissue infection, septicemia, central nervous system, obstetric/gynecologic, two or more, or none of these), identified through ICD-9-CM codes (Supplemental Table 1) and positive blood cultures at sepsis onset.[26]

Multiple imputation was used to account for missing data in severity-of-illness covariates (described further in the Supplemental Methods). In contrast to laboratory data, vital signs and Glasgow Coma scale are inconsistently reported by hospitals in Cerner HealthFacts but data availability was substantially higher in 2013–2013 vs 2009–2012. Therefore, we conducted a sensitivity analysis in the subset of patients admitted in 2013–2015. In the 2013–2015 subset, we also conducted a sensitivity analysis replacing all physiologic parameters (laboratory data, vasopressors, mechanical ventilation, vital signs, Glasgow Coma Scale) with the Sequential Organ Failure Assessment (SOFA) score in order to create a more parsimonious model based on an established severity-of-illness score.[24, 27] Lastly, we conducted a sensitivity analysis limited to patients across the entire 2009–2015 study cohort with no missing covariates. All tests of significance used two-sided p-values at ≤0.05. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.3.1 (r-project.org).

## RESULTS

### Patient Characteristics

The study cohort included 2,216,032 adult hospital encounters from 136 hospitals (Figure 1). The highest geographic representation of hospitals was from the South (35%), and most were nonteaching facilities (60%) and had fewer than 200 beds (65%) (Supplemental Table 2). Of the 2.2 million hospitalized patients, 95,154 had sepsis (4.3%), and 11,534 (12.1%) of these were hospital-onset (0.5% of the entire hospitalized cohort). Of the hospital-onset sepsis patients, 4,840 (42.0%) were in an ICU on the day of sepsis onset.

Patient characteristics are shown in Table 1. Compared to community-onset sepsis, hospital-onset sepsis patients were slightly younger (median age 66 vs 68) but had more comorbidities (median AHRQ Elixhauser score 14 vs 11) including heart failure (26.2% vs 21.8%), renal disease (23.6% vs 19.7%), and cancer (17.7% vs 11.2%) ($p<0.001$ for all comparisons). Hospital-onset sepsis patients had higher rates of intra-abdominal infections (20.6% vs 15.6%) but slightly lower rates of pneumonia (23.9% vs 25.6%), urinary tract infections (24.1% vs 27.3%), and skin/soft tissue infection (6.9% vs 7.8%) (Figure 2A). Hospital-onset sepsis patients also had higher rates of positive blood cultures (18.8% vs 15.5%). The distribution of the most frequent bloodstream pathogens differed between the two groups; Escherichia, *Staphylococcus aureus*, and Streptococcus species were the 3 most common pathogens in community-onset sepsis, while *Staphylococcus aureus*, Enterococcus, and Candida species were the most common in hospital-onset sepsis (Table 2). Hospital-onset sepsis patients had higher SOFA scores at sepsis onset (median 4 vs 3, $p<0.001$) and met Adult Sepsis Event organ dysfunction criteria more often from vasopressors (48.0% vs 30.5%) and mechanical ventilation (25.4% vs 21.8%) as opposed to elevated lactate (31.2% vs 41.5%) and doubling in creatinine (26.2% vs 40.1%) (Figure 2B). Among hospital-onset sepsis patients with cancer diagnoses (n=2,040), 550 (27.0%) had leukopenia (as defined by white blood cell count $<2.0 \times 10^9$ cells/L) on the day of sepsis onset, compared to 1,084 of 9,494 (11.4%) hospital-onset sepsis patients without cancer ($p<0.001$).

Hospitalized patients without sepsis (n=2,120,878) tended to be younger than either community or hospital-onset sepsis (median age 59), with fewer comorbidities (median Elixhauser score 0) and rarely had diagnosis codes for infectious syndromes or laboratory-confirmed bacteremia (Table 1).

