Infection After Intracerebral Hemorrhage
Risk Factors and Association With Outcomes in the Ethnic/Racial Variations of Intracerebral Hemorrhage Study

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Background and Purpose—Risk factors for infections after intracerebral hemorrhage (ICH) and their association with outcomes are unknown. We hypothesized there are predictors of poststroke infection and infections drive worse outcomes.

Methods—We determined prevalence of infections in a multicenter, triethnic study of ICH. We performed univariate and multivariate analyses to determine the association of infection with admission characteristics and hospital complications. We performed logistic regression on association of infection with outcomes after controlling for known determinants of prognosis after ICH (volume, age, infratentorial location, intraventricular hemorrhage, and Glasgow Coma Scale).

Results—Among 800 patients, infections occurred in 245 (31%). Admission characteristics associated with infection in multivariable models were ICH volume (odds ratio [OR], 1.02/mL; 95% confidence interval [CI], 1.01–1.03), lower Glasgow Coma Scale (OR, 0.91 per point; 95% CI, 0.87–0.95), deep location (reference lobar: OR, 1.90; 95% CI, 1.28–2.88), and black race (reference white: OR, 1.53; 95% CI, 1.01–2.32). In a logistic regression of admission and hospital factors, infections were associated with intubation (OR, 3.1; 95% CI, 2.1–4.5), dysphagia (with percutaneous endoscopic gastrostomy: OR, 3.19; 95% CI, 2.03–5.05 and without percutaneous endoscopic gastrostomy: OR, 2.11; 95% CI, 1.04–4.23), pulmonary edema (OR, 3.71; 95% CI, 1.29–12.33), and deep vein thrombosis (OR, 5.6; 95% CI, 1.86–21.02), but not ICH volume or Glasgow Coma Scale. Infected patients had higher discharge mortality (16% versus 8%; P=0.001) and worse 3-month outcomes (modified Rankin Scale ≥3; 80% versus 51%; P<0.001). Infection was an independent predictor of poor 3-month outcome (OR, 2.6; 95% CI, 1.8–3.9).

Conclusions—There are identifiable risk factors for infection after ICH, and infections predict poor outcomes.

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Key Words: cerebral hemorrhage ■ infection ■ outcomes assessment (health care) ■ risk factors

Medical complications are an important contributor to mortality and morbidity after stroke, accounting for approximately half of all deaths. There is an increasing body of literature on the importance of infection before and after acute ischemic stroke, but information on infections after intracerebral hemorrhage (ICH) is limited. A recent meta-analysis of poststroke infection in a mixed group of >130 000 patients with ischemic and hemorrhagic stroke found a 30% infection rate, with pneumonia and urinary tract infection (UTI) rates of 10% each. Other studies have identified risk factors for poststroke infection, including age, stroke severity, volume of infarct, premorbid dependence, and enteral feeding. Specific risk factors have been identified for particular sites of infection, such as intubation, dysphagia, congestive heart failure, and male sex for pneumonia, and female sex and prior strokes for UTI. One study proposed that the risk of infection is because of not only hospitalization but also a poststroke immunodepression. Nosocomial infections have a deleterious effect on outcomes in mixed stroke cohorts, with odds ratios (ORs) for poor long-term outcome ranging from 3 to 11. No large studies have examined the incidence of poststroke infections or their impact on outcomes in a pure ICH cohort. Three small studies (n=62–148) using single-institution databases found poststroke infection rates of 51% to 58%, although...
2 studies were intensive care unit specific.\textsuperscript{11–13} A study of 201 patients with ICH from the Virtual International Stroke Trials Archive found a much lower rate of poststroke infection (11%).\textsuperscript{14} In multivariate analyses, post-ICH infection was associated with high National Institutes of Health Stroke Scale scores, age, C-reactive protein levels, and invasive procedures.

Given the lack of robust data on infection after ICH, we sought to determine the rate of poststroke infections and their impact on outcomes of patients enrolled in the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) Study, a large, prospective, National Institute of Neurological Disorders and Stroke–funded multicenter study of ICH. We hypothesized that factors present on admission are associated with developing nosocomial infection, and that such infections would be deleterious to outcomes.

