Risk of Acute Stroke After Hospitalization for Sepsis
A Case-Crossover Study

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Background and Purpose—Infections have been found to increase the risk of stroke over the short term. We hypothesized that stroke risk would be highest shortly after a sepsis hospitalization, but that the risk would decrease, yet remain up to 1 year after sepsis.

Methods—This case-crossover analysis utilized data obtained from the California State Inpatient Database of the Healthcare Cost and Utilization Project. All stroke admissions were included. Exposure was defined as hospitalization for sepsis or septicemia 180, 90, 30, or 15 days before stroke (risk period) or similar time intervals exactly 1 or 2 years before stroke (control period). Conditional logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (95% CI) for the association between sepsis/septicemia and ischemic or hemorrhagic stroke.

Results—Ischemic (n=37 377) and hemorrhagic (n=12 817) strokes that occurred in 2009 were extracted where 3188 (8.5%) ischemic and 1101 (8.6%) hemorrhagic stroke patients had sepsis. Sepsis within 15 days before the stroke placed patients at the highest risk of ischemic (OR, 28.36; 95% CI, 20.02–40.10) and hemorrhagic stroke (OR, 12.10; 95% CI, 7.54–19.42); however, although the risk decreased, it remained elevated 181 to 365 days after sepsis for ischemic (OR, 2.59; 95% CI, 2.20–3.06) and hemorrhagic (OR, 3.92; 95% CI 3.29–4.69) strokes. There was an interaction with age (P=0.0006); risk of developing an ischemic stroke within 180 days of hospitalization for sepsis increased 18% with each 10-year decrease in age.

Conclusions—Risk of stroke is high after sepsis, and this risk persists for up to a year. Younger sepsis patients have a particularly increased risk of stroke after sepsis. **(*Stroke*. 2017;48:574-580. DOI: 10.1161/STROKEAHA.116.016162.)**

Key Words: intracranial hemorrhages ■ ischemic stroke ■ sepsis ■ stroke

Stroke is the fifth leading cause of death in the United States and the leading cause of serious long-term adult disability, with ≈795 000 stroke events in the United States each year.[1] Although much is known about long-term stroke risk factors, such as hypertension, diabetes mellitus, and atherosclerotic disease, much less is known about short-term risk factors, or triggers, for stroke.[2]

Infection has been identified as a potential risk factor and trigger for stroke. Chronic infection, as assessed by serologies against several common bacterial and viral infections, was associated with increased long-term stroke risk.[3] In a case-crossover analysis from the Cardiovascular Health Study, a recent hospitalization for infection was associated with an increased risk of stroke.[4]

Recent evidence suggests that severe sepsis is associated with new-onset atrial fibrillation, thereby increasing risk of stroke.[5] Furthermore, a population-based cohort study from Denmark showed that ≈80% of cardiovascular events after exposure to bacteremia occurred during the index hospitalization.[6] Although other work shows that the risk of stroke is the highest in the first 3 to 15 days after infection.[4,7] We hypothesized that sepsis would be associated with risk of stroke after hospitalization for septicemia and that the risk would be highest closest in time to the event.

Methods

Study Setting and Inclusion/Exclusion Criteria

This case-crossover analysis utilized data obtained from the California State Inpatient Database, Healthcare Cost and Utilization Project, and Agency for Healthcare Research and Quality for 2007 to 2009. Under Healthcare Cost and Utilization Project, claims data for each discharge is collected, deidentified, and standardized from various states and then made available to researchers. The California State Inpatient Database contains data for all patients hospitalized in nonfederal acute care California hospitals. Data elements include demographic information such as age, sex, race, and insurance payer. For each admission discharge diagnosis code (up to 25 *International Classification of Diseases*-Ninth Revision [ICD-9] codes), month of discharge, length of stay in hospital, and Agency for Healthcare Research and Quality comorbidity measures are available. There are designations for primary diagnosis and whether the condition was present on arrival for each ICD-9 code, allowing identification of

Received November 21, 2016; final revision received December 20, 2016; accepted December 28, 2016.

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Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.116.016162**

preexisting diagnoses versus complications that arise during hospitalization. A visitlink variable allows for tracking a patient over time through multiple hospital admissions.

The study population comprised patients with an ischemic or hemorrhagic stroke during hospitalization in any nonfederal acute care hospital in California in the year 2009. The exposure of interest was septicemia or sepsis. A case-crossover analysis was used to investigate the association between septicemia/sepsis and subsequent stroke. This design is useful in studying acute events, such as stroke, brought on by exposures that transiently increase the risk for having an event.[8] Data from a relatively short risk period preceding the event (case period) is compared with another control time period in the same individual, and exposures that are present more frequently in the risk period than the control period can be considered to be precipitants. In this study, design cases act as their own controls, and thus the design inherently controls for interindividual variability and confounding.[4]