### Risk of Death from Acquiring Hospital-Onset Sepsis

Compared to hospitalized patients who never developed sepsis, those who acquired hospital-onset sepsis were more frequently admitted to the ICU (60.7% vs 8.7%), had longer hospital lengths-of-stay (median 19 vs 4 days) and ICU length-of-stays (median 6 vs 3 days), and died more often (33.4% vs 1.6%) ($p<0.001$ for all). Without adjustment for baseline characteristics and severity-of-illness, the hazard ratio for death associated with hospital-onset sepsis was 5.1 (95% 4.9–5.3). Adjusting for confounders diminished but did not eliminate the increased risk of death associated with hospital-onset sepsis (hazard ratio 3.0, 95% CI 2.9–3.2) (full model shown in Supplemental Table 3).

The quantity of missing data in 2013–2015 vs the entire 2009–2015 cohort is shown in Supplemental Table 4. A sensitivity analysis restricting the cohort to patients admitted from 2013–2015 (with more complete vital sign and GCS data) demonstrated similar results, as did sensitivity analyses using the SOFA score for severity-of-illness adjustment and restricting the cohort to patients without any missing covariates (Supplemental Table 5).

### Risk of Death in Hospital-Onset vs Community-Onset Sepsis

Compared with community-onset sepsis, patients with hospital-onset sepsis had longer hospital lengths-of-stay (median 19 vs 8 days), were admitted to the ICU more often (60.7% vs 44.1%), had longer ICU lengths-of-stay (median 6 vs 4 days), and had higher in-hospital

mortality rates (33.4% vs 16.8%, unadjusted odds ratio 2.5, 95% CI 2.4–2.6). On multivariate analysis, hospital-onset sepsis remained significantly associated with higher risk of in-hospital death compared to community-onset sepsis (adjusted odds ratio 2.1, 95% CI 2.0–2.2) (full model shown in Supplemental Table 3). Sensitivity analyses limited to hospitalizations in 2013–2015, using the SOFA score for severity-of-illness adjustment, and restricting the cohort to patients without any missing covariates yielded similar results (Supplemental Table 5).

## DISCUSSION

Using clinical data from a large cohort of U.S. hospitals, we found that hospital-onset sepsis complicated 1 in 200 hospitalizations and increased the hazard of death 3-fold in patients initially admitted without sepsis after adjusting for baseline characteristics and severity-of-illness on admission. Hospital-onset sepsis accounted for 1 in 8 sepsis cases; these patients had more comorbidities and more organ dysfunction than those with community-onset sepsis. After adjusting for confounders, hospital-onset sepsis was still associated with a 2-fold higher odds of death compared to community-onset sepsis.

Our estimates of the burden of hospital-onset sepsis fall within the range reported using administrative data.[8–10] Using present-on-admission flags and an “implicit” sepsis definition based on infection and organ dysfunction codes, Page et al. found that 11% of sepsis cases in academic hospitals in the University HealthSystems Consortium were hospital-acquired, with mortality rates of 19% vs 9% for community-onset sepsis.[8] Another analysis in the Premier Healthcare Database using explicit sepsis codes reported hospital-onset sepsis accounted for 13% of all sepsis cases, with mortality rates of 31% vs 13% for present-on-admission sepsis.[10] Similar findings were reported in a 6-hospital system in Texas using explicit sepsis codes.[9]

Our analysis expands on these prior studies by using CDC Adult Sepsis Event criteria, which are more sensitive than explicit sepsis codes, more specific than implicit sepsis codes, and allow for more consistency in sepsis detection between hospitals.[1] Adult Sepsis Events are also better suited to identifying the timing of sepsis onset since present-on admission codes are variably applied by hospitals and often inaccurate.[15–17] This reduces the risk of misclassification and allows for better adjustment for time-dependent bias. Our analysis also incorporated detailed physiologic and laboratory data to provide more robust risk-adjustment than possible using administrative data alone.