\section*{Methods}

\subsection*{Study Protocol}
A detailed methodology of ERICH has been published.\textsuperscript{15} The ERICH study is a multicenter case–control study of ICH that aims to identify genetic variation and differences in the distribution of risk factors and imaging characteristics that may affect risk of ICH in a triethnic group of white, black, and Hispanic patients. A prospective hot-pursuit method of subject enrollment, in which each recruitment center reviews admission, emergency room, and intensive care unit logs for potential ICH cases, was used to limit survival bias.\textsuperscript{15} The study was approved by the Institutional Review Boards of University of Cincinnati and each enrolling site. Informed consent was obtained from all subjects or legal representatives.

\subsection*{Case Definition}
This article represents an analysis of the first 1400 cases enrolled in the ERICH study. All cases met the following eligibility criteria: diagnosis of spontaneous ICH (including warfarin-related and peripartum ICH); age \( \geq 18 \) years; resides near recruiting center; non-Hispanic white, non-Hispanic black, or Hispanic by self-report; and ability of patient or legal representative to provide informed consent. Glasgow Coma Scale (GCS) scores were recorded for patients who presented to the emergency department of the recruitment site; GCS was unavailable for patients who were directly admitted, transferred from outside emergency departments, or inpatients at ictus.

To assess risk factors for infection and their impact on outcomes, the analytic design involved the following exclusion criteria: death, withdrawal of care, or discharge to hospice within 72 hours of admission; infection within 2 weeks of admission; premorbid modified Rankin Scale (mRS) \( \geq 3 \). Patients with missing key data (computed tomographic results; GCS, 3-month outcomes) were also excluded.

\subsection*{Computed Tomographic Scans}
ICH location was assigned by the blinded central imaging center, which was blinded to clinical data. ICH volume was measured using Analyze 9.0 (Mayo Clinic) using previously described methods.\textsuperscript{16}

\subsection*{Ascertainment of Infections}
Nosocomial infections were identified throughout the entire hospital stay by treating physicians and reported on chart abstraction forms on hospital discharge. Research staff involved in chart abstraction received instructions on how to fill out data collection forms, including specifying infections, although guidance was limited. Categories of infection included respiratory, urinary, bloodstream, meningitis/ventriculitis, and other. The chart abstraction form and pertinent material from the manual of procedures are available in the online-only Data Supplement.

\subsection*{Hospital Complications}
Major neurosurgical procedures were defined as craniotomy/craniectomy for clot evacuation, stereotactic clot aspiration, or thrombolytic injection into ventricles. External ventricular drain and ventriculoperitoneal shunt placement were not considered as major neurosurgical procedures.

\subsection*{Outcomes}
Three-month outcomes were assessed using the mRS. We defined good outcome as an mRS of 0 to 2, which has been shown to be as effective as shift analysis in large trials.\textsuperscript{17}

\subsection*{Statistical Analysis}
Comparisons of patients with and without infection were based on \( \chi^2 \) tests, \( t \)-tests, Wilcoxon signed-rank tests, or Cochran–Armitage trend test as appropriate. Associations of admission characteristics and hospital-related complications with risk of infection were tested by logistic regression. Logistic regression models were used to test the association of nosocomial infection and the components of the ICH score\textsuperscript{19} with

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Post–intracerebral hemorrhage infection by type and race. CNS indicates central nervous system; and UTI, urinary tract infection.}
\end{figure}
Results

Description of the Cohort

We enrolled 1400 individuals into ERICH between September 10, 2010, and December 31, 2012, of which 600 patients were excluded from this analysis (counts not mutually exclusive): poor outcome (mRS ≥3) at discharge and 3 months. Receiver operating characteristic curves were generated for outcome models based on ICH score components alone plus addition of poststroke infection. All analyses were performed using SAS version 9.3 (Cary, NC).