Exposure and Covariates

The previous exposure was defined as hospitalization for sepsis 365, 180, 90, 30, or 15 days before stroke (case period) or similar time intervals exactly 1 or 2 years before stroke (control period). Septicemia or sepsis was defined by the following diagnostic codes present on arrival at any diagnostic position: 038.xx (septicemia), 020.0 (septicemic), 790.7 (bacteremia), 117.9 (disseminated fungal infection), 112.5 (disseminated candida infection), 995.91(sepsis), 995.92 (severe sepsis), or 785.52 (septic shock).[5] These diagnostic codes have been previously used in identification of sepsis cases in administrative datasets.[5] Patients with admission codes for endocarditis and meningococcemia were not included in the sample as these are known direct risk factors for stroke. Septicemia or sepsis before stroke was considered as an exposure event. Risk time periods assessed were 0 to 15, 0 to 30, 0 to 90, 0 to 180, and 0 to 365 days.[6,7] In addition to the risk time periods described above, we assessed the risk of stroke within the time intervals 0 to 15, 16 to 30, 31 to 90, 91 to 180, and 181 to 365 days.

Outcomes

Ischemic stroke was defined using ICD-9 codes 433.x1 (x, the fourth digit, can vary to specify a specific arterial distribution), 434 (excluding 434.x0), or 436 present at any diagnostic position between DX1 and DX12. Cases were excluded if any traumatic brain injury ICD-9-CM codes (800–804, 850–854) or rehabilitation care ICD-9-CM code (V57) was present as the primary diagnosis.[8] Hemorrhagic stroke was defined with ICD-9 codes 430 to 431 present at any diagnostic position.[9]

The California State Inpatient Database does not provide separable dates for each ICD-9 code within the same hospitalization, potentially limiting the assignment of temporal relationships among events within each admission. Simply deleting all hospital admissions in which stroke and sepsis occurred together, however, would lead to missing many cases of in-hospital stroke that were precipitated by sepsis. Thus, 2 different data sets were created, one utilizing more restrictions on cases than the other. In both data sets, we only included sepsis present on arrival, to avoid the inclusion of patients who developed sepsis as a complication of stroke (reverse causation). In the first data set (the primary analytic sample), all hospital admissions in which both stroke and sepsis were present on arrival were omitted, to avoid uncertain temporality. The second data set (the restrictive data set) omitted all admissions for which any kind of stroke and sepsis occurred in the same admission during all 3 years of data. Thus, using the restrictive data set analysis, all comparisons were only between separate admissions for stroke and sepsis. In addition, any sepsis that may have occurred in the previous years because of a stroke was also removed from the analysis in the second data set. In the restrictive data set, strokes that may have occurred because of hospitalization with sepsis were deleted if stroke was indicated to be present on admission.

Statistical Analysis

Conditional logistic regression stratified on the variable visitlink, a variable created within the database to link patients in the sample without identifying information, was used to compute odds ratios (ORs) and 95% confidence intervals (95% CI) for any hospital admission with stroke within 0 to 15, 0 to 30, 0 to 180, and 0 to 365 days after exposure. We further assessed risk of stroke post sepsis at nonoverlapping time intervals after sepsis by investigating the risk at 0 to 15, 16 to 30, 31 to 90, 91 to 180, and 181 to 365 days. Ischemic and hemorrhagic stroke were studied separately for each time period. Interactions between sepsis and age and sex and diabetes mellitus were investigated, and stratification by age performed as indicated. All hypothesis tests performed during the analysis of the primary end points are 2 sided and use an α of 0.05.

Results

Primary Analysis Study Population

A total of 37 377 ischemic strokes and 12 817 hemorrhagic strokes that occurred in 2009 were extracted in the primary data set. Of the ischemic strokes, 3188 (8.5%) had at least 1 case of sepsis in the 365-day risk period before their stroke. Among hemorrhagic strokes, 1101 (8.6%) had at least 1 case of sepsis in the 365-day risk period before their stroke.

Mean hospital length of stay was higher in patients with both stroke and sepsis (ischemic stroke, 9.7±16.8 days; hemorrhagic stroke, 13.2±19.7 days) than in patients with stroke only (ischemic, 4.9±7.9 days; hemorrhagic, 8.2±11.9 days; Table 1). The frequencies of comorbidities such as diabetes mellitus, chronic obstructive pulmonary disease, paralysis, and renal failure were higher in patients with both stroke and sepsis or septicemia than in patients with stroke only (Table 1). The higher prevalence of paralysis among those with sepsis and stroke could reflect previous stroke or that patients with sepsis are more likely to have embolic strokes or severe strokes that are more likely to involve paralysis. It is difficult to assess these possibilities because we did not have the granular detail that would allow us to assess stroke severity or etiologic from these data.

Sepsis was associated with an increased risk of ischemic (OR, 28.36; 95% CI, 20.02–40.10) and hemorrhagic (OR, 12.10; 95% CI, 7.54–19.42) stroke within 15 days. The risk of stroke after sepsis persisted as the time interval from sepsis to stroke increased, but the magnitude of the risk decreased as the time interval was increased (Table 2). The risk of ischemic (OR, 3.92; 95% CI, 3.58–4.29) and hemorrhagic stroke (OR, 7.38; 95% CI, 6.54–8.34) remained significantly elevated after increasing the time interval to 365 days after the sepsis event.