There are relatively few other data on the additional risk of death conferred by developing sepsis in the hospital. One prospective study found that among patients initially admitted to the ICU with a non-infectious diagnosis, ICU-onset infections carried an attributable mortality fraction of 21%.[28] Two single-center cohorts estimated an adjusted hazard ratio of 1.5 and adjusted odds ratio of 1.7, respectively, for mortality associated with nosocomial infection after controlling for confounders.[29, 30] Our study provides sepsis-specific estimates and is more generalizable since it draws from a larger cohort of hospitals and also includes non-ICU patients. The latter is particularly important since we found that more than half of hospital-onset sepsis events occurred outside of the ICU.

Our findings also shed light on specific differences in the types of patients that develop hospital-onset versus community-onset sepsis. For example, cancer was more common in hospital-onset sepsis patients. Cancer patients receiving chemotherapy agents that induce neutropenia or other immunosuppressed states may be predisposed to hospital-onset sepsis, and sepsis is associated with very poor outcomes in this population.[31] This is supported by the high rate of leukopenia (27%) when hospital-onset sepsis developed in cancer diagnoses in our dataset. Patterns of infections were also different, with more intra-abdominal infections in hospital-onset sepsis. This is concordant with reports suggesting that surgical patients have higher rates of hospital-onset sepsis.[8] The higher severity-of-illness in hospital-onset sepsis patients was reflected by higher SOFA scores and more frequent need for vasopressors and mechanical ventilation at sepsis onset, whereas community-onset sepsis more frequently had elevated lactate levels and acute kidney injury.

The persistent two-fold higher odds of death with hospital-onset versus community-onset sepsis even after risk-adjustment begs the question of whether this is due to residual confounding or potentially modifiable care factors. One potential explanation is the higher incidence of antibiotic-resistant strains in hospital-acquired infections, which may contribute to inappropriate empiric antibiotics and higher mortality in hospital-onset sepsis.[32, 33] In addition, inpatient clinical teams may be slower to recognize and manage hospital-onset sepsis compared to clinicians in the emergency department, where a large amount of attention has been paid to implementing sepsis recognition and treatment bundles.[3–7, 34] Underscoring these differences, prior studies have found that serum lactates are less likely to be drawn in hospital-onset sepsis, while a recent analysis found lower compliance with the Centers for Medicare and Medicaid Services “SEP-1” bundle in hospital-onset vs community-onset sepsis cases.[35–37] This may point to an opportunity to reduce sepsis morbidity and mortality by developing systems to improve recognition and management of hospital-onset sepsis.[11]

Our study has important limitations. First, our findings may not necessarily generalize to all hospitals, particularly to large academic hospitals as these were underrepresented in our sample. Second, our definition of community-onset sepsis does not distinguish infections acquired in prior healthcare settings from infections acquired in the community. However, we included admission from healthcare facilities as a covariate in our models. Third, we defined community-onset and hospital-onset sepsis as mutually exclusive groups, but some patients with community-onset sepsis also develop hospital-onset sepsis. Our results may therefore underestimate the incidence of hospital-onset sepsis. Fourth, we relied on administrative data to identify the likely source of infection, which may have limited accuracy and variable performance across hospitals. Fifth, data missingness was high in our dataset for vital signs and Glasgow Coma Scale. However, results of our regression analyses were consistent in sensitivity analyses limiting the cohort to the later years when these data were more populated, and in patients with non-missing data. Sixth, the granularity of severity-of-illness variables was limited to calendar days, and it is possible that our analyses might have inadvertently adjusted for abnormal physiology on the causal pathway from sepsis onset to death. More precise severity-of-illness adjustment at the moment of sepsis onset or immediately prior might yield more reliable estimates of the mortality risk with hospital-onset versus community-onset sepsis. However, identifying the exact sepsis “time

zero" is a major challenge even on detailed medical reviews, particularly for hospital-onset sepsis.[38] Furthermore, adjusting for the worst physiologic parameters around the day of sepsis onset rather than the preceding day allowed for parity in our comparison of hospital-onset vs community-onset sepsis since patients in the latter group presented to the hospital with sepsis. Lastly, as with all observational studies, our findings are at risk for residual confounding. Potential important factors we were unable to adjust for due to dataset limitations included vasopressor doses, PaO2:FiO2 ratios, patient insurance status, admitting service for hospitalized patients, Medicare Severity Diagnosis Related Groups, and antibiotic-resistance patterns. There may also be other subtle markers of frailty as well as concurrent acute illnesses in hospitalized patients that develop sepsis that cannot be easily measured using EHR and administrative data. This is an important topic for future research.