Table 1. Admission Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Infection (n=245)</th>
<th>No Infection (n=555)</th>
<th>P Value</th>
<th>Respiratory (n=134)</th>
<th>UTI (n=125)</th>
<th>Sepsis (n=22)</th>
<th>CNS (n=15)</th>
<th>Other (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
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</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>59 (15)</td>
<td>60 (14)</td>
<td>0.55</td>
<td>59 (16)</td>
<td>61 (15)</td>
<td>59 (12)</td>
<td>56 (13)</td>
<td>53 (17)</td>
</tr>
<tr>
<td>Sex: females</td>
<td>93 (38)</td>
<td>223 (40)</td>
<td>0.55</td>
<td>41 (31)</td>
<td>62 (50)</td>
<td>6 (27)</td>
<td>4 (27)</td>
<td>6 (38)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>White</td>
<td>53 (22)</td>
<td>148 (27)</td>
<td>...</td>
<td>32 (24)</td>
<td>23 (18)</td>
<td>5 (23)</td>
<td>3 (20)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Black</td>
<td>120 (49)</td>
<td>216 (39)</td>
<td>...</td>
<td>63 (47)</td>
<td>69 (55)</td>
<td>11 (50)</td>
<td>9 (60)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>72 (29)</td>
<td>191 (34)</td>
<td>0.03</td>
<td>39 (29)</td>
<td>33 (26)</td>
<td>6 (27)</td>
<td>3 (20)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Medical history</td>
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<tr>
<td>Surgery within 30 days</td>
<td>5 (2)</td>
<td>21 (4)</td>
<td>0.20</td>
<td>2 (2)</td>
<td>3 (2)</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>HIV+</td>
<td>5 (2)</td>
<td>4 (1)</td>
<td>0.10</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>3 (14)</td>
<td>*</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Cancer</td>
<td>20 (8)</td>
<td>66 (12)</td>
<td>0.11</td>
<td>8 (6)</td>
<td>12 (10)</td>
<td>2 (9)</td>
<td>*</td>
<td>2 (13)</td>
</tr>
<tr>
<td>ESRD/HD</td>
<td>4 (2)</td>
<td>8 (1)</td>
<td>0.84</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>2 (9)</td>
<td>*</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>62 (25)</td>
<td>149 (27)</td>
<td>0.65</td>
<td>30 (22)</td>
<td>35 (28)</td>
<td>5 (23)</td>
<td>3 (20)</td>
<td>5 (31)</td>
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<tr>
<td>Dementia</td>
<td>13 (5)</td>
<td>25 (5)</td>
<td>0.61</td>
<td>9 (7)</td>
<td>5 (4)</td>
<td>*</td>
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<td>*</td>
</tr>
<tr>
<td>Social history</td>
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<tr>
<td>Active smoker</td>
<td>55 (23)</td>
<td>117 (21)</td>
<td>0.61</td>
<td>33 (25)</td>
<td>27 (22)</td>
<td>5 (24)</td>
<td>6 (40)</td>
<td>5 (31)</td>
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<tr>
<td>Heavy drinker</td>
<td>29 (13)</td>
<td>63 (12)</td>
<td>0.70</td>
<td>20 (16)</td>
<td>14 (12)</td>
<td>2 (11)</td>
<td>2 (15)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Urine toxicology (+)</td>
<td>32 (16)</td>
<td>73 (17)</td>
<td>0.89</td>