In analyses utilizing nonoverlapping time intervals from sepsis to stroke (Table 3), the risk of ischemic stroke was greatest in the first 15 days post-sepsis hospitalization, decreased markedly from 16 to 30 days after sepsis, but remained increased by ≈2.5-fold out as long as 181 to 365 days after sepsis. The pattern for hemorrhagic stroke was somewhat different, with an elevated risk in the first 15 days, with the risk decreasing more linearly for time intervals 16 to 30, 31 to 90, 91 to 180, and 181 to 365 days (Table 3). The risk remained ≈4× higher even in the 181- to 365-day interval.

Secondary Analysis

A total of 37 377 ischemic strokes and 12 817 hemorrhagic strokes that occurred in 2009 were in the secondary restrictive

Table 1. Baseline Characteristics of Ischemic and Hemorrhagic Stroke Patients With and Without Sepsis/Septicemia Preceding Stroke

Variable	All Ischemic Stroke Cases (n=37 377)	Ischemic Stroke Cases Without Exposure to Septicemia (n=34 189)	Ischemic Stroke Cases With Exposure to Septicemia (n=3188)	All Hemorrhagic Stroke Cases (n=12 817)	Hemorrhagic Stroke Cases Without Exposure to Sepsis (n=11 716)	Hemorrhagic Stroke Cases With Exposure to Sepsis (n=1101)
Age, y	71.7	71.5	74.1	66.7	66.4	69.3
SD (range)	14.6 (18–104)	14.6 (18–104)	13.6 (18–101)	16.9 (18–101)	17 (18–101)	15.8 (18–97)
No. of chronic conditions	6.8	6.7	8.3	6	5.8	7.8
SD (range)	2.9 (1–22)	2.8 (1–22)	3.1 (1–21)	2.9 (1–101)	2.8 (1–20)	3.1 (1–18)
Length of stay, d	5.4	4.9	9.7	8.6	8.2	13.2
SD (range)	9.1 (0–351)	7.9 (0–345)	16.8 (0–351)	12.8 (0–274)	11.9 (0–253)	19.7 (0–274)
Women, n (%)	19 476 (52.2)	17 798 (52.2)	1678 (52.8)	6123 (48.2)	5626 (48.4)	497 (45.3)
Race, n (%)						
White	21 824 (60.87)	20 081 (61.2)	1743 (56.9)	6443 (53.4)	5956 (54)	487 (46.5)
Black	3601 (10.4)	3239 (9.9)	362 (11.8)	1030 (8.5)	913 (8.3)	117 (11.2)
Hispanic	6528 (18.2)	5900 (18)	628 (20.5)	2708 (22.4)	2436 (22)	272 (26)
Asian/pacific Islander	3237 (9)	2956 (9)	281 (9.2)	1615 (13.4)	1458 (13.2)	157 (15)
Other	640 (1.76)	591 (1.8)	49 (1.6)	269 (2.23)	255 (2.3)	14 (1.3)
Disposition of patient at discharge, n (%)						
Died in hospital	2098 (5.62)	1788 (5.2)	310 (9.7)	2732 (21.3)	2528 (21.6)	204 (18.5)
AHRQ comorbidity measures, n (%)						
Valvular disease	3236 (8.7)	2896 (8.5)	340 (10.7)	660 (5.15)	586 (5)	74(6.7)
Metastatic cancer	560 (1.5)	489 (1.4)	71 (2.2)	341 (2.7)	296 (2.5)	45(4)
Renal failure	5502 (14.7)	4556 (13.3)	946 (29.7)	1528 (11.9)	1224 (10.4)	304 (27.6)
Congestive heart failure	5332 (14.3)	4521 (13.2)	811 (25.4)	1229 (9.6)	1012 (8.62)	217 (19.7)
Chronic pulmonary disease	5338 (14.3)	4661 (13.6)	677 (21.2)	1547 (12)	1344 (11.5)	203 (18.4)
Coagulopathy	1128 (3)	888 (2.6)	240 (7.5)	995 (7.8)	822 (7)	173 (15.7)
Psychoses	1428 (3.8)	1253 (3.6)	175 (4.5)	455 (3.5)	401 (3.4)	54 (4.9)
Peripheral vascular disorders	3385 (9)	2979 (8.7)	406 (12.7)	688 (5.4)	577 (4.9)	111 (10)
Paralysis	1882 (5.04)	1580 (4.6)	302 (9.5)	897 (7)	769 (6.6)	128 (11.6)
Other neurological disorders	718 (1.9)	489 (1.4)	229 (7.2)	528 (4.1)	412 (3.5)	116 (10.5)
Hypertension (combine uncomplicated and complicated)	29 982 (80.2)	27 450 (80.3)	2532 (79.4)	9357 (73)	8509 (72.6)	848 (77)
Drug abuse	966 (2.6)	897 (2.6)	69 (2.2)	554 (4.2)	505 (4.3)	39 (3.5)
Diabetes mellitus with chronic complications	3278 (8.8)	2798 (8.2)	480 (15)	654 (5.1)	530 (4.5)	124 (11.3)
Diabetes mellitus, uncomplicated	9477 (25.4)	8566 (25)	911 (28.6)	2636 (20.6)	2342 (20)	294 (26.7)
Rheumatoid arthritis/collagen vascular diseases	897 (2.4)	788 (2.3)	109 (3.4)	247 (1.9)	219 (1.9)	28 (2.54)
Alcohol abuse	1510 (4)	1399 (4)	111 (3.5)	864 (6.7)	791 (6.8)	73 (6.6)