In conclusion, in this large U.S. cohort we found that hospital-onset sepsis complicated 1 in 200 hospital admissions, accounted for 1 in 8 sepsis cases, and preferentially afflicted ill patients. Even after adjusting for severity-of-illness, hospital-onset sepsis patients were twice as likely to die as community-onset sepsis patients; in patients admitted without sepsis, hospital-onset sepsis tripled the risk of death. These findings underscore the importance of targeting hospital-onset sepsis with surveillance, prevention, and quality improvement efforts.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

**Financial Support:** This work was funded by the Centers for Disease Control and Prevention (U54CK000484), the Agency for Healthcare Research and Quality (K08HS025008 to C.R.), and intramural funds from the National Institutes of Health Clinical Center and National Institute of Allergy and Infectious Diseases (S.S.K.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality or the National Institutes of Health.

**Copyright form disclosure:** Rhee received support for article research from the Agency for Healthcare Research and Quality and the Centers for Disease Control and Prevention (CDC). Drs. Rhee and Klompas received funding from UptoDate. Dr. Fram's institution received funding from Harvard Pilgrim Health Care Institute; he received funding from Commonwealth Informatics; and he disclosed work for hire. Dr. Kadri received support for article research from the National Institutes of Health, and he disclosed government work. Dr. Klompas' institution received funding from the CDC and Massachusetts Department of Public Health. The remaining authors have disclosed that they do not have any potential conflicts of interest.

## REFERENCES

1. Rhee C, Dantes R, Epstein L et al.: Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009–2014. JAMA 2017, 318(13):1241–1249. [PubMed: 28903154]
2. Rhee C, Jones TM, Hamad Y et al.: Prevalence, Underlying Causes, and Preventability of Sepsis-Associated Mortality in US Acute Care Hospitals. JAMA Netw Open 2019, 2(2):e187571. [PubMed: 30768188]
3. Rivers E, Nguyen B, Havstad S et al.: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001, 345(19):1368–1377. [PubMed: 11794169]
4. Pro CI, Yealy DM, Kellum JA et al.: A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014, 370(18):1683–1693. [PubMed: 24635773]