<td>20 (18)</td>
<td>17 (17)</td>
<td>5 (26)</td>
<td>1 (8)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Case type</td>
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</tr>
<tr>
<td>ICH</td>
<td>241 (98)</td>
<td>543 (98)</td>
<td>0.62</td>
<td>133 (99)</td>
<td>122 (98)</td>
<td>22 (100)</td>
<td>15 (100)</td>
<td>15 (94)</td>
</tr>
<tr>
<td>Deep</td>
<td>163 (68)</td>
<td>317 (58)</td>
<td>...</td>
<td>86 (65)</td>
<td>88 (72)</td>
<td>16 (73)</td>
<td>13 (87)</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Lobar</td>
<td>51 (21)</td>
<td>162 (30)</td>
<td>...</td>
<td>32 (24)</td>
<td>23 (19)</td>
<td>4 (18)</td>
<td>6 (40)</td>
<td></td>
</tr>
<tr>
<td>Brain stem</td>
<td>13 (5)</td>
<td>22 (4)</td>
<td>...</td>
<td>8 (6)</td>
<td>5 (4)</td>
<td>1 (5)</td>
<td>2 (13)</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>14 (6)</td>
<td>42 (8)</td>
<td>0.04</td>
<td>7 (5)</td>
<td>6 (5)</td>
<td>1 (5)</td>
<td>*</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Primary IVH</td>
<td>4 (2)</td>
<td>12 (2)</td>
<td>0.62</td>
<td>3 (2)</td>
<td>3 (2)</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>ICH (primary)</td>
<td>9 (4)</td>
<td>15 (3)</td>
<td>0.46</td>
<td>7 (5)</td>
<td>3 (2)</td>
<td>1 (5)</td>
<td>*</td>
<td>1 (6)</td>
</tr>
<tr>
<td>ICH volume, median (IQR)</td>
<td>17 (7–39)</td>
<td>9 (3–20)</td>
<td>&lt;0.001</td>
<td>19 (8–40)</td>
<td>15 (5–30)</td>
<td>17 (8–44)</td>
<td>20 (5–31)</td>
<td>27 (19–51)</td>
</tr>
<tr>
<td>ED data</td>
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<tr>
<td>Initial temp, mean (SD)</td>
<td>97.9 (1.2)</td>
<td>97.8 (1.4)</td>
<td>0.25</td>
<td>97.9 (1.4)</td>
<td>98.0 (1.1)</td>
<td>97.9 (0.8)</td>
<td>97.9 (1.1)</td>
<td>97.9 (0.8)</td>
</tr>
<tr>
<td>GCS-total, median (IQR)</td>
<td>13 (8–115)</td>
<td>15 (13–15)</td>
<td>&lt;0.001</td>
<td>11 (6–15)</td>
<td>14 (10–15)</td>
<td>13 (11–15)</td>
<td>8 (6–12)</td>
<td>14 (11–15)</td>
</tr>
<tr>
<td>Coma/posturing</td>
<td>61 (26)</td>
<td>52 (10)</td>
<td>&lt;0.001</td>
<td>43 (33)</td>
<td>26 (21)</td>
<td>4 (20)</td>
<td>2 (13)</td>
<td>3 (19)</td>
</tr>
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<td>Initial laboratories</td>
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</tr>
<tr>
<td>WBC&gt;10</td>
<td>103 (43)</td>
<td>177 (33)</td>
<td>0.006</td>
<td>58 (44)</td>
<td>45 (37)</td>
<td>9 (43)</td>
<td>5 (33)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Serum blood sugar, median (IQR)</td>
<td>138 (115–177)</td>
<td>126 (105–162)</td>
<td>&lt;0.001</td>
<td>140 (118–182)</td>
<td>135 (111–174)</td>
<td>122 (105–149)</td>
<td>134 (121–178)</td>
<td>149 (120–235)</td>
</tr>
<tr>
<td>HbA1C, median (IQR)</td>
<td>5.7 (5.3–6.6)</td>
<td>5.9 (5.4–6.6)</td>
<td>0.10</td>
<td>5.7 (5.4–6.6)</td>
<td>5.8 (5.4–6.7)</td>
<td>5.6 (5.4–6.7)</td>
<td>5.8 (5.3–6.8)</td>
<td>5.5 (5.1–7.3)</td>
</tr>
</tbody>
</table>