AHRQ indicates Agency for Healthcare Research and Quality.

data set. Of the ischemic strokes, 2301 (6.2%) had at least 1 case of sepsis in the 365-day risk period before their stroke. Among hemorrhagic strokes, 879 (6.9%) had at least 1 case of sepsis in the 365-day risk period before their stroke.

Hospitalization with sepsis within 15 days was associated with an elevated risk of ischemic (OR, 5.28; 95% CI, 3.65–7.64) and hemorrhagic stroke (OR, 3.45; 95% CI, 2.52–5.54). The risk of stroke after sepsis persisted after increasing the time interval to 365 days after the sepsis event, and the magnitude of risk decreased as the time interval increased (Table 4). The risk of ischemic (OR, 3.86; 95% CI, 3.59–4.15) and hemorrhagic stroke (OR, 4.14; 95% CI,

Table 2. Cumulative Association of Hospitalization for Sepsis or Septicemia With Risk of Ischemic and Hemorrhagic Stroke, Based on Case-Crossover Analysis (Using Data Set 1*)

Data Set 1	OR (95% CI)	
	Ischemic Stroke	Hemorrhagic Stroke
Hospitalization for sepsis/ septicemia within 15 d before stroke	28.4 (20.0–40.1)	12.1 (7.54–19.4)
Hospitalization for sepsis/ septicemia within 30 d before stroke	13.9 (10.9–17.5)	16.0 (11.8–21.8)
Hospitalization for sepsis/ septicemia within 90 d before stroke	6.46 (5.56–7.50)	12.3 (9.34–15.2)
Hospitalization for sepsis/ septicemia within 180 d before stroke	4.97 (4.40–5.61)	9.78 (8.34–11.5)
Hospitalization for sepsis/ septicemia within 365 d before stroke	3.92 (3.58–4.29)	7.38 (6.54–8.34)

All $P<0.0001$. CI indicates confidence interval; and OR, odds ratio.

*Data set 1: in the first data set, all hospital admissions in which both stroke and sepsis were present on arrival were deleted.

3.68–4.67) remained elevated in the interval up to 365 days after the sepsis event.

In analyses of nonoverlapping time periods (Table 5), risk of ischemic stroke was similar, ranging from ≈4- to 6-fold, throughout all time periods. We found the risk of hemorrhagic stroke was also similar across time intervals, with the risk slightly decreasing with each increase in time interval from sepsis event (Table 5).

Interactions With Age, Sex, and Diabetes Mellitus

The risk of having an ischemic stroke within 180 days of hospitalization for sepsis varied significantly with age (P value for interaction = 0.0006). The change in the OR for the association of sepsis with stroke risk increased 18% with each 10-year decrease in age (OR per 10-year age decrease, 1.18; 95% CI, 1.05–1.45). No significant interaction with age was seen in the hemorrhagic stroke data set. We further investigated this interaction by stratifying the data set into age categories (<45, 45–65, and >65 years). These groups were chosen based on previous age categories used for stroke. The risk for those aged <45 years was highest (OR for stroke associated with sepsis, 6.00; 95% CI, 1.62–22.1), followed by similar risk profiles for those aged 45 to 65 (OR, 2.57; 95% CI, 1.71–3.85) and >65 (OR, 2.32; 95% CI, 1.86–2.91).

The risk of ischemic stroke within 180 days of hospitalization for sepsis also varied significantly with diabetes mellitus status (P=0.044). Individuals with diabetes mellitus had a slightly lower risk (OR, 4.11; 95% CI, 3.59–4.70) of ischemic stroke within 180 days of hospitalization for sepsis when compared with individuals without diabetes mellitus (OR, 5.39; 95% CI, 5.00–5.82). There was no significant interaction with diabetes mellitus status in the hemorrhagic stroke data set (P=0.3473).

There was no interaction with sex (P=0.440).

Discussion

We found that sepsis increased the risk of stroke as long as 365 days after an admission with sepsis. The risk of stroke was highest within 15 days after sepsis, with the risk of stroke decreasing as the time from sepsis increased. The magnitude of the association still remained as high as a 3-fold increase in odds of a stroke at 180 days for both ischemic and hemorrhagic stroke. We also found that the magnitude of association was greater for younger patients.