5. Investigators A, Group ACT, Peake SL et al.: Goal-directed resuscitation for patients with early septic shock. N Engl J Med 2014, 371(16):1496–1506. [PubMed: 25272316]
6. Seymour CW, Gesten F, Prescott HC et al.: Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. N Engl J Med 2017, 376(23):2235–2244. [PubMed: 28528569]
7. Venkatesh AK, Slesinger T, Whittle J et al.: Preliminary Performance on the New CMS Sepsis-1 National Quality Measure: Early Insights From the Emergency Quality Network (E-QUAL). Ann Emerg Med 2018, 71(1):10–15 e11. [PubMed: 28789803]
8. Page DB, Donnelly JP, Wang HE: Community-, Healthcare-, and Hospital-Acquired Severe Sepsis Hospitalizations in the University HealthSystem Consortium. Crit Care Med 2015, 43(9):1945–1951. [PubMed: 26110490]
9. Jones SL, Ashton CM, Kiehne LB et al.: Outcomes and Resource Use of Sepsis-associated Stays by Presence on Admission, Severity, and Hospital Type. Med Care 2016, 54(3):303–310. [PubMed: 26759980]
10. Paoli CJ, Reynolds MA, Sinha M et al.: Epidemiology and Costs of Sepsis in the United States-An Analysis Based on Timing of Diagnosis and Severity Level. Crit Care Med 2018.
11. Schorr C, Odden A, Evans L et al.: Implementation of a multicenter performance improvement program for early detection and treatment of severe sepsis in general medical-surgical wards. J Hosp Med 2016, 11 Suppl 1:S32–S39. [PubMed: 27805796]
12. Rhee C, Jentzsch MS, Kadri SS et al.: Variation in Identifying Sepsis and Organ Dysfunction Using Administrative Versus Electronic Clinical Data and Impact on Hospital Outcome Comparisons. Crit Care Med 2018.
13. Jolley RJ, Sawka KJ, Yergens DW et al.: Validity of administrative data in recording sepsis: a systematic review. Crit Care 2015, 19(1):139. [PubMed: 25887596]
14. Iwashyna TJ, Odden A, Rohde J et al.: Identifying patients with severe sepsis using administrative claims: patient-level validation of the angus implementation of the international consensus conference definition of severe sepsis. Med Care 2014, 52(6):e39–43. [PubMed: 23001437]
15. Goldman LE, Chu PW, Osmond D et al.: The accuracy of present-on-admission reporting in administrative data. Health Serv Res 2011, 46(6pt1):1946–1962. [PubMed: 22092023]
16. Meddings J, Saint S, McMahon LF Jr.: Hospital-acquired catheter-associated urinary tract infection: documentation and coding issues may reduce financial impact of Medicare's new payment policy. Infect Control Hosp Epidemiol 2010, 31(6):627–633. [PubMed: 20426577]
17. Meddings JA, Reichert H, Rogers MA et al.: Effect of nonpayment for hospital-acquired, catheter-associated urinary tract infection: a statewide analysis. Ann Intern Med 2012, 157(5):305–312. [PubMed: 22944872]
18. Centers for Disease Control and Prevention: Hospital Toolkit for Adult Sepsis Surveillance [https://www.cdc.gov/sepsis/pdfs/Sepsis-Surveillance-Toolkit-Mar-2018_508.pdf]
19. Rhee C, Dantes RB, Epstein L et al.: Using objective clinical data to track progress on preventing and treating sepsis: CDC's new 'Adult Sepsis Event' surveillance strategy. BMJ Qual Saf 2018.
20. Choudhry SA, Li J, Davis D et al.: A public-private partnership develops and externally validates a 30-day hospital readmission risk prediction model. Online J Public Health Inform 2013, 5(2):219. [PubMed: 24224068]
21. Goyal A, Spertus JA, Gosch K et al.: Serum potassium levels and mortality in acute myocardial infarction. JAMA 2012, 307(2):157–164. [PubMed: 22235086]
22. Lagu T, Pekow PS, Shieh MS et al.: Validation and Comparison of Seven Mortality Prediction Models for Hospitalized Patients With Acute Decompensated Heart Failure. Circ Heart Fail 2016, 9(8).
23. Petrick JL, Nguyen T, Cook MB: Temporal trends of esophageal disorders by age in the Cerner Health Facts database. Ann Epidemiol 2016, 26(2):151–154 e151–154. [PubMed: 26762962]
24. Rhee C, Zhang Z, Kadri SS et al.: Sepsis Surveillance Using Adult Sepsis Events Simplified eSOFA Criteria Versus Sepsis-3 Sequential Organ Failure Assessment Criteria. Crit Care Med 2019, 47(3):307–314. [PubMed: 30768498]
25. Moore BJ, White S, Washington R et al.: Identifying Increased Risk of Readmission and In-hospital Mortality Using Hospital Administrative Data: The AHRQ Elixhauser Comorbidity Index. Med Care 2017, 55(7):698–705. [PubMed: 28498196]