All data are n (%) unless noted. P values are for infection vs no infection. CNS indicates central nervous system; ED, emergency department; ESRD, end-stage renal disease; GCS, Glasgow Coma Scale; HbA1c, glycated hemoglobin; HD, hemodialysis; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; IQR, interquartile range; SAH, subarachnoid hemorrhage; UTI, urinary tract infection; and WBC, white blood cell.

*No observations.

poor outcome (mRS ≥3) at discharge and 3 months. Receiver operating characteristic curves were generated for outcome models based on ICH score components alone plus addition of poststroke infection. All analyses were performed using SAS version 9.3 (Cary, NC).
mean age of the included 800 subjects was 60 (±14) years; 60% of the subjects were men, and the racial/ethnic distribution was 25% white, 42% black, and 33% Hispanic.

Prevalence and Predictors of Infections

Poststroke infections occurred in 245 of the 800 patients (31%). Respiratory infections were the most common infection followed by UTI (17% and 16%, respectively). Multiple infections were seen in 8% of patients. Figure 1 shows rates of infection by type and race. Infection rates were higher in blacks than in whites and Hispanics (36% versus 26% and 27%; \( P = 0.03 \)), largely driven by UTIs (21% versus 11% and 13%; \( P = 0.005 \)).

Admission characteristics are reported in Table 1. Admission factors associated with infection in univariate analyses (\( P < 0.05 \)) included ICH volume (17 versus 9 mL; \( P < 0.0001 \)), black race (49% versus 39%; \( P = 0.03 \)), location (deep, 68% versus 58%; \( P = 0.04 \)), admission GCS (13 versus 15; \( P < 0.0001 \)), white blood cell count (>10K; 43% versus 33%; \( P = 0.006 \)), and glucose (138 versus 126 mg/dL; \( P = 0.0003 \)). In logistic regression models, poststroke infections were associated with ICH volume (OR, 1.02/mL; 95% CI, 1.01–1.03), GCS (per point: OR, 0.91; 95% CI, 0.87–0.95), deep location (reference lobar: OR, 1.90; 95% CI, 1.28–2.88), and black race (reference white: OR, 1.53; 95% CI, 1.01–2.32).

Hospital-related complications (Table 2) associated with infection with \( P < 0.001 \) included major neurosurgical procedures (35% versus 14%; \( P < 0.0001 \)), external ventricular drain placement (37% versus 15%; \( P < 0.0001 \)), intubation (63% versus 25%; \( P < 0.0001 \)), bowel-bladder dysfunction (7% versus 1%; \( P < 0.0001 \)), pulmonary edema (6% versus 1%; \( P < 0.0001 \)), decubitus ulcer (4% versus 1%; \( P = 0.0008 \)), deep vein thrombosis (8% versus 1%; \( P < 0.0001 \)), and dysphagia requiring percutaneous endoscopic gastrostomy (34% versus 8%; \( P < 0.0001 \)). In multivariate models including both admission and hospital-related factors, infections were associated with intubation (OR, 3.08; 95% CI, 2.1–4.51), dysphagia with and without polyethylene glycol (with percutaneous endoscopic gastrostomy: OR, 3.19;
95% CI, 2.03–5.05 and without percutaneous endoscopic gastrostomy: OR, 2.11; 95% CI, 1.04–4.23), pulmonary edema (OR, 3.71; 95% CI, 1.29–12.33), and deep vein thrombosis (OR, 5.6; 95% CI, 1.86–21.02), whereas ICH volume, location, and GCS did not reach statistical significance.

Infections as a Predictor of Outcomes
Patients with infection were more likely to die in the hospital (16% versus 8%; \( P = 0.001 \)). Figure 2 demonstrates 3-month outcomes by infection status and type. The presence of infection had a significant impact on 3-month outcomes—80% of patients with infections had poor 3-month outcomes versus 51% in those without infection (\( P < 0.0001 \)). The infection type also affected outcomes—patients with lone respiratory infections had worse outcomes versus those with lone urinary infections (86% versus 69%; \( P = 0.005 \)). Logistic regression (Table 3) that included poststroke infection along with the components of the ICH score revealed that poststroke infection remained strongly predictive of 3-month poor outcome (OR, 2.6; 95% CI, 1.8–3.9). Respiratory infections had a greater impact on poor 3-month outcomes than urinary infections (respiratory: OR, 4.0; 95% CI, 2.3–7.3 and urinary: OR, 1.7; 95% CI, 1.1–2.8). Receiver operating characteristic curves based on ICH score components plus poststroke infection were improved compared with curves based on ICH score components alone; the c-statistic increased from 0.747 to 0.778 for discharge outcomes and from 0.788 to 0.806 for 3-month outcomes (Figure 3).