These findings are consistent with studies investigating the association of sepsis on stroke in Taiwan, although in our US population, the relationship was stronger with ischemic stroke than with hemorrhagic stroke.[9,10] Associations between sepsis and vascular disease are plausible given the role of endothelial dysfunction in sepsis pathophysiology.[11] Sepsis leads to systemic inflammation, hemodynamic dysfunction and collapse, and coagulopathy, thereby increasing the risk for stroke.[12,13] Chronic medical conditions, including obesity, diabetes mellitus, heart disease, and smoking, have also been associated with chronic inflammation and subsequent increased risk of developing future sepsis, in addition to being risk factors for stroke.[14–20] These conditions could be a source of confounding because the risk factors could be associated with both sepsis and stroke risk; however, by using the case-crossover analysis, we minimized interindividual confounding. Moreover, inflammatory biomarkers measured at a healthy baseline have been linked to sepsis risk in the REGARDS cohort (Reasons for Geographic and Racial Differences in Stroke) and have been

Table 3. Association of Hospitalization for Sepsis or Septicemia in Nonoverlapping Time Intervals With Risk of Ischemic and Hemorrhagic Stroke, Based on Case-Crossover Analysis (Using Data Set 1*)

Data Set 1	OR (95% CI)	
	Ischemic Stroke	Hemorrhagic Stroke
Hospitalization for sepsis/ septicemia 0–15 d before stroke	28.4 (20.0–40.1)	12.1 (7.54–19.4)
Hospitalization for sepsis/ septicemia 16–30 d before stroke	4.00 (2.86–5.60)	8.42 (5.82–12.2)
Hospitalization for sepsis/ septicemia 31–90 d before stroke	2.53 (2.07–3.09)	5.48 (4.21–7.13)
Hospitalization for sepsis/ septicemia 91–180 d before stroke	2.46 (2.03–2.99)	4.79 (3.87–5.92)
Hospitalization for sepsis/ septicemia 181–365 d before stroke	2.59 (2.20–3.06)	3.92 (3.29–4.69)

All $P<0.0001$. CI indicates confidence interval; and OR, odds ratio.

*Data set 1: in the first data set all hospital admissions in which both stroke and sepsis were present on arrival were deleted.

Table 4. Cumulative Association of Hospitalization for Sepsis or Septicemia With Risk of Ischemic and Hemorrhagic Stroke, Based on Case-Crossover Analysis (Using Data Set 2*)

Data Set 2	OR (95% CI)	
	Ischemic Stroke	Hemorrhagic Stroke
Hospitalization for sepsis/ septicemia within 15 d before stroke	5.28 (3.65–7.64)	3.45 (2.04–5.84)
Hospitalization for sepsis/ septicemia within 30 d before stroke	6.35 (5.07–7.94)	4.69 (3.32–6.62)
Hospitalization for sepsis/ septicemia within 90 d before stroke	4.78 (4.17–5.49)	4.60 (3.68–5.76)
Hospitalization for sepsis/ septicemia within 180 d before stroke	4.23 (3.85–4.67)	4.53 (3.86–5.32)
Hospitalization for sepsis/ septicemia within 365 d before stroke	3.86 (3.59–4.15)	4.14 (3.68–4.67)

All $P<0.0001$. CI indicates confidence interval; and OR, odds ratio.

*The second data set deleted all admissions in which any kind of stroke and sepsis occurred in the same admission from all 3 years of data. Thus, the comparison was only between separate admissions for stroke and sepsis.

linked to risk of stroke in other cohorts.[21–27] Another study identified a potential mechanism through sepsis-induced atrial fibrillation.[4–7,9] Furthermore, serological evidence of infection was associated with a modestly increased risk of incident stroke in population-based studies, with common bacterial and herpesvirus infections associated with increased stroke risk.[4] Our study demonstrates that there is an even greater increased risk of stroke after a more severe infectious event such as sepsis, indicating a potential dose–response relationship with time from infectious or inflammatory burden and risk of stroke. It is unclear whether the increased risk of stroke after sepsis is because of the shared risk factors and comorbid conditions that place a patient at risk for both sepsis and stroke or whether sepsis is independently associated with risk of stroke. Studies on sepsis mortality indicate that sepsis patients are at increased risk of mortality post-sepsis and that 70% of the deaths were because of cardiovascular or pulmonary disease.[28] These findings support our hypothesis that among the sepsis patients who survive their sepsis hospitalization, they are at increased risk of cardiovascular disease and stroke, and subsequent mortality because of their disease. Whether this is because of sepsis susceptibility or post-sepsis inflammatory effects is unknown.