26. Rhee C, Zhang Z, Kadri SS et al.: Sepsis Surveillance Using Adult Sepsis Events Simplified eSOFA Criteria Versus Sepsis-3 SOFA Criteria. Crit Care Med In Press.
27. Vincent JL, Moreno R, Takala J et al.: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996, 22(7): 707–710. [PubMed: 8844239]
28. van Vught LA, Klein Klouwenberg PM, Spitoni C et al.: Incidence, Risk Factors, and Attributable Mortality of Secondary Infections in the Intensive Care Unit After Admission for Sepsis. JAMA 2016, 315(14):1469–1479. [PubMed: 26975785]
29. Koch AM, Nilsen RM, Eriksen HM et al.: Mortality related to hospital-associated infections in a tertiary hospital; repeated cross-sectional studies between 2004–2011. Antimicrob Resist Infect Control 2015, 4:57. [PubMed: 26719795]
30. Fabbro-Peray P, Sotto A, Defez C et al.: Mortality attributable to nosocomial infection: a cohort of patients with and without nosocomial infection in a French university hospital. Infect Control Hosp Epidemiol 2007, 28(3):265–272. [PubMed: 17326016]
31. Williams MD, Braun LA, Cooper LM et al.: Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. Crit Care 2004, 8(5):R291–298. [PubMed: 15469571]
32. Tabah A, Koulenti D, Laupland K et al.: Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study. Intensive Care Med 2012, 38(12):1930–1945. [PubMed: 23011531]
33. Kadri SS, Adjemian J, Lai YL et al.: Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and Outcome of Resistance to All First-line Agents. Clin Infect Dis 2018, 67(12):1803–1814. [PubMed: 30052813]
34. Lundberg JS, Perl TM, Wiblin T et al.: Septic shock: an analysis of outcomes for patients with onset on hospital wards versus intensive care units. Crit Care Med 1998, 26(6):1020–1024. [PubMed: 9635649]
35. Rhee C, Murphy MV, Li L et al.: Lactate Testing in Suspected Sepsis: Trends and Predictors of Failure to Measure Levels. Crit Care Med 2015, 43(8):1669–1676. [PubMed: 25962082]
36. Han X, Edelson DP, Snyder A et al.: Implications of Centers for Medicare & Medicaid Services Severe Sepsis and Septic Shock Early Management Bundle and Initial Lactate Measurement on the Management of Sepsis. Chest 2018, 154(2):302–308. [PubMed: 29804795]
37. Rhee C, Filbin MR, Massaro AF et al.: Compliance With the National SEP-1 Quality Measure and Association With Sepsis Outcomes: A Multicenter Retrospective Cohort Study. Crit Care Med 2018, 46(10):1585–1591. [PubMed: 30015667]
38. Rhee C, Brown SR, Jones TM et al.: Variability in determining sepsis time zero and bundle compliance rates for the centers for medicare and medicaid services SEP-1 measure. Infect Control Hosp Epidemiol 2018:1–3.