![Figure 2. Three-month functional outcome by infection status. mRS indicates modified Rankin Scale; and UTI, urinary tract infection.](image)

### Table 3. Multivariate Analyses for 3-Month Outcomes by Infection Status and Type

<table>
<thead>
<tr>
<th>Variable</th>
<th>Any Infection</th>
<th>P Value</th>
<th>Respiratory Infection</th>
<th>P Value</th>
<th>Urinary Infection</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of 3-mo mRS≥3 (n=800) Multivariate Models</td>
<td></td>
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</tr>
<tr>
<td>Infection type</td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Any infection</td>
<td>2.6 (1.8–3.9)</td>
<td>&lt;0.0001</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Respiratory</td>
<td>...</td>
<td>...</td>
<td>4.0 (2.3–7.3)</td>
<td>&lt;0.0001</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Urinary</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1.7 (1.1–2.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age (≥80), y</td>
<td>11.6 (5.2–30.9)</td>
<td>&lt;0.0001</td>
<td>11.7 (5.2–31.2)</td>
<td>&lt;0.0001</td>
<td>11.6 (5.2–31.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GCS</td>
<td>5–12</td>
<td>3.5 (2.2–5.5)</td>
<td>&lt;0.0001</td>
<td>3.5 (2.3–5.6)</td>
<td>&lt;0.0001</td>
<td>3.9 (2.5–6.1)</td>
</tr>
<tr>
<td>3–4</td>
<td>2.1 (0.9–5.7)</td>
<td>0.1</td>
<td>1.8 (0.7–5.0)</td>
<td>0.2</td>
<td>2.7 (1.1–7.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>ICH volume ≥30 mL</td>
<td>5.4 (3.1–9.9)</td>
<td>&lt;0.0001</td>
<td>5.6 (2.2–10.3)</td>
<td>&lt;0.0001</td>
<td>6.0 (3.4–11.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>2.2 (1.3–3.7)</td>
<td>0.002</td>
<td>2.2 (1.3–3.7)</td>
<td>0.002</td>
<td>2.2 (1.3–3.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>IVH</td>
<td>2.3 (1.6–3.3)</td>
<td>&lt;0.0001</td>
<td>2.5 (1.7–3.5)</td>
<td>&lt;0.0001</td>
<td>2.4 (1.7–3.4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale; and OR, odds ratio.
Discussion

We found that almost one third of the patients with ICH in our multicenter, multiethnic cohort study developed infections during acute hospitalization, and that several factors present on admission are predictive of the occurrence of infection. Pneumonias and UTIs comprised most infections, and a quarter of infected patients developed multiple infections. The rate of nosocomial infection in this ICH cohort is consistent with a recent meta-analysis of a mixed ischemic and hemorrhagic stroke cohort.3 We further found that poststroke infections increase the risk of adverse outcomes, including disability and mortality.

Poststroke infection was strongly associated with known risk factors for infection: poor GCS, intubation, dysphagia, pulmonary edema, and invasive procedures.11–14 Infection was also associated with deep vein thrombosis, possibly because of deep vein thrombosis-related fever prompting infectious evaluations, or possibly as a marker for long hospital stays.