In addition, we found that younger patients were at a further increased risk of stroke after sepsis compared with older patients; for every decade younger age, the risk increased by ≈20% for ischemic, but not for hemorrhagic, stroke after sepsis. These findings are similar to the findings of Lee et al,[9] but we did not see an interaction with age and hemorrhagic stroke, only with age and ischemic stroke. This could be because of the differences in the underlying populations between the 2 studies (Taiwan versus United States), as well as the fact that the cases and controls in their study were selected based on exposure, rather than on outcome, which would tend to inflate their estimates of the association.

Although the risk of stroke is greater in older adults, ≈10% to 14% of all strokes occur in people aged 18 to 45 years.[29–35] Conventional risk factors such as hypertension, diabetes mellitus, and smoking, moreover, may not fully account for the risk of stroke in patients aged 18 to 45 years.[36] The increasing prevalence of stroke in the young, coupled with greater heterogeneity in stroke cause within the younger age group than in the older stroke population, presents a unique and vulnerable patient population where risk reduction efforts are of increasing importance.

The interaction with diabetes mellitus reducing the risk of stroke after sepsis is different than what has been reported in the literature. There was not an interaction with diabetes mellitus in the CHS study (Cardiovascular Health Study), but there was an interaction with intima-media thickness as a measure of atherosclerosis.[37] Furthermore, although the risk in general is greatest shortly after sepsis, the risk does remain elevated out to 365 days post-sepsis. This could indicate that the diseases covary, which is supported by the data on the number of chronic conditions, or that these patients are sicker patients in general. Another explanation could be a long-term biological effect from the sepsis event. Other studies have shown long-term effects of pneumonia on risk of stroke, and considering the toll sepsis takes on the inflammatory system, this effect could be more pronounced after sepsis than it is after pneumonia.[37] Furthermore, we do not have information on baseline inflammation and risk of stroke. We do not know whether the risk returns to a presepsis baseline or if the elevated risk remains during the life course after sepsis. If the risk of stroke remains elevated post-sepsis, this could be because of the inflammation itself or it could reflect the comorbidities and complications associated with hospitalization for sepsis.

Table 5. Association of Hospitalization for Sepsis or Septicemia at Each Specific Time Interval With Risk of Ischemic and Hemorrhagic Stroke, Based on Case-Crossover Analysis (Using Data Set 2*)

Data Set 2	OR (95% CI)	
	Ischemic Stroke	Hemorrhagic Stroke
Hospitalization for sepsis/ septicemia 0–15 d before stroke	5.28 (3.65–7.63)	3.45 (2.04–5.84)
Hospitalization for sepsis/ septicemia 15–30 d before stroke	4.58 (3.56–5.89)	3.74 (2.52–5.54)
Hospitalization for sepsis/ septicemia 30–90 d before stroke	3.34 (2.85–3.91)	3.63 (2.77–4.76)
Hospitalization for sepsis/ septicemia 90–180 d before stroke	3.14 (2.76–3.57)	3.62 (2.93–4.48)
Hospitalization for sepsis/ septicemia 180–365 d before stroke	2.94 (2.65–3.26)	3.25 (2.73–3.86)

All $P<0.0001$. CI indicates confidence interval; and OR, odds ratio.

*The second data set deleted all admissions in which any kind of stroke and sepsis occurred in the same admission from all 3 years of data. Thus, the comparison was only between separate admissions for stroke and sepsis.

Our study has limitations. Prospective case ascertainment and detailed clinical information were not available. For example, we did not have data on specific infectious causes of sepsis. We relied on administrative data diagnosis codes, and information on stroke severity was not available. The exclusion criteria could have excluded stroke cases that were more severe, as stroke severity is associated with risk of sepsis during stroke hospitalization. The comorbidities were captured through the Agency for Healthcare Research and Quality comorbidity measures, which are based on discharge diagnoses. This could under-report the comorbidities commonly associated with stroke. We were only able to capture patients who were hospitalized, and in the state of California. Patients who had hospitalizations in other states, or who died of an event before being admitted to a hospital, were not captured. The case-crossover design also does not account for the increased risk associated with the aging of the patient over time and their concomitant development of new risk factors. To minimize these concerns, however, we limited the control time windows to the previous 2 years. Another limitation is the potential for immortal time bias, as the extended risk of stroke over time could be influenced by the high long-term mortality associated with sepsis. The discrepancy between the proportions of ischemic and hemorrhagic stroke in our study (66% ischemic) when compared with all strokes in the United States (87% ischemic) could be because of the exclusions we applied for this study, as well as the fact that ischemic stroke hospitalizations are more likely not to be hospitalized.

Our study has strengths, as well, however. By utilizing the case-crossover design, in which each patient served as his or her own control, we eliminated interindividual variability. The use of a large administrative database increases the generalizability of the study. Moreover, our very large sample size allowed us to detect interactions with age and diabetes mellitus and to study associations among populations of patients that are often difficult to capture, including young and hemorrhagic stroke patients.