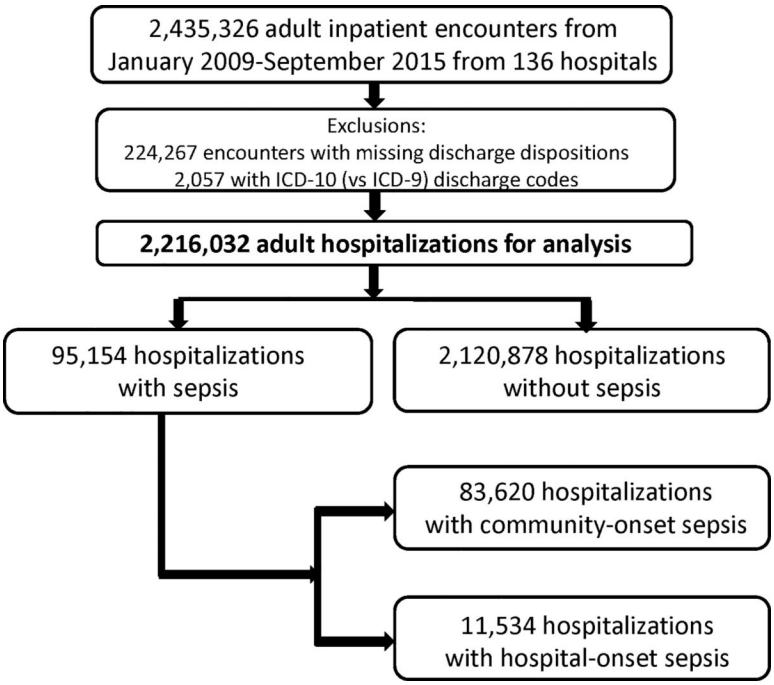


**Figure 1.**
Study cohort derivation from Cerner HealthFacts dataset

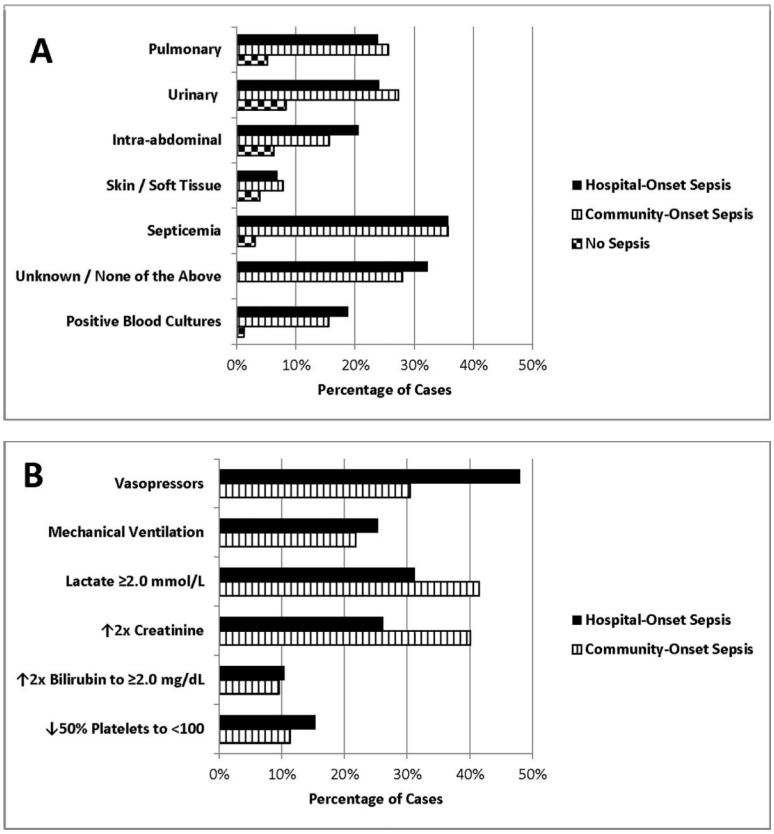


**Figure 2. Comparison of major clinical characteristics in patients with hospital-onset sepsis, community-onset sepsis, and no sepsis.**

**A**, Infectious diagnoses and syndromes in patients with hospital-onset vs community-onset sepsis vs no sepsis. All categories were identified by ICD-9-CM discharge diagnosis codes, except for positive blood cultures (obtained by microbiology data). **B,** Dysfunctional organs (by Centers for Disease Control and Prevention Adult Sepsis Event Criteria) at sepsis onset.

**Table 1.**

Characteristics of Hospitalized Patients with Hospital-Onset Sepsis, Community-Onset Sepsis, and No Sepsis

| Characteristics | No Sepsis (N=2,120,878) | Community-Onset Sepsis (N=83,620) | Hospital-Onset Sepsis (N=11,534) |
|---|---|---|---|
| Median Age (IQR) | 59 (42–74) | 68 (55–80) | 66 (55–77) |
| Sex | | | |
| Male (or Unknown[a]) | 868171 (40.9%) | 40,093 (48.0%) | 6,186 (53.6%) |
| Female | 1,252,707 (59.1%) | 43,519 (52.0%) | 5,348 (46.4%) |
| Race | | | |
| White | 1,524,588 (71.9%) | 61,744 (73.8%) | 7,826 (67.9%) |
| Black | 401,836 (18.9%) | 15,408 (18.4%) | 2,766 (24.0%) |
| Other (or Unknown)[a] | 194,4454 (9.2%) | 6,468 (7.7%) | 942 (8.2%) |
| Select Comorbidities[b] | | | |
| Cancer | 122,410 (5.8%) | 9,365 (11.2%) | 2,040 (17.7%) |
| Chronic Lung Disease | 332,744 (15.7%) | 19,843 (23.7%) | 2,439 (21.2%) |
| Congestive Heart Failure | 217,932 (10.3%) | 18,260 (21.8%) | 3,025 (26.2%) |
| Diabetes | 465,303 (21.9%) | 24,789 (29.6%) | 3,205 (27.8%) |
| Liver Disease | 54,828 (2.6%) | 4,813 (5.8%) | 851 (7.4%) |
| Neurologic Disease | 181,685 (8.6%) | 14,866 (17.8%) | 1,728 (15.0%) |
| Peripheral Vascular Disease | 46,832 (2.2%) | 6,663 (8.0%) | 1,428 (12.4%) |
| Renal Disease | 222,006 (10.5%) | 16,482 (19.7%) | 2,720 (23.6%) |
| AHRQ Elixhauser Score[c] | 0 (-1–8) | 11 (3–20) | 14 (5–24) |
| Admitted from Healthcare Facility[d] | 138,192 (6.5%) | 9,571 (11.5%) | 1,523 (13.2%) |
| ICU on Day of Sepsis Onset | N/A | 32,692 (39.1%) | 4,840 (42.0%) |
| SOFA Score on Day of Sepsis Onset | N/A | 3 (2–5) | 4 (2–7) |
| Positive Blood Cultures | 25,098 (1.2%) | 12,951 (15.5%) | 2,163 (18.8%) |
| Hospital LOS | 4 (3–6) | 8 (5–13) | 19 (12–30) |
| Admitted to ICU | 184,671 (8.7%) | 36,868 (44.1%) | 7,006 (60.7%) |
| ICU LOS | 3 (2–4) | 4 (3–7) | 6 (3–11) |
| Death | 32,937 (1.6%) | 14,025 (16.8%) | 3,851 (33.4%) |

Abbreviations: AHRQ = Agency for Healthcare Research and Quality, ICU = intensive care unit, SOFA = Sequential Organ Failure Assessment, LOS = length-of-stay.

[a]Sex was missing in 499 cases (0.02%) and race was missing in 40,699 cases (1.8%).

[b]The cancer comorbidity includes the Elixhauser categories of solid tumor without metastases, metastatic tumor, and lymphoma. It also includes codes for leukemia. Diabetes includes diabetes with and without complications.

[c]The AHRQ Elixhauser score is weighted and allows for negative points for comorbidities with an inverse association with mortality.

[d]Healthcare facilities include acute care hospitals, non-acute care facilities, hospice, and ambulatory surgery centers.

p-values were <0.001 for all comparisons between hospital-onset and community-onset sepsis.

**Table 2.**

Top 10 Most Frequent Blood Culture Pathogens in Patients with Community-Onset vs Hospital-Onset Sepsis

| Rank | Community-Onset Sepsis (n=12951) | Hospital-Onset Sepsis (n=2,163) |
|---|---|---|
| 1 | Escherichia – 2,876 (22.2%) | Staphylococcus aureus - 514 (23.8%) |
| 2 | Staphylococcus aureus - 2,592 (20.0%) | Enterococcus - 243 (11.2%) |
| 3 | Streptococcus – 2,283 (17.6%) | Candida - 240 (11.1%) |
| 4 | Klebsiella – 1,090 (8.4%) | Escherichia - 236 (10.9%) |
| 5 | Enterococcus – 806 (6.2%) | Klebsiella - 220 (10.2%) |
| 6 | Candida - 566 (4.4%) | Streptococcus - 160 (7.4%) |
| 7 | Proteus - 476 (3.7%) | Pseudomonas – 133 (6.1%) |
| 8 | Pseudomonas – 454 (3.6%) | Enterobacter – 73 (3.4%) |
| 9 | Enterobacter – 290 (2.2%) | Acinetobacter – 43 (2.0%) |
| 10 | Serratia – 139 (1.1%) | Bacteroides – 36 (1.7%) |

For each hospitalization, only the first positive blood culture was counted.