Surprisingly, was not an association with age despite being a well-established general risk factor for nosocomial infection.19 Blacks had substantially higher rates of infection, especially UTIs where the rate was almost double that of whites. Although race is not a well-established risk factor for nosocomial infection, there seems to be an ICH-specific race susceptibility to infection. One potential mechanism might be related to the low white blood cell count seen in blacks.20 Although low white blood cell counts have not conferred an increased nosocomial infection risk among blacks generally, it may potentially influence the susceptibility to poststroke immunodepression. Infections were also more common in deep hemorrhages, which were more common in blacks than in lobar hemorrhages. Although we adjusted for location, it is possible there was some residual confounding. It is also possible that some of the increased infection rate may represent racial bias in ascertainment and surveillance of infection. Further studies are needed to confirm these findings and to investigate possible pathogeneses of this racial disparity.
Our results highlight the deleterious impact of infections on outcome after ICH. Despite controlling for components of the ICH score, poststroke infection remained a strong contributor to poor 3-month outcomes. Although respiratory infections were more deleterious than urinary infections, both worsened outcomes. Models including infection and ICH score components resulted in superior prediction of 3-month outcomes compared with models including only ICH score components. Infection, therefore, does not seem to be merely a marker of high-grade hemorrhages, but rather contributes independently to outcomes. The contribution of infection to poor outcomes was of similar magnitude as poor GCS, infratentorial location, or intraventricular hemorrhage.

Potential mechanisms by which infection may worsen outcomes after ICH include inflammation, promotion of secondary neuronal injury, disruption of neuronal regeneration and neuroplasticity, and cardiopulmonary deconditioning. In ischemic stroke models, lymphocyte-deficient mice are protected from ischemia, and reconstitution of the immune system with noncentral nervous system antigen-specific lymphocytes is known to worsen the ischemia. Infection, by enhancing proinflammatory cascades and causing a general activation of lymphocytes, might lead to secondary neuronal injury and worse functional outcomes after ICH.

Our results should encourage stroke practitioners to be vigilant about prevention and treatment of infections. The reduction of mortality in stroke units is often achieved by reducing the morbidity of immobilization and secondary complications—early physical therapy, removal of urinary catheters, and early dysphagia screening. One randomized control trial examined the use of prophylactic moxifloxacin in patients with ischemic stroke with middle cerebral artery territory lesions and National Institutes of Health Stroke Scale >11. This small study of 80 patients showed a reduction in infections in the per protocol analysis (17% versus 42%), but no improvement in outcomes. Whether prophylactic antibiotics could be targeted to a high-risk group to improve outcomes after ICH is a possible future area of inquiry.

There are significant strengths to this study. It is a multi-center study with a large and diverse population. Infections are diagnosed as part of the usual clinical care of these patients, so the data should be generalizable. In addition, hot pursuit is used to limit survival bias within the cohort. Limitations of the study include varying definitions and surveillance methods for infection and lack of specifics on infection timing, severity, and treatment. The present analysis was not a prespecified focus of the ERICH study, and as a secondary analysis of data collected as part of a genetic study, it is therefore hypothesis generating. Research staff involved in chart abstraction receive intensive training and detailed instructions, repeated on a regular basis, on how to complete data collection forms, including specifying UTI, respiratory, and central nervous system infections. The design of the study is to recruit equal numbers of white, black, and Hispanic patients. Thus, this is not a population-based study as blacks and Hispanics are over-represented compared with the overall US population. In keeping with the purpose of the study, the current analysis is thus equally powered to detect infection by race/ethnicity and thereby avoid a racial bias toward detection in only non-Hispanic whites. Finally, temperatures were not recorded throughout the study and concurrent fever, a known independent risk factor for poor outcome after ICH, is a potential moderator of the association of infection and poor outcome found in the present analysis.

In conclusion, infection is a common and serious complication after ICH. Some groups, particularly blacks, seem to be at increased risk for infection after ICH. Future studies are warranted to investigate feasibility and efficacy of interventions to reduce infections after ICH.

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Disclosures
Dr Rosand discloses fees from Boehringer Ingelheim unrelated to this study. The other authors report no conflicts.

References
Infection After Intracerebral Hemorrhage: Risk Factors and Association With Outcomes in the Ethnic/Racial Variations of Intracerebral Hemorrhage Study
Aaron S. Lord, Carl D. Langefeld, Padmini Sekar, Charles J. Moomaw, Neeraj Badjatia, Anastasia Vashkevich, Jonathan Rosand, Jennifer Osborne, Daniel Woo and Mitchell S.V. Elkind

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SUPPLEMENTAL MATERIALS

1. Hospital Complications Chart Abstraction Form
2. Pertinent information from Manual of Procedures
COMPLICATIONS / NEW DIAGNOSES

Circle all significant complications/new diagnoses documented during hospitalization.

(CX-1) = a-fib developed during stay     (CX-18) = fall/injury
(CX-2) = anxiety                       (CX-19) = GI bleed
(CX-3) = bowel/bladder dysfunction      (CX-20) = hallucinations
(CX-4) = brain edema                    (CX-21) = headaches
(CX-5) = cardiac arrest                 (CX-22) = herniation
(CX-6) = cellulitis                     (CX-23) = hyperglycemia
(CX-8) = chest pain / angina            (CX-24) = hypertensive crisis
(CX-9) = CHF / pulmonary edema          (CX-25) = hypoglycemia
(CX-10) = confusion / agitation         (CX-26) = hypotensive episode
(CX-11) = decubitus ulcer               (CX-27) = MI
(CX-12) = dehydration                   (CX-28) = pneumonia
(CX-13) = depression (newly diagnosed)  (CX-29) = pulmonary edema
(CX-14) = dizziness                     (CX-30) = pulmonary embolus
(CX-15) = DVT                           (CX-31) = seizure
(CX-16) = dysphagia, not requiring peg / ng (CX-32) = sepsis
(CX-17) = dysphagia, requiring peg / ng  (CX-33) = UTI

Specify complications / new diagnoses not listed above:

(CX-7a) _______________________________  (CX-7e) _______________________________
(CX-7b) _______________________________  (CX-7f) _______________________________
(CX-7c) _______________________________  (CX-7g) _______________________________
(CX-7d) _______________________________  (CX-7h) _______________________________

(CX-13) NOTES: __________________________________________________________________________
________________________________________________________________________________________
________________________________________________________________________________________
________________________________________________________________________________________
If patient received a one-time IVPB or dose of an AED the beginning and end date should be the same. The start time and stop time should be the same and the dose should be the same.

IT-31-IT-35: document any new AED or titration

IT-21: Was rFVIIa administered following onset of ICH within 48 hours of hospitalization - Recombinant activated factor VII – NovoSeven® - If yes, document date time and dose.

OTHER PRO-THROMBOTIC THERAPY GIVEN FOLLOWING ONSET (within 48 hours of hospitalization)

IT-22: FFP- fresh frozen plasma – if yes, document date time and total units given

IT-25: Vitamin K – if yes document date time and total units given

IT-23: Cryoprecipitate – frozen blood products. If yes, document date, time and total units given

IT-24: Platelets: if yes, document date, time and total units given

IT-28: Pro-thrombotic complex: If yes, document date, time and total units given

Page 24: Clinical Course

CC-16: Was patient made DNR during hospitalization? If yes, document date and time the order was written on the patients chart.

CC-17: Was patient made DNI (do no intubate) during hospitalization? If yes, document date and time the order was written in the patients chart.

CC-18: Was patient made comfort care measures only? If yes, document date and time the order was written in the patients chart.

CC-2: Did the patient have a subsequent stroke or TIA?: This should only be marked for events that would be considered as a separate event. For example, a patient may experience an ischemic or another hemorrhagic stroke event later in their hospitalization remote from their initial hemorrhagic stroke.

CC-3-4: If yes to CC-2 document date and type of event

Page 25: Complications/New Diagnoses: PLEASE PAY CLOSE ATTENTION TO THIS PAGE. GO THROUGH PROGRESS NOTES, NURSES NOTES, H&P AND DISCHARGE SUMMARY FOR COMPLICATIONS.

CX-1-Cx-33: Circle any complications that occur during the hospitalization. If this is an in-hospital stroke, list only those events that occurred after the stroke was diagnosed. The discharge summary is a good place to start; you are not expected to read every word in the chart to determine this. Refer to the discharge summary for significant complications.

CX-7a-7h: list any other significant complications not mentioned above