This study suggests that sepsis patients remain at risk for stroke as long as 365 days from their sepsis hospitalization, with the risk being greatest shortly after the sepsis admission. Younger sepsis patients have an increased risk of stroke after sepsis admission. This study identifies a unique group of patients at increased risk for stroke. Future studies are needed to confirm these relationships in other patient populations, determine whether and when the risk returns to a baseline level of risk, investigate mechanisms of the increased risk of stroke after sepsis, and determine effective strategies to reduce this risk.

Sources of Funding

Dr Boehme was supported by National Institute of Neurological Disorders and Stroke (NINDS) National Institute of Health (NIH) T32 NS007153-31 and L30 NS093600 grants. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NINDS or the NIH.

Disclosures

Dr Elkind receives compensation for providing consultative services for Biotelemetry/Cardionet, BMS-Pfizer Partnership, Boehringer-Ingelheim, and Sanofi-Regeneron; serves on the National, Founders Affiliate, and New York City chapter boards of the American Heart Association/American Stroke Association and receives royalties from UpToDate for chapters related to cryptogenic stroke. The other authors report no conflicts.

References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29–e322. doi: 10.1161/CIR.0000000000000152.
2. Elkind MS. Why now? Moving from stroke risk factors to stroke triggers. *Curr Opin Neurol*. 2007;20:51–57. doi: 10.1097/WCO.0b013e328012da75.
3. Elkind MS, Ramakrishnan P, Moon YP, Boden-Albala B, Liu KM, Spitalnik SL, et al. Infectious burden and risk of stroke: the northern Manhattan study. *Arch Neurol*. 2010;67:33–38. doi: 10.1001/archneurol.2009.271.
4. Elkind MS, Carty CL, O'Meara ES, Lumley T, Lefkowitz D, Kronmal RA, et al. Hospitalization for infection and risk of acute ischemic stroke: the Cardiovascular Health Study. *Stroke*. 2011;42:1851–1856. doi: 10.1161/STROKEAHA.110.608588.
5. Walkey AJ, Hammill BG, Curtis LH, Benjamin EJ. Long-term outcomes following development of new-onset atrial fibrillation during sepsis. *Chest*. 2014;146:1187–1195. doi: 10.1378/chest.14-0003.
6. Dalager-Pedersen M, Søgaard M, Schønheyder HC, Nielsen H, Thomsen RW. Risk for myocardial infarction and stroke after community-acquired bacteremia: a 20-year population-based cohort study. *Circulation*. 2014;129:1387–1396. doi: 10.1161/CIRCULATIONAHA.113.006699.
7. Clayton TC, Thompson M, Meade TW. Recent respiratory infection and risk of cardiovascular disease: case-control study through a general practice database. *Eur Heart J*. 2008;29:96–103. doi: 10.1093/eurheartj/ehm516.
8. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol*. 1991;133:144–153.
9. Lee JT, Chung WT, Lin JD, Peng GS, Muo CH, Lin CC, et al. Increased risk of stroke after septicaemia: a population-based longitudinal study in Taiwan. *PloS One*. 2014;9:e89386. doi: 10.1371/journal.pone.0089386.
10. Ou SM, Chu H, Chao PW, Lee YJ, Kuo SC, Chen TJ, et al. Long-term mortality and major adverse cardiovascular events in sepsis survivors. A nationwide population-based study. *Am J Respir Crit Care Med*. 2016;194:209–217. doi: 10.1164/rccm.201510-2023OC.
11. Aird WC. Endothelium as a therapeutic target in sepsis. *Curr Drug Targets*. 2007;8:501–507.
12. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29:1303–1310.
13. Kellum JA, Kong L, Fink MP, Weissfeld LA, Yealy DM, Pinsky MR, et al; GenIMS Investigators. Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) study. *Arch Intern Med*. 2007;167:1655–1663. doi: 10.1001/archinte.167.15.1655.
14. Wang HE, Shapiro NI, Griffin R, Safford MM, Judd S, Howard G. Chronic medical conditions and risk of sepsis. *PloS One*. 2012;7:e48307. doi: 10.1371/journal.pone.0048307.
15. Cave MC, Hurt RT, Frazier TH, Matheson PJ, Garrison RN, McClain CJ, et al. Obesity, inflammation, and the potential application of pharmaconutrition. *Nutr Clin Pract*. 2008;23:16–34. doi: 10.1177/011542650802300116.
16. Mathieu P, Poirier P, Pibarot P, Lemieux I, Després JP. Visceral obesity: the link among inflammation, hypertension, and cardiovascular disease. *Hypertension*. 2009;53:577–584. doi: 10.1161/HYPERTENSIONAHA.108.110320.
17. Tousoulis D. Inflammation in atherosclerosis: current therapeutic approaches. *Curr Pharm Des*. 2011;17:4087–4088.
18. Brooks-Worrell B, Palmer JP. Immunology in the Clinic Review Series; focus on metabolic diseases: development of islet autoimmune disease in type 2 diabetes patients: potential sequelae of chronic inflammation. *Clin Exp Immunol*. 2012;167:40–46. doi: 10.1111/j.1365-2249.2011.04501.x.
19. Rosner SA, Ridker PM, Zee RY, Cook NR. Interaction between inflammation-related gene polymorphisms and cigarette smoking on the risk of myocardial infarction in the Physician's Health Study. *Hum Genet*. 2005;118:287–294. doi: 10.1007/s00439-005-0052-6.

20. Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. *J Autoimmun*. 2010;34:J258–J265. doi: 10.1016/j.jaut.2009.12.003.
21. Chamorro A, Amaro S, Vargas M, Obach V, Cervera A, Torres F, et al. Interleukin 10, monocytes and increased risk of early infection in ischaemic stroke. *J Neurol Neurosurg Psychiatry*. 2006;77:1279–1281. doi: 10.1136/jnnp.2006.100800.
22. Haeusler KG, Schmidt WU, Föhring F, Meisel C, Helms T, Jungehulsing GJ, et al. Cellular immunodepression preceding infectious complications after acute ischemic stroke in humans. *Cerebrovasc Dis*. 2008;25:50–58. doi: 10.1159/000111499.
23. Emsley HC, Hopkins SJ. Acute ischaemic stroke and infection: recent and emerging concepts. *Lancet Neurol*. 2008;7:341–353. doi: 10.1016/S1474-4422(08)70061-9.
24. Emsley HC, Smith CJ, Hopkins SJ. Infection and brain-induced immunodepression after acute ischemic stroke. *Stroke*. 2008;39:e7, author reply e8. doi: 10.1161/STROKEAHA.107.500447.
25. Vogelgesang A, Grunwald U, Langner S, Jack R, Bröker BM, Kessler C, et al. Analysis of lymphocyte subsets in patients with stroke and their influence on infection after stroke. *Stroke*. 2008;39:237–241. doi: 10.1161/STROKEAHA.107.493635.
26. Dirnagl U, Klehmet J, Braun JS, Harms H, Meisel C, Ziemssen T, et al. Stroke-induced immunodepression: experimental evidence and clinical relevance. *Stroke*. 2007;38(2 suppl):770–773. doi: 10.1161/01.STR.0000251441.89665.bc.
27. Meisel C, Schwab JM, Prass K, Meisel A, Dirnagl U. Central nervous system injury-induced immune deficiency syndrome. *Nat Rev Neurosci*. 2005;6:775–786. doi: 10.1038/nrn1765.
28. Wang HE, Szychowski JM, Griffin R, Safford MM, Shapiro NI, Howard G. Long-term mortality after community-acquired sepsis: a longitudinal population-based cohort study. *BMJ Open*. 2014;4:e004283. doi: 10.1136/bmjopen-2013-004283.
29. Putaala J, Metso AJ, Metso TM, Konkola N, Kraemer Y, Haapaniemi E, et al. Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: the Helsinki young stroke registry. *Stroke*. 2009;40:1195–1203. doi: 10.1161/STROKEAHA.108.529883.
30. Adams HP Jr, Kappelle LJ, Biller J, Gordon DL, Love BB, Gomez F, et al. Ischemic stroke in young adults. Experience in 329 patients enrolled in the Iowa Registry of stroke in young adults. *Arch Neurol*. 1995;52:491–495.
31. Kittner SJ, Stern BJ, Wozniak M, Buchholz DW, Earley CJ, Feeser BR, et al. Cerebral infarction in young adults: the Baltimore-Washington Cooperative Young Stroke Study. *Neurology*. 1998;50:890–894.
32. Jacobs BS, Boden-Albala B, Lin IF, Sacco RL. Stroke in the young in the northern Manhattan stroke study. *Stroke*. 2002;33:2789–2793.
33. Qureshi AI, Safdar K, Patel M, Janssen RS, Frankel MR. Stroke in young black patients. Risk factors, subtypes, and prognosis. *Stroke*. 1995;26:1995–1998.
34. Naess H, Nyland HI, Thomassen L, Aarseth J, Nyland G, Myhr KM. Incidence and short-term outcome of cerebral infarction in young adults in western Norway. *Stroke*. 2002;33:2105–2108.
35. George MG, Tong X, Kuklina EV, Labarthe DR. Trends in stroke hospitalizations and associated risk factors among children and young adults, 1995-2008. *Ann Neurol*. 2011;70:713–721. doi: 10.1002/ana.22539.
36. Ji R, Schwamm LH, Pervez MA, Singhal AB. Ischemic stroke and transient ischemic attack in young adults: risk factors, diagnostic yield, neuroimaging, and thrombolysis. *JAMA Neurol*. 2013;70:51–57. doi: 10.1001/jamaneurol.2013.575.
37. Corrales-Medina VF, Alvarez KN, Weissfeld LA, Angus DC, Chirinos JA, Chang CC, et al. Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. *JAMA*. 2015;313:264–274. doi: 10.1001/jama.2014.18229.

Stroke
Journal of the American Heart Association

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Stroke. 2017;48:574-580; originally published online February 14, 2017;
doi: 10.1161/STROKEAHA.116.016162
